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## The Effects of Continuous Positive Airway Pressure on Prehypertension and Masked Hypertension in Men With Severe Obstructive Sleep Apnea

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**Abstract**—Obstructive sleep apnea and hypertension are common conditions that frequently coexist. Continuous positive airway pressure (CPAP) reduces blood pressure in patients with obstructive sleep apnea and sustained hypertension. However, the impact of CPAP on patients with obstructive sleep apnea and prehypertension and masked hypertension, conditions associated with increased cardiovascular risk, is unknown. Thirty-six male patients (age,  $43 \pm 7$  years; body mass index,  $28.8 \pm 3.0$  kg/m<sup>2</sup>) with untreated severe obstructive sleep apnea (apnea–hypopnea index,  $56 \pm 22$  events/hr on polysomnography) with diagnostic criteria for prehypertension and/or masked hypertension, based on office and 24-hour ambulatory blood pressure monitoring, respectively, were studied. The patients randomized to no treatment (control;  $n=18$ ) or CPAP ( $n=18$ ) for 3 months had similar frequency of prehypertension and masked hypertension at study entry. There were no significant changes in blood pressure in patients randomized to the control group. In contrast, patients randomized to CPAP presented significant reduction in office systolic (from  $126 \pm 5$  to  $121 \pm 7$  mm Hg;  $P=0.001$ ) and a trend for diastolic blood pressure (from  $75 \pm 7$  to  $73 \pm 8$  mm Hg;  $P=0.08$ ) as well as a significant decrease in daytime and nighttime systolic and diastolic blood pressure ( $P<0.05$  for each comparison). There was a significant reduction in the frequency of prehypertension (from 94% to 55%;  $P=0.02$ ) and masked hypertension (from 39% to 5%;  $P=0.04$ ) only in the CPAP group. In conclusion, effective CPAP therapy promotes significant reduction in the frequency of prehypertension and masked hypertension by promoting significant blood pressure reductions in patients with severe obstructive sleep apnea. (*Hypertension*. 2011;57[part 2]:549-555.) • **Online Data Supplement**

**Key Words:** blood pressure ■ cardiovascular disease ■ CPAP ■ hypertension ■ masked hypertension ■ prehypertension ■ sleep apnea

Hypertension remains a major cause of cardiovascular complications worldwide with a prevalence that increases in parallel with increasing age.<sup>1</sup> The terminology and thresholds to define abnormal blood pressure have changed overtime, reflecting the progressive awareness that intervention in the precursors of hypertension are effective in reducing future cardiovascular risk.<sup>2,3</sup> The term “prehypertension” was introduced by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and was defined as a systolic blood pressure (BP) of 120 to 139 mm Hg and a diastolic BP of 80 to 89 mm Hg.<sup>1</sup> Although prehypertension is not considered a special category of hypertension,<sup>1</sup> it is frequently a precursor of sustained hypertension and increasingly associated with an excess morbidity and mortality from cardiovascular disease.<sup>4</sup> Similarly, masked hypertension, a condition characterized by normal office BP and abnormal 24-hour ambulatory BP (ABPM), may also be a precursor of

sustained hypertension and is also an independent cardiovascular risk factor when compared with true normotensive subjects.<sup>2</sup> Despite this evidence, the impact of recognition and treatment of comorbid conditions on BP in patients with prehypertension and masked hypertension remains poorly understood.

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction during sleep resulting in intermittent hypoxia and arousals from sleep.<sup>5</sup> OSA is common in the general population, and the prevalence is strikingly high among patients with sustained hypertension (approximately 50%).<sup>6</sup> There is growing evidence that OSA participates in the genesis of hypertension through several mechanisms, including sympathetic overactivation, oxidative stress, systemic inflammation, and increased arterial stiffness.<sup>7,8</sup> The treatment of OSA with continuous positive airway pressure (CPAP) is able to reduce BP in patients with OSA and sustained hypertension.<sup>8</sup> However, patients with

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OSA frequently present several comorbid conditions, and the treatment of OSA rarely normalizes BP to the point that antihypertensive medications can be discontinued. Moreover, the effects of CPAP on BP may be extremely dependent on the BP status at study entry and tend to be higher in patients with high levels of BP,<sup>9</sup> reaching minimal or no effects in patients with normal BP.<sup>10,11</sup>

The association among OSA, prehypertension, and masked hypertension has gained recent interest. To the best of our knowledge, no studies have attempted to study prehypertension in patients with OSA. On the other hand, at least 2 independent studies showed that masked hypertension is common among patients with OSA and apparent normal BP when ABPM is performed.<sup>12,13</sup> This raises the question whether OSA treatment can reduce or even normalize BP in patients with prehypertension and masked hypertension. Therefore, this randomized study was designed to evaluate the impact of the treatment of OSA with CPAP on BP in patients with severe OSA and no overt comorbid conditions with prehypertension and/or masked hypertension. Some of the results of this study have been previously reported in the form of an abstract.<sup>14</sup>

## Methods

### Subjects

We recruited consecutive male patients from the Sleep Laboratory, Heart Institute (InCor), University of São Paulo Medical School with a recent diagnosis of severe OSA (apnea–hypopnea index >30 events/hr) by polysomnography, under no antihypertensive medications, and considered as normotensive based on office BP <140/90 mm Hg.<sup>1</sup> According to our inclusion criteria, all participants had to have the diagnosis of prehypertension and/or masked hypertension (see subsequent definitions) based on office BP and 24-hour ABPM. Subjects who were >60 years as well as with a history of sustained hypertension, body mass index (BMI) >40 kg/m<sup>2</sup>, diabetes mellitus, cerebrovascular disease, arrhythmias, heart failure, valvular heart disease, renal failure, smoking, regular alcohol intake, and taking any medication were excluded from the study. All patients with OSA were naive to treatment. The local Ethics Committee approved the protocol, and all participants gave written informed consent.

### Office BP

BP measurements were determined by the average results of 2 readings of systolic and diastolic BP obtained at 5-minute intervals using an automatic device (Model Hem-711Ac; Omron Healthcare, Inc, Bannockburn, IL) after participants had been seated in a chair with feet on the floor and arm supported at heart level for at least 5 minutes.<sup>1</sup> Prehypertension was defined on the basis of office BP measurements and was defined by a systolic BP between 120 and 139 or diastolic BP between 80 and 89 mm Hg.<sup>1</sup>

### 24-Hour ABPM

Twenty-four-hour ABPM was evaluated using a SpaceLabs device (Model 90207). BP was measured every 10 minutes during the day (8 AM to 11 PM) and every 20 minutes during the night (11 PM to 8 AM) with an appropriate cuff placed on a nondominant arm. Participants were instructed to perform their ordinary daily activities and not to move their arm during the ongoing measurement. Activity, bedtime, and time on awakening from sleep were recorded by participants on diaries. Patients were classified as having normal awake BP if the corresponding value was <135 mm Hg systolic and <85 mm Hg diastolic.<sup>15</sup> The normal sleep BP was considered to be <120/70 mm Hg.<sup>15</sup> The normal BP dip was defined separately for systolic and diastolic BP as a  $\geq 10\%$  reduction in BP during sleep compared with the awake period. Nondipping was defined as a

decrease of <10%. According to the definition adopted by current guidelines and systematic reviews, masked hypertension was considered to be present when patients had normal clinical BP values (<140/90 mm Hg) but abnormal diurnal ambulatory blood pressure monitoring ( $\geq 135$  or  $\geq 85$  mm Hg).<sup>16</sup>

### Sleep Evaluation

All patients underwent a standard overnight polysomnography (EM-BLA; Flaga hf. Medical Devices, Reykjavik, Iceland), including electroencephalography, electro-oculography, electromyography, oximetry, measurements of airflow (oronasal thermistor and pressure cannula), and measurements of rib cage and abdominal movements during breathing, as previously described.<sup>17</sup> Apnea was defined as complete cessation of airflow for at least 10 seconds associated with oxygen desaturation of 3%. Hypopnea was defined as a significant reduction (>50%) in respiratory signals for at least 10 seconds associated with oxygen desaturation of 3%. The apnea–hypopnea index was calculated as the total number of respiratory events (apneas plus hypopneas) per hour of sleep. In addition, subjective daytime sleepiness was evaluated by using the Epworth Sleepiness Scale. A total score >10 was considered excessive daytime sleepiness.<sup>18</sup> Patients randomized to CPAP underwent a full-night CPAP titration study, during which the pressure was adjusted to abolish apnea and hypopnea.

### Study Design

Patients were randomly assigned to no treatment (control) or treatment with CPAP (Respironics, Inc, Murrysville, PA) for 3 months. An independent staff prepared a randomization list by computer in advance. Our protocol involved 1 visit per week in the first month and thereafter twice per month. CPAP compliance was objectively measured by downloading a card (Smart Card; Respironics, Inc) that contains the time counter of the device. Office and 24-hour ABPM were performed at study entry and after 3 months. At study termination, CPAP was offered and initiated in the patients randomized to the control arm.

### Statistical Analysis

Data were analyzed with SPSS 10.0 statistical software. Baseline characteristics of patients with OSA according to the group assigned were compared by 2-tailed unpaired *t* tests for continuous variables and 2-tailed Fisher exact test or  $\chi^2$  test for nominal variables. Two-way repeated-measures analysis of variance and Tukey test were used to compare differences within and between groups in variables measured at baseline and 3 months. In the CPAP group, we performed Pearson correlation coefficient to correlate the magnitude of BP fall with possible explanatory mechanisms, including improvement in sleep parameters and CPAP compliance. A value of  $P < 0.05$  was considered significant.

## Results

We initially selected 120 normotensive patients with severe OSA. Forty-five patients did not present any exclusion criteria and filled the criteria of normal BP based on careful office BP. We further excluded 9 patients because of absence of both prehypertension and masked hypertension after clinical and ABPM evaluation ( $n=4$ ); failure to perform ABPM ( $n=3$ ); and initiation of CPAP therapy before study entry ( $n=2$ ). Therefore, our final sample comprised 36 patients. The patients were predominantly middle-aged and overweight with severe OSA (Table 1). Patients assigned to control or CPAP groups were similar regarding all parameters, including age, BMI, glucose, lipid profile, office BP, heart rate, 24-hour ABPM, frequency of nondipping as well as frequency of prehypertension and masked hypertension (Table 1).

**Table 1. Baseline Characteristics**

Variable	Total (n=36)	Control (n=18)	CPAP (n=18)	P
Age, years	43±7	44±7	43±7	0.85
Whites, %	75	78	72	1.0
BMI, kg/m <sup>2</sup>	28.8±3.0	29.0±2.6	28.5±3.3	0.64
Office systolic BP, mm Hg	127±6	127±6	126±5	0.44
Office diastolic BP, mm Hg	76±8	76±9	75±7	0.69
Heart rate, beats/min	79±11	80±11	77±12	0.57
Glucose, mg/dL	92±8	91±9	93±7	0.62
Total cholesterol, mg/dL	215±43	220±47	210±40	0.50
Triglycerides, mg/dL	166±75	176±76	156±76	0.43
<b>ABPM data</b>				
ABPM—24-hour systolic BP, mm Hg	122±7	121±9	122±5	0.65
ABPM—24-hour diastolic BP, mm Hg	79±6	78±6	79±5	0.75
ABPM—daytime systolic BP, mm Hg	127±8	126±10	127±5	0.77
ABPM—daytime diastolic BP, mm Hg	83±6	83±7	83±5	1.0
ABPM—nighttime systolic BP, mm Hg	111±8	111±8	112±7	0.52
ABPM—nighttime diastolic BP, mm Hg	69±7	68±7	70±8	0.42
Prehypertension, no. (%)	34 (94)	17 (94)	17 (94)	1.0
Masked hypertension, no. (%)	14 (39)	7 (39)	7 (39)	1.0
Overlap pre- and masked hypertension, no. (%)	12 (33)	6 (33)	6 (33)	1.0
Nondipping pattern, no. (%)	15 (42)	6 (33)	9 (50)	0.50
<b>Sleep data</b>				
AHI, events/hour	56±22	58±23	55±20	0.66
Awake oxygen saturation, %	94±2	95±2	94±2	0.56
Minimal oxygen saturation, %	76±9	77±12	75±7	0.69
Arousals/hour	46±23	47±24	44±22	0.76
Epworth Sleepiness Scale	12±5	11±5	12±5	0.78

Values are mean±SD.  
AHI indicates apnea–hypopnea index.

The optimal CPAP pressure determined in the patients assigned to CPAP during the titration sleep study was 10.4±1.0 cm of water (range, 9.0 to 13.0 cm of water). CPAP decreased the apnea–hypopnea index to 5.0±2.1 events/hour and raised the minimum oxygen saturation to 90%±3%. Daytime sleepiness was significantly reduced after the CPAP therapy (from 12±5 to 7±3; *P*<0.01). The CPAP was used for 5.2±0.7 hours per night (range, 4.1 to 6.4 hours).

No significant changes in BMI occurred in either group across the study (Table 2). There were no significant changes in the heart rate, office BP, and ABPM over the study period in the control group (Table 2). The frequency of nondipping did not change significantly across the study in the control (33% versus 39%; *P*=1.0) as well as in the CPAP group (50% versus 39%; *P*=0.74). Patients randomized to CPAP presented significant reduction in the office systolic BP and a strong trend in diastolic BP (Table 2). ABPM also showed a significant drop in daytime systolic daytime diastolic as well as nighttime systolic and diastolic BP in patients randomized to CPAP (Table 2). Figures 1 and 2 show the individual values of systolic and diastolic BP before and after the randomization based on office and 24-hour ABPM, respectively. In the control group, the frequency of prehypertension

and masked hypertension did not significantly change after 3 months (Figures 1A and 2A). In contrast to the control group, the frequency of prehypertension decreased significantly from 17 patients (94%) to 10 patients (55%; *P*=0.02; Figure 1B) and the frequency of masked hypertension decreased from 7 patients (39%) to 1 patient (5%; *P*=0.041; Figure 2B). Individual changes in the office systolic and diastolic BP as well as for awake systolic and diastolic BP derived from 24-hour ABPM are presented in the supplemental file (see <http://hyper.ahajournals.org>). The magnitude of office systolic BP drop in the CPAP-treated group correlated with directly with the magnitude of apnea–hypopnea index decrease (*r*=0.497; *P*=0.036), with the CPAP adherence (*r*=0.858; *P*=0.00001), and with changes in lowest O<sub>2</sub> saturation during sleep (*r*=0.520; *P*=0.027). The magnitude of office systolic ABPM drop showed a nonsignificant correlation (trend) with CPAP adherence (*r*=0.401; *P*=0.09).

### Discussion

To the best of our knowledge, this is the first study that evaluated the impact of CPAP on prehypertension and masked hypertension in patients with OSA. In this randomized study, 3 months of effective treatment with CPAP

**Table 2. Characteristics at Baseline and After 3 Months of Randomization in OSA Groups**

Variables	Control Group			Group Receiving CPAP		
	Baseline	3 Months	<i>P</i>	Baseline	3 Months	<i>P</i>
BMI, kg/m <sup>2</sup>	29.0±2.6	29.1±2.5	0.70	28.5±3.3	28.5±3.3	0.92
Office systolic BP, mm Hg	127±6	128±6	0.42	126±5	121±7	0.001*
Office diastolic BP, mm Hg	76±9	78±11	0.30	75±7	73±8	0.08†
Heart rate, beats/min	80±11	79±9	0.77	77±12	76±10	0.58
ABPM—24-hour systolic BP, mm Hg	121±9	125±11	0.11	122±5	117±7	0.004*
ABPM—24-hour diastolic BP, mm Hg	78±6	80±9	0.23	79±5	74±6	0.0001*
ABPM—daytime systolic BP, mm Hg	126±10	129±12	0.23	127±5	122±7	0.005*
ABPM—daytime diastolic BP, mm Hg	83±7	84±9	0.59	83±5	78±6	0.0001*
ABPM—nighttime systolic BP, mm Hg	111±8	115±10	0.15	112±7	105±9	0.005*
ABPM—nighttime diastolic BP, mm Hg	68±7	71±10	0.36	70±9	64±8	0.003*

Values are mean±SD.

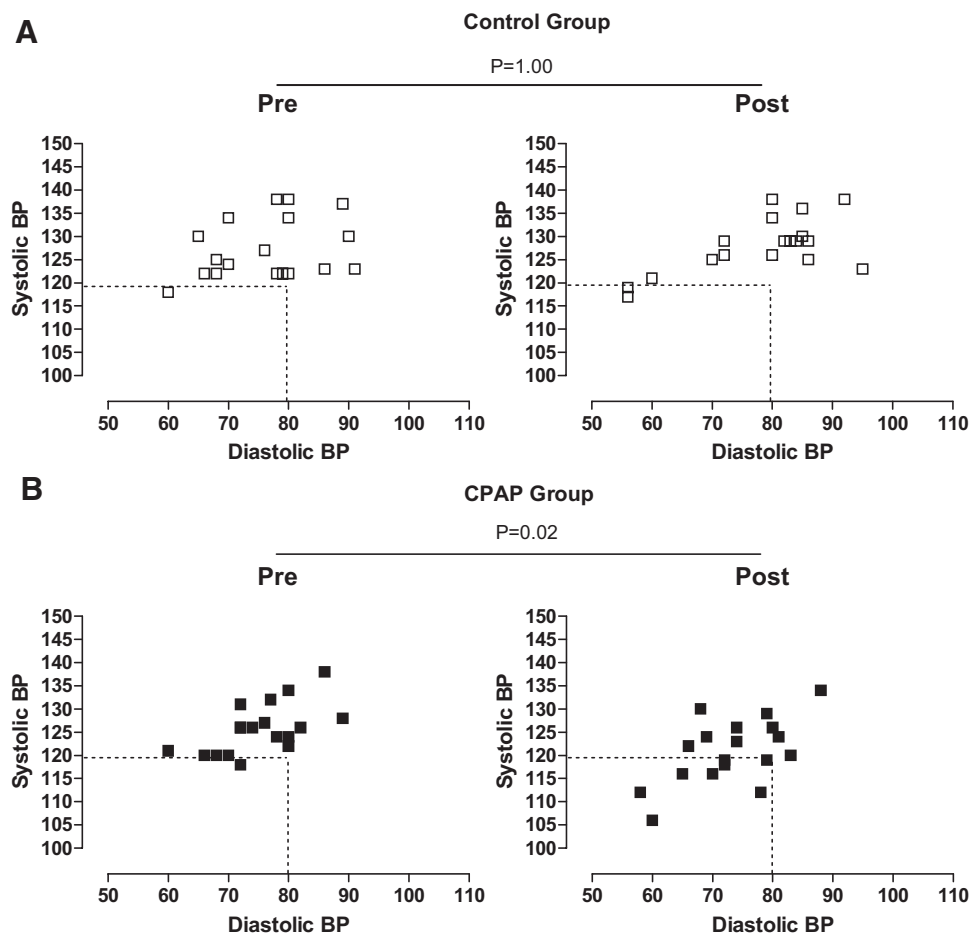
\**P*<0.01 for the comparison between the groups.

†*P*<0.05 for the comparison between the groups.

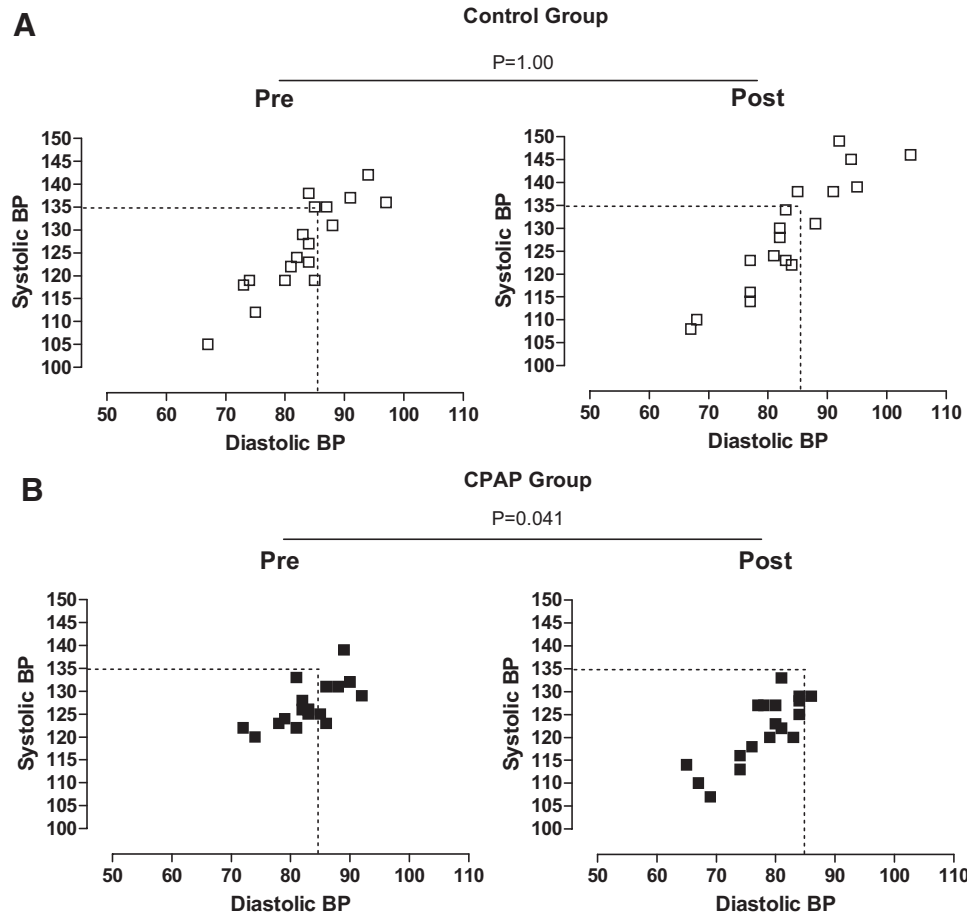
significantly decreased both office BP and ABPM and resulted in a 42% drop in the frequency of prehypertension (17 to 10 patients) and an 87% drop in the frequency of masked hypertension (7 to 1 patient). Together, these results support the concept that OSA may be a risk factor for both prehy-

pertension and masked hypertension and that the early recognition and treatment of OSA may prevent the development of sustained hypertension.

The prevalence of prehypertension among adults in the United States has been estimated to be approximately 31%,<sup>19</sup>



**Figure 1.** Effects of CPAP on prehypertension in patients with severe OSA. Individual systolic and diastolic BP values in the control (A) and in the CPAP group (B) at baseline (Pre) and after 3 months of randomization (Post). Dashed lines denote the cutoff for prehypertension diagnosis. In the control group, 2 patients with borderline diastolic BP at baseline surpassed the cutoff for sustained hypertension after 3 months.



**Figure 2.** Effects of CPAP on masked hypertension in patients with severe OSA. Individual systolic and diastolic BP values in the control (A) and in the CPAP group (B) at baseline (Pre) and after 3 months of randomization (Post). Dashed lines denote the cutoff used for masked hypertension diagnosis.

whereas the overall prevalence of masked hypertension in apparently normotensive subjects drawn from the general population varies from 8% to 20%.<sup>20</sup> There is converging evidence that prehypertension and masked hypertension are independently associated with target organ damage, markers of atherosclerosis, and an excess morbidity and mortality from cardiovascular disease.<sup>4,21–25</sup> Both conditions are commonly observed in the same individual and are associated with additive effects in the occurrence of cardiovascular events.<sup>26</sup> However, the risk factors and mechanisms leading to these conditions are not completely understood.<sup>27</sup> OSA may be associated with prehypertension and masked hypertension for at least 3 reasons. First, OSA is common among patients with hypertension with an estimated prevalence ranging between 38% and 82%.<sup>6,28,29</sup> Second, several risk factors previously identified for prehypertension<sup>1</sup> and masked hypertension,<sup>27</sup> including increasing age, male gender, physical inactivity, use of alcohol, diabetes, history of stroke, and coronary heart disease, overlap with the typical risk factors for OSA. Third, the pathophysiological mechanisms linking OSA to sustained hypertension, including sympathetic overactivation, oxidative stress, systemic inflammation, and increased arterial stiffness,<sup>7</sup> may also be causal mechanisms linking OSA to prehypertension and masked hypertension. Our study therefore raises the possibility that OSA is a

treatable condition that may modulate several cases of prehypertension and masked hypertension.

Among patients with OSA, the frequency of hypertension is as high as 50%.<sup>30</sup> To the best of our knowledge, the frequency of prehypertension in patients with OSA considered to have normal BP is unknown. Two recent independent reports<sup>12,13</sup> found that approximately one third of patients with OSA who were considered to be normotensive based on office BP presented with masked hypertension. In 1 study, the frequency of masked hypertension in patients with OSA with moderate to severe OSA was significantly higher than age- and BMI-matched control subjects (no OSA).<sup>13</sup> In the present study, we extended these findings by showing that the treatment of OSA significantly decreases the frequency of both prehypertension and masked hypertension, suggesting that OSA is an independent risk factor for both conditions. As pointed out before, because prehypertension and masked hypertension are associated with cardiovascular risk<sup>2,4</sup> and OSA is also independently related to cardiovascular mortality,<sup>31,32</sup> it is reasonable to speculate that treatment of OSA can decrease cardiovascular risk by reducing several factors, including these 2 precursors of sustained hypertension.

The effects of the treatment of OSA on BP have been extensively studied with results that varied widely. For instance, a recent meta-analysis carefully evaluated 15 ran-

domized trials and found that the average fall in BP after CPAP was 2.46 and 1.83 mm Hg on systolic and diastolic BP, respectively.<sup>33</sup> However, the meta-analysis evaluated distinct populations with a wide spectrum of diagnosis and status, ranging from normotensive to controlled and uncontrolled hypertension, a previous diagnosis of hypertension, patients with and without a number of different antihypertensive medications, and patients with and without several comorbid conditions.<sup>34</sup> BP monitoring in these studies also varied widely, ranging from solely office BP, ABPM up to beat-to-beat BP monitoring.<sup>35–37</sup> Moreover, the adherence to CPAP treatment also varied across studies.<sup>33</sup> The wide variability may be largely dependent on baseline BP status and has been reported to fall as much as 10 mm Hg in patients with resistant hypertension<sup>9</sup> down to minimal or nonsignificant effects in patients with normal BP.<sup>10,11,35</sup> Therefore, the effects of CPAP in patients with close to normal BP may be limited by a “floor effect.” Our study, therefore, is the first to show that BP may be reduced or even normalized in patients with conditions that may represent precursors of sustained hypertension. We strongly believe that our results may be explained by including patients with severe OSA under effective treatment of CPAP. Indeed, we observed a strong correlation between CPAP adherence and office systolic BP decrease. In addition, the significant BP drops after CPAP suggest that OSA may be the main determinant of prehypertension and masked hypertension in a substantial proportion of these patients.

Our study has some strengths and limitations. Strengths of our study include the availability of polysomnography data, considered the “gold standard” for the diagnosis of OSA. Second, our data were based on 24-hour ABPM using actual sleep and wake times recorded by participants and not arbitrary preset times. Limitations were that we only involved male patients with severe OSA. Therefore, these results could not be extrapolated to females and to patients with mild forms of OSA. On the other hand, the exclusion of females may help to avoid circadian variation of BP mainly related to oral contraceptives, hormone replacement, and menopause.<sup>38,39</sup> Second, our sample size is relatively small to detect differences in some parameters such as frequency of nondipping or the magnitude of the BP decrease in patients with and without masked hypertension after CPAP treatment. The significant fall in all BP variables derived from 24-hour ABPM and not in the office diastolic BP may be related to the small sample size. Finally, patients were aware of their treatment assignments and a placebo group using CPAP with ineffective pressure to open the airway was not included. On the other hand, sham CPAP is not inert and may raise BP.<sup>40</sup> Moreover, the BP analyses were obtained in a blind fashion.

### Perspectives

The present study found that effective OSA treatment with CPAP can reduce the frequency of prehypertension and masked hypertension. These results support the concept that patients with severe OSA considered normotensive in the office should be screened with a 24-hour ABPM to evaluate the presence of masked hypertension. On the other hand, the previous evidence<sup>13</sup> and the present study also suggest that

patients with prehypertension and masked hypertension should be evaluated by the presence of OSA given the high prevalence of both conditions in these patients. Moreover, the present study also suggests that early identification and treatment of OSA in apparently healthy, normotensive individual may prevent the development of hypertension. As already mentioned, because of the small sample size, further studies using a large population of patients with OSA should be convenient to test this hypothesis.

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### Disclosures

None.

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***Online Supplement***

**The Effects of Continuous Positive Airway Pressure on PreHypertension  
and Masked Hypertension in Men with Severe Obstructive Sleep Apnea**

**Running title: OSA, prehypertension and masked hypertension**

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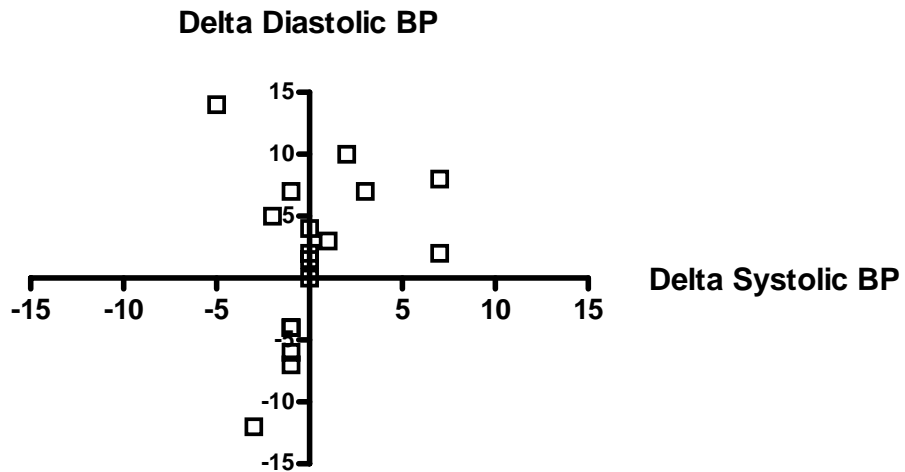
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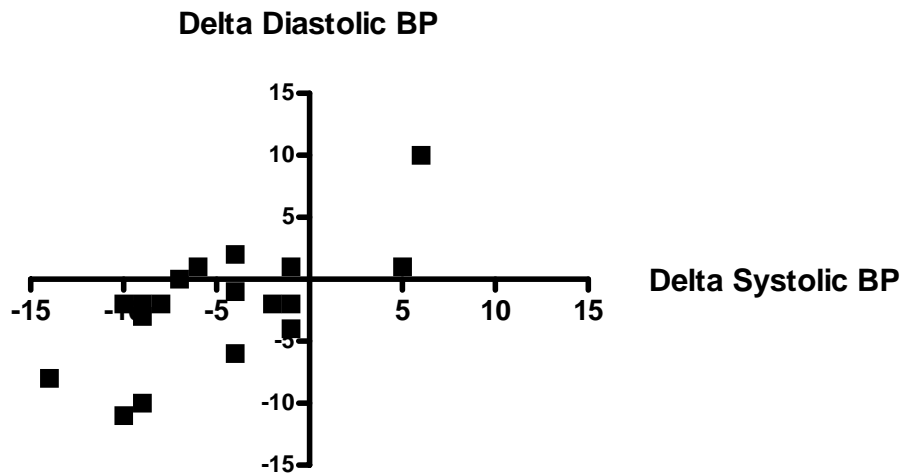
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Figure: Individual changes in the office and awake blood pressure (BP) in patients with severe Obstructive Sleep Apnea submitted to no treatment (Control) or Continuous Positive Airway Pressure (CPAP) for 3 months.  $P < 0.05$  for the comparison between the groups.

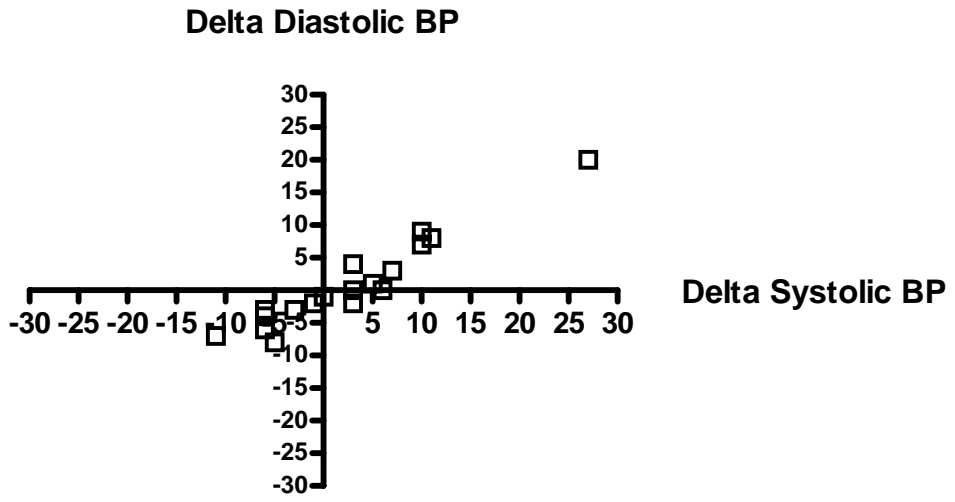
### Office BP - Control Group



### Office BP - CPAP Group



### Awake BP - Control Group



### Awake BP - CPAP Group

