Obstructive Sleep Apnea
The Most Common Secondary Cause of Hypertension Associated With Resistant Hypertension


Abstract—Recognition and treatment of secondary causes of hypertension among patients with resistant hypertension may help to control blood pressure and reduce cardiovascular risk. However, there are no studies systematically evaluating secondary causes of hypertension according to the Seventh Joint National Committee. Consecutive patients with resistant hypertension were investigated for known causes of hypertension irrespective of symptoms and signs, including aortic coarctation, Cushing syndrome, obstructive sleep apnea, drugs, pheochromocytoma, primary aldosteronism, renal parenchymal disease, renovascular hypertension, and thyroid disorders. Among 125 patients (age: 52±1 years, 43% males, systolic and diastolic blood pressure: 176±31 and 107±19 mm Hg, respectively), obstructive sleep apnea (apneahypopnea index: >15 events per hour) was the most common condition associated with resistant hypertension (64.0%), followed by primary aldosteronism (5.6%), renal artery stenosis (2.4%), renal parenchymal disease (1.6%), oral contraceptives (1.6%), and thyroid disorders (0.8%). In 34.4%, no secondary cause of hypertension was identified (primary hypertension). Two concomitant secondary causes of hypertension were found in 6.4% of patients. Age >50 years (odds ratio: 5.2 [95% CI: 1.9–14.2]; P<0.01), neck circumference ≥41 cm for women and ≥43 cm for men (odds ratio: 4.7 [95% CI: 1.3–16.9]; P=0.02), and presence of snoring (odds ratio: 3.7 [95% CI: 1.3–11]; P=0.02) were predictors of obstructive sleep apnea. In conclusion, obstructive sleep apnea appears to be the most common condition associated with resistant hypertension. Age >50 years, large neck circumference measurement, and snoring are good predictors of obstructive sleep apnea in this population. (Hypertension. 2011;58:00-00.)

Key Words: hypertension ■ causes ■ sleep apnea ■ obstructive ■ blood pressure ■ prevalence

Hypertension (HTN) affects approximately one third of the adult population and remains the most important cardiovascular risk factor in the general population. Two to 30% of the hypertensive population have resistant HTN defined as uncontrolled blood pressure (BP) despite the concurrent use of 3 antihypertensive agents, including a diuretic, or the need for ≥3 medications to control BP. Patients with resistant HTN represent a special risk group because they are at increased risk of target organ damage and cardiovascular complications compared with patients with well-controlled HTN. The systematic search for secondary causes of HTN is mandatory among patients with resistant HTN because it includes reversible conditions that may help to control BP. Moreover, the prevalence of secondary causes of HTN is thought to be greater in patients with resistant HTN than in patients with controlled HTN. Previous studies reported that the most prevalent causes of secondary HTN are renal parenchymal disease and renal artery stenosis. However, the prevalence of secondary causes of HTN in patients with resistant HTN quoted in current guidelines is derived from studies with several limitations, including the selection of only certain categories of secondary causes of HTN, failure to classify resistant HTN according to contemporary definitions, and absence of systematic evaluation of the most frequent causes of HTN.

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep. OSA has been newly recognized as a secondary cause of HTN according to the Seventh Joint National Committee. There is mounting evidence that OSA is common among patients with HTN, ranging from 37% to 56%. Among patients with resistant HTN, the prevalence of OSA is extremely high, ranging from 70% to 83%. However, these previous studies were small and performed in a single population.

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From the Sleep Laboratory, Pulmonary Division (R.P.P., L.F.D., K.G.d.P., A.C.S.A., G.L.-F.), and Hypertension Unit (L.F.D., L.A.B., E.M.K.), Heart Institute, Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil; Sleep and Heart Laboratory, Pronto Socorro Cardiológico de Pernambuco (R.P.P.), Universidade de Pernambuco, Pernambuco, Brazil; Department of Hypertension and Nephrology (C.C.G., M.G.S., C.A.), Instituto Dante Pazzanese de Cardiologia, São Paulo, São Paulo, Brazil; University of Toronto (T.D.B.), Toronto, Ontario, Canada.
Correspondence to Geraldo Lorenzi-Filho, Sleep Laboratory, Pulmonary Division, Heart Institute (InCor), Av Enéas Carvalho de Aguiar 44, São Paulo, Brazil. E-mail geraldo.lorenzi@incor.usp.br
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center. More importantly, all of these investigations in patients with resistant HTN did not evaluate the predictors of OSA in this population and also did not investigate the other causes of secondary HTN. OSA triggers a cascade of adverse effects, including increased sympathetic activity, systemic inflammation, and metabolic dysregulation that may contribute to poor BP control. Moreover, the treatment of OSA by continuous positive airway pressure during sleep can reduce BP in patients with masked HTN, and specially in resistant HTN.

In the present study, we sought to systematically investigate the prevalence of secondary causes of HTN among patients with resistant HTN. Based on the recent literature, we hypothesized that OSA is the most common known secondary cause of HTN associated with resistant HTN. Because OSA is largely underdiagnosed in the resistant HTN population, we also sought to investigate clinical predictors of OSA.

Methods

Patients

Consecutive patients with resistant HTN evaluated in the outpatient hypertension units of 2 independent cardiology hospitals in São Paulo, Brazil (Instituto do Coração-InCor, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, and Instituto Dante Pazzanese de Cardiologia), were recruited in the period from February 2008 to April 2010. Resistant HTN was defined as uncontrolled office BP (≥140/90 mm Hg) despite the concurrent use of 3 antihypertensive agents of different classes prescribed at optimal dosage, including a diuretic or the necessity of regular use of ≥3 medications to control BP. BP measurements were determined on separate occasions by ≥3 readings of systolic and diastolic (phase V) BPs obtained at 5-minute intervals with a conventional mercury sphygmomanometer, after patients had been seated for 15 minutes. BP values were determined by the average of the 2 last measures. In the first evaluation, BP was also measured in the lower limbs using an appropriate cuff to determine whether significant differences in BP (≥20 mm Hg) between upper and lower limbs were present to suggest coarctation of the aorta.

Evaluations

All of the patients underwent a clinical and routine laboratory evaluation, which included measurement of glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, hemoglobin, and creatinine levels. Patients were classified as having metabolic syndrome, as described previously. Obesity was considered when body mass index was ≥30 kg/m2. Twenty-four-hour ambulatory BP monitoring was performed with a SpaceLabs device (model 90207, SpaceLabs, Redmond, WA). Briefly, BP was measured every 10 minutes during the day (8:00 AM to 11:00 PM) and every 20 minutes during the night (11:00 PM to 8:00 AM). A nondipping pattern of BP during the night was defined as a drop in systolic or diastolic BP of <10% compared with daytime BP.

All of the participants were submitted to a standardized evaluation described below to investigate secondary causes of HTN irrespective of any clinical sign or symptom. If no secondary causes of HTN were identified, patients were considered as having primary HTN. The local ethics committees approved the protocol, and all of the participants provided written informed consent before participation. Patients who did not undergo a complete evaluation or who did not fulfill criteria for resistant HTN were excluded.

Investigation of Secondary Causes of HTN

Obstructive Sleep Apnea

All of the patients were evaluated by full polysomnography in the sleep laboratory using standard techniques and scoring criteria to monitor sleep stages and arousals from sleep, as described previously. Apneas were defined as a total absence of oronasal flow for ≥10 seconds and hypopneas as a clear decrease (>50%) in amplitude of oronasal flow for ≥10 seconds, followed by a 3% desaturation and/or arousal. The apnea-hypopnea index was obtained by dividing the total number of apneas and hypopneas by total sleep time. OSA was considered present when apnea-hypopnea index was ≥15 events per hour of sleep. This conservative cutoff was adopted because of the greater impact of moderate-to-severe OSA on BP control.

Snoring was considered to be present if ≥2 of the following characteristics were present, snoring louder than talking, snoring >3 to 4 nights a week, snoring that bothered the bed partner, and awareness that they stop breathing during sleep >3 to 4 nights a week referred by the bed partner. The Epworth Sleepiness Scale was used to evaluate the degree of subjective excessive daytime sleepiness. Briefly, the patient rates the probability of falling asleep (0–3) in 8 different situations, and a score >10 points represents the presence of excessive daytime sleepiness. A neck circumference of ≥41 cm or ≥43 cm for women and men, respectively, was used to identify a body habitus that put subjects at increased risk of OA.

Primary Aldosteronism

Paired morning plasma aldosterone and plasma renin activity were performed. Patients under spironolactone use withdrew this medication 3 weeks before the blood sample. In patients with aldosterone-renin ratio >20, aldosterone suppression test was performed according to current guidelines. Briefly, primary hyperaldosteronism was diagnosed when plasma aldosterone determined after 2 L of intravenous saline infusion over 4 hours was >10 ng/dL. To diagnose aldosterone-producing adenoma or adrenal hyperplasia, all of the patients with confirmed primary hyperaldosteronism were submitted to a computed tomographic scan of the adrenal glands.

Renal Artery Stenosis

Doppler renal artery ultrasonography or renal scan with 99mTc-diphosphonate triamidate penta-acetic acid (DTPA) was performed as the screening methods according to physician discretion. Doppler renal artery ultrasonography measurements were performed using a 3.5-MHz transducer (Toshiba Aplio XV, Crawley, West Sussex, United Kingdom). The pulsatility index was calculated, and a side-to-side difference of >0.20 was used as a criterion for renal artery stenosis. In addition, acceleration of the blood flow velocity during early systole was measured, and an acceleration of the blood flow >3 m/s2 was used as a criterion for renal artery stenosis.

Renal scan with 99mTc-DTPA was performed using a large field of view gamma camera (Siemens Basicam, Milpitas, CA). One-second images were acquired immediately after the bolus injection of 740 mBq 99mTc-DTPA during the first minute, followed by 30 images with 1-minute duration. The exams were analyzed visually, and 2 time-activity curves were also generated for the first minute (flow time-activity curve) and for the remaining 30 minutes (function curve). Individual renal relative function was considered abnormal if there was a difference of >10% between the kidneys. Patients with a positive screening for renal artery stenosis underwent gadolinium-enhanced magnetic resonance arteriography and, if necessary, were further referred for catheter angiography for final diagnosis and treatment of renal artery stenosis.

Renal Parenchyma Disease

In all of the patients, measurement of serum creatinine was performed. Patients who had a estimated glomerular filtration rate <30 ml/min based on the Modification of Diet in Renal Disease study equation were defined as having renal parenchyma disease, as advised by current guidelines.

Other Causes

History of alcoholism, adrenergic medications, and oral contraceptives was systematically investigated. Pheochromocytoma was screened by determination of 24-hour urinary excretion of metanephrines. Serum thyroid-stimulating hormone and free thyroxine were measured to evaluate thyroid function. Patients with systolic pressure...
differences between upper and lower limbs >20 mm Hg were further investigated for aortic coarctation. In addition, all of the patients had a chest radiograph. Patients with clinical signs and symptoms of Cushing syndrome were evaluated by measurements of 24-hour urinary free cortisol.2

Statistical Analysis

Quantitative variables were expressed as mean ± SD. Categorical variables were expressed as frequency distribution and were compared using the $\chi^2$ or Fisher exact test. Univariate and multiple logistic regression (backward stepwise) analyses were used to determine the predictors of OSA in the entire population. Possible explanatory variables used as independent variables included demographic, clinical, and ambulatory BP monitoring values. Variables with a $P$ value <0.1 in univariate analysis were entered into the multivariate model. A $P$ value <0.05 was considered significant. Data were analyzed using the Statistical Package for Social Sciences, version 17.0, statistical software (SPSS, Chicago, IL).

Results

We initially evaluated 186 patients during the recruitment period, and 61 were excluded, resulting in a population of 125 patients (Figure 1). The population studied was generally middle aged, with a slight majority of women (Table 1). Secondary associated causes of HTN are summarized in Figure 2. OSA was present in 64.0% of the patients. Severe OSA (apnea-hypopnea index ≥30) was present in 40 patients (32.0%). Plasma aldosterone/renin >20 was present in 14 patients (11.2%). These patients underwent an aldosterone suppression test, and only 7 patients (5.6%) were diagnosed as having primary aldosteronism. Computed tomographic scan of adrenal glands was performed in the latter group (n=7), and 1 patient was diagnosed with aldosterone-producing adenoma (0.8%). Thirteen patients had a positive screening test for renal artery stenosis. Among this latter
Table 1. Anthropometric and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N=125)</th>
<th>No OSA (N=45)</th>
<th>OSA (N=80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52±10</td>
<td>48±10</td>
<td>55±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>43</td>
<td>27</td>
<td>53</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.5±6.2</td>
<td>29.0±4.3</td>
<td>32.9±6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>39.3±4.1</td>
<td>37.3±4</td>
<td>40.4±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>103±14</td>
<td>96±10</td>
<td>107±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White, %</td>
<td>48</td>
<td>46</td>
<td>49</td>
<td>0.83</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>6</td>
<td>11</td>
<td>3</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>30</td>
<td>20</td>
<td>35</td>
<td>0.08</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>3.2</td>
<td>4.5</td>
<td>2.5</td>
<td>0.54</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>80</td>
<td>71</td>
<td>85</td>
<td>0.06</td>
</tr>
<tr>
<td>Metabolic syndrome, %*</td>
<td>67</td>
<td>53</td>
<td>75</td>
<td>0.013</td>
</tr>
<tr>
<td>Familial history of HTN, %</td>
<td>78</td>
<td>88</td>
<td>78</td>
<td>0.74</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±14</td>
<td>73±12</td>
<td>68±15</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>176±31</td>
<td>179±28</td>
<td>174±32</td>
<td>0.44</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>107±19</td>
<td>109±17</td>
<td>106±20</td>
<td>0.44</td>
</tr>
<tr>
<td>No. of drugs, n</td>
<td>6 (5–8)</td>
<td>6 (5–7)</td>
<td>7 (5–9)</td>
<td>0.08</td>
</tr>
<tr>
<td>No. of antihypertensive drugs, n</td>
<td>5 (4–6)</td>
<td>5 (4–5)</td>
<td>5 (4–6)</td>
<td>0.97</td>
</tr>
<tr>
<td>Thiazides/loop diuretics, %</td>
<td>98</td>
<td>100</td>
<td>96</td>
<td>0.19</td>
</tr>
<tr>
<td>Spironolactone, %</td>
<td>30</td>
<td>31</td>
<td>29</td>
<td>0.78</td>
</tr>
<tr>
<td>β-blocker, %</td>
<td>85</td>
<td>82</td>
<td>86</td>
<td>0.55</td>
</tr>
<tr>
<td>ACEI, %</td>
<td>78</td>
<td>85</td>
<td>75</td>
<td>0.22</td>
</tr>
<tr>
<td>Calcium channel blocker, %</td>
<td>94</td>
<td>89</td>
<td>95</td>
<td>0.21</td>
</tr>
<tr>
<td>ARB, %</td>
<td>26</td>
<td>24</td>
<td>26</td>
<td>0.82</td>
</tr>
<tr>
<td>Centrally acting drugs</td>
<td>59</td>
<td>62</td>
<td>58</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Values are mean±SD. Variables with skewed distribution are presented as median (interquartile range). HTN indicates hypertension; BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; AHI, apnea-hypopnea index. *Data are based on Adult Treatment Panel III.

Table 2. Twenty-Four-Hour Ambulatory Blood Pressure Monitoring According to the Presence or Absence of Obstructive Sleep Apnea

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N=125)</th>
<th>No OSA (N=45)</th>
<th>OSA (N=80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic daytime ABP</td>
<td>146.6±1.2</td>
<td>149±25</td>
<td>144±18</td>
<td>0.29</td>
</tr>
<tr>
<td>Diastolic daytime ABP</td>
<td>89±16</td>
<td>93±17</td>
<td>87±14</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic nocturnal ABP</td>
<td>135±21</td>
<td>137±25</td>
<td>134±18</td>
<td>0.58</td>
</tr>
<tr>
<td>Diastolic nocturnal ABP</td>
<td>78±15</td>
<td>81±16</td>
<td>76±14</td>
<td>0.08</td>
</tr>
<tr>
<td>Systolic nocturnal dipping ABP, mm Hg</td>
<td>7.0±8.3</td>
<td>8.0±7.7</td>
<td>6.4±8.6</td>
<td>0.35</td>
</tr>
<tr>
<td>Diastolic nocturnal dipping ABP, mm Hg</td>
<td>12.6±8.8</td>
<td>12.7±7.8</td>
<td>12.6±9.3</td>
<td>0.96</td>
</tr>
<tr>
<td>Systolic nondipping, %</td>
<td>61</td>
<td>53</td>
<td>65</td>
<td>0.24</td>
</tr>
<tr>
<td>Diastolic nondipping, %</td>
<td>39</td>
<td>36</td>
<td>41</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Values are mean±SD. Variables with skewed distribution are presented as median (interquartile range). ABP indicates ambulatory blood pressure (available in 104 patients); OSA, obstructive sleep apnea.

The characteristics of the population according to the presence or absence of OSA are presented in Table 1. Among patients with OSA, age, body mass index, and the proportion of men and of those with metabolic syndrome were higher than in patients without OSA. Twenty-four-hour ambulatory BP monitoring values did not differ between patients without and with OSA in these patients with resistant HTN (Table 2). Laboratory and sleep study results of the entire population, and divided according to the absence or presence of OSA, are presented in Table 3. The level of serum creatinine was higher and of high-density lipoprotein cholesterol was lower in those with compared with those without OSA.

We also investigated the characteristics associated with OSA. Sensitivity and specificity for both abnormal systolic and diastolic BP dipping patterns during the night to diagnose (26%). Eight patients (6.4%) had OSA plus another secondary cause of HTN, including 4 patients with primary aldosteronism, 2 patients with renal parenchymal disease, 1 patient with hypothryroidism, and 1 patient with renal artery stenosis. Forty-three patients (34.4%) had no identifiable causes of HTN and were considered as having primary HTN. There were no differences in the frequency of secondary forms of HTN between the 2 centers (Figure S1, available in the online Data Supplement, please see http://hyper.ahajournals.org).

The characteristics of the population according to the presence or absence of OSA are presented in Table 1. Among patients with OSA, age, body mass index, and the proportion of men and of those with metabolic syndrome were higher than in patients without OSA. Twenty-four-hour ambulatory BP monitoring values did not differ between patients without and with OSA in these patients with resistant HTN (Table 2). Laboratory and sleep study results of the entire population, and divided according to the absence or presence of OSA, are presented in Table 3. The level of serum creatinine was higher and of high-density lipoprotein cholesterol was lower in those with compared with those without OSA.

We also investigated the characteristics associated with OSA. Sensitivity and specificity for both abnormal systolic and diastolic BP dipping patterns during the night to diagnose
OSA were 64% and 39% and 47% and 64%, respectively. Large neck circumference and diabetes mellitus had low sensitivity (33% and 36%) but high specificity (84% and 80%), respectively, to diagnose OSA. Snoring and dyslipidemia also had relatively high sensitivity (87%) but poor specificity (57% and 30%), respectively, to diagnose OSA. Univariate logistic regression identified male sex, large neck circumference, snoring, metabolic syndrome, age >50 years, and obesity as predictors of OSA among patients with resistant HTN. A multivariate model identified large neck circumference, snoring, and age >50 years as independent predictors of OSA among patients with resistant HTN (Table 4). After performing a collinearity test, we excluded multicollinearity in the variables included in our model.

### Discussion

Our study systematically evaluated for the first time the usual forms of secondary HTN using the contemporary classification adopted by the Seventh Joint National Committee and included an evaluation for OSA in a consecutive sample of patients with resistant HTN from 2 independent tertiary centers. Our data gave rise to several novel findings. First, almost two thirds of the patients presented some secondary cause of HTN, a much higher prevalence than described in previous studies. Second, OSA was by far the most common secondary condition associated with resistant HTN. Third, snoring, age >50 years, and large neck circumference were predictors of OSA in this population. In contrast, excessive daytime sleepiness, a common symptom in patients with

### Table 3. Laboratory and Sleep Results According to the Presence or Absence of Obstructive Sleep Apnea

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N=125)</th>
<th>No OSA (N=45)</th>
<th>OSA (N=80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.94 (0.77–1.28)</td>
<td>0.86 (0.70–1.04)</td>
<td>1.00 (0.80–1.41)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>100 (91–117)</td>
<td>98 (85–110)</td>
<td>101 (93–128)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>192 (168–218)</td>
<td>193 (169–211)</td>
<td>191 (197–221)</td>
<td>0.77</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>114 (97–137)</td>
<td>108 (92–133)</td>
<td>119 (99–138)</td>
<td>0.20</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>44 (37–52)</td>
<td>47 (40–53)</td>
<td>42 (35–49)</td>
<td>0.04</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>131 (90–189)</td>
<td>110 (79–175)</td>
<td>140 (107–198)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14 (13–15)</td>
<td>14 (13–15)</td>
<td>14 (13–16)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Sleep variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No OSA (N=45)</th>
<th>OSA (N=80)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring, %</td>
<td>77</td>
<td>54</td>
<td>86</td>
</tr>
<tr>
<td>Epworth sleepiness scale, score</td>
<td>8 (5–13)</td>
<td>7 (4–11)</td>
<td>10 (6–14)</td>
</tr>
<tr>
<td>AHI, events/hour</td>
<td>18 (10–40)</td>
<td>7 (3–11)</td>
<td>30 (20–51)</td>
</tr>
<tr>
<td>Arousals, n</td>
<td>106 (53–189)</td>
<td>60 (29–95)</td>
<td>142 (95–237)</td>
</tr>
<tr>
<td>Mean SaO₂, %</td>
<td>95 (94–96)</td>
<td>95 (94–97)</td>
<td>95 (93–96)</td>
</tr>
<tr>
<td>Lowest SaO₂, %</td>
<td>94 (92–95)</td>
<td>93 (91–94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SaO₂ &lt;90%, % of sleep time</td>
<td>0.7 (0–8.5)</td>
<td>0 (0–0.4)</td>
<td>4.0 (0.3–17.0)</td>
</tr>
</tbody>
</table>

Variables with skewed distribution are presented as median (interquartile range) unless otherwise specified. AHI indicates apnea-hypopnea index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OSA, obstructive sleep apnea; SaO₂, arterial oxyhemoglobin saturation.

### Table 4. Predictors of Obstructive Sleep Apnea Among Patients With Resistant Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>SE</th>
<th>P</th>
<th>OR (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3.00</td>
<td>0.65</td>
<td>0.006</td>
<td>4.7 (1.3–16.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Large neck circumference</td>
<td>2.77</td>
<td>0.65</td>
<td>0.032</td>
<td>1.3 (1.3–11.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.40</td>
<td>0.55</td>
<td>0.42</td>
<td>3.7 (1.3–11.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Snoring</td>
<td>5.43</td>
<td>0.55</td>
<td>0.001</td>
<td>3.7 (1.3–11.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>2.63</td>
<td>0.52</td>
<td>0.015</td>
<td>5.2 (1.9–14.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age &gt;50 y</td>
<td>4.97</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td>5.2 (1.9–14.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic nondipping</td>
<td>0.60</td>
<td>0.20</td>
<td>0.62</td>
<td>0.8 (0.3–2.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diastolic nondipping</td>
<td>0.14</td>
<td>0.36</td>
<td>0.61</td>
<td>0.8 (0.3–2.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>1.24</td>
<td>0.97</td>
<td>0.035</td>
<td>0.035 (0.013–0.061)</td>
<td>0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.20</td>
<td>0.038</td>
<td>0.20</td>
<td>0.8 (0.3–2.3)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Data are presented as odds ratios (95% CIs).
OSA, was not a good predictor of OSA in this resistant HTN population. Because the treatment of OSA can reduce BP, our results, therefore, suggest that the systematic search for and treatment of OSA should be included in the management of patients with resistant HTN.

The prevalence of secondary causes of HTN is believed to be higher among patients with resistant HTN than in the general hypertensive population. However, most studies of causes and prevalence of resistant HTN quoted in text books are >30 years old, before contemporary concepts, such as definitions, investigation, and management of HTN, were well defined, and more importantly, before OSA became recognized as a secondary cause of HTN. Primary aldosteronism was found in 5.6% in our population and is, therefore, in line with some of the previous studies that showed a prevalence ranging from 5% to 25%. The reasons for a much higher prevalence of primary aldosteronism in a few studies may reflect a referral bias related to the search for only 1 specific disease. The prevalence of renal parenchymal disease in our study (1.6%) is within the range of that reported in the literature (2% to 5%). Therefore, the most important and novel finding of our study was that the most common secondary cause of HTN that we identified in our resistant HTN population was OSA. The 64% prevalence of OSA is consistent with previous smaller studies that suggested a prevalence of OSA of ~80%. One recent study evaluated secondary causes of HTN in a heterogeneous group of patients who visited an emergency department with a diagnosis of hypertensive urgency/emergency. OSA was present in 70.8% of the patients, whereas other causes of HTN were much less common. However, this study did not involve patients with resistant HTN, and some patients had no previous history of HTN. Our study, therefore, makes a significant contribution to the literature by showing that, compared with other recognized secondary causes of HTN, OSA was far more commonly associated with resistant HTN.

The reasons for the high prevalence of OSA among patients with resistant HTN are probably multiple. First, both resistant HTN and OSA may share common risk factors. The population studied in the present study was obese (body mass index: ~32 kg/m²). Obesity, a common feature of patients with resistant HTN, is also a well-known risk factor for OSA. Second, recent evidence demonstrates that, compared with patients with controlled HTN, those with resistant HTN have a higher apnea-hypopnea index that is proportional to a greater degree of fluid volume displacement from the legs into the neck overnight. Such overnight rostral fluid shift may play a major role in the genesis of upper airway obstruction during sleep. Lastly, the high prevalence of OSA among patients with resistant HTN may be an indication that OSA is contributing to their poor BP control. There are several mechanisms by which OSA could contribute to poor BP control. These include increased sympathetic nervous system activity, decreased baroreflex sensitivity, vascular endothelial dysfunction, and altered metabolism of salt and water. The observation that treating OSA in patients with resistant HTN causes a greater fall in BP than in normotensive patients and patients with controlled HTN supports a causal relationship between OSA and drug-resistant HTN. The treatment of OSA with continuous positive airway pressure can reduce BP, and, therefore, diagnosis and treatment of OSA may play a significant role in the management of patients with resistant HTN. However, these studies did not provide strong evidence yet, and further studies evaluating the effect of continuous positive airway pressure treatment on BP control are necessary.

Despite the growing awareness of OSA, it is estimated that most patients remain undiagnosed. One reason for this may be a lack of daytime somnolence, as indicated by relatively low Epworth Sleepiness Scale scores in our patients with OSA (Table 3). This symptom, one of the main reasons for referral to sleep laboratories to rule out OSA, was not a predictor of OSA in our study. It has been shown that, compared with patients without cardiovascular diseases, those with heart failure and stroke have less subjective daytime sleepiness at any given level of OSA severity. It may be that, for reasons yet to be determined, patients with resistant HTN also have relatively little daytime somnolence. The lack of daytime somnolence in patients with resistant HTN and other cardiovascular diseases may help to explain the low clinical suspicion and recognition of OSA in patients with these disorders. We have demonstrated that, in our patients, increased age, large neck circumference, and snoring are useful tools for predicting OSA. The nondipping pattern of BP during the night has been reported as a feature of patients with OSA. However, these reports did not specifically address patients with resistant HTN. In contrast to those reports, we were not able to find an association between the nocturnal dipping pattern and the presence of OSA. It is possible that antihypertensive medications attenuated this phenomenon.

Our study has some limitations. One potential limitation is that patients with severe forms of renal parenchymal disease may be referred directly to a renal clinic, decreasing its frequency in our population. However, there were no restrictions to evaluate patients with renal disease and resistant HTN in both cardiology centers. Second, adrenal vein sampling for aldosterone measurement is the most appropriate method to determine subtypes of primary aldosteronism rather than blood samples and adrenal imaging. However, this procedure is invasive and not used in clinical routine. Finally, because of the cross-sectional nature of this study, it is not possible to demonstrate that the secondary forms of HTN identified in our patients were causes of their resistant HTN. However, because there is a growing body of evidence that the treatment of OSA reduces BP, it is likely that, in many instances, treatment of OSA would lower BP. Strengths of our study are the relative large number of patients evaluated, the strict protocol used following current recommendations to evaluate resistant HTN, and the involvement of 2 cardiology centers dedicated to evaluating patients with resistant HTN, suggesting the generalizability of the results.

Perspectives
Our study demonstrated that OSA was the most common coexisting treatable secondary form of HTN associated with drug-resistant HTN. Age >50 years, large neck circumference measurement, and snoring are good predictors of OSA.
in this population. These findings may help to improve the recognition and treatment of OSA that ultimately may contribute to decrease the cardiovascular risk in patients with resistant HTN.

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Disclosures None.

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Bradley and Geraldo Lorenzi-Filho

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Obstructive Sleep Apnea: the Commonest Secondary Cause of Hypertension
Associated with Resistant Hypertension

Online Supplement

Short title: Secondary Causes of Resistant Hypertension

Rodrigo P. Pedrosa, MD, PhD\textsuperscript{a,b}; Luciano F. Drager, MD, PhD\textsuperscript{a,c}; Carolina C. Gonzaga, MD\textsuperscript{d}; Marcio G. Sousa, MD\textsuperscript{d}; Lilian K. G de Paula, RpT\textsuperscript{a}; Aline C. S. Amaro, RpT\textsuperscript{a}; Celso Amodeo, MD, PhD\textsuperscript{d}; Luiz A. Bortolotto, MD, PhD\textsuperscript{c}; Eduardo M. Krieger, MD, PhD\textsuperscript{c}; T. Douglas Bradley, MD\textsuperscript{e} and Geraldo Lorenzi-Filho, MD, PhD\textsuperscript{a}

\textsuperscript{a} Sleep Laboratory, Pulmonary Division, Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brasil.

\textsuperscript{b} Sleep and Heart Laboratory, Pronto Socorro Cardiológico de Pernambuco (PROCAPE) da Universidade de Pernambuco, Brasil.

\textsuperscript{c} Hypertension Unit, Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brasil.

\textsuperscript{d} Department of Hypertension and Nephrology, Instituto Dante Pazzanese de Cardiologia, São Paulo, São Paulo, Brasil.

\textsuperscript{e} University of Toronto, Toronto, Ontario, Canada.

Corresponding author:
Geraldo Lorenzi-Filho, MD, PhD.
Sleep Laboratory, Pulmonary Division
Heart Institute (InCor)
Av. Enéas Carvalho de Aguiar, 44
São Paulo, Brazil
Phone/fax number: 55-11-30695486

E-mail: geraldo.lorenzi@incor.usp.br
Obstructive Sleep Apnea: the Commonest Secondary Cause of Hypertension Associated with Resistant Hypertension

Table S1 – Distribution of secondary causes associated with resistant hypertension according to the 2 centers.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Center 1</th>
<th>Center 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=77</td>
<td>N=48</td>
<td></td>
</tr>
<tr>
<td>Obstructive sleep apnea, %</td>
<td>62.3</td>
<td>66.7</td>
<td>0.62</td>
</tr>
<tr>
<td>Primary hypertension, %</td>
<td>36.4</td>
<td>31.3</td>
<td>0.56</td>
</tr>
<tr>
<td>Primary aldosteronism, %</td>
<td>5.2</td>
<td>6.3</td>
<td>0.42</td>
</tr>
<tr>
<td>Renal artery stenosis, %</td>
<td>2.6</td>
<td>2.1</td>
<td>0.67</td>
</tr>
<tr>
<td>Oral contraceptives, %</td>
<td>2.6</td>
<td>0</td>
<td>0.38</td>
</tr>
<tr>
<td>Renal parenchimal disease, %</td>
<td>2.6</td>
<td>0</td>
<td>0.38</td>
</tr>
<tr>
<td>Thyroid disfunction, %</td>
<td>0</td>
<td>2.1</td>
<td>0.38</td>
</tr>
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</table>

Center 1: Instituto do Coração (InCor). Center 2: Instituto Dante Pazzanese de Cardiologia.