Obstructive Sleep Apnea, Masked Hypertension, and Arterial Stiffness in Men

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BACKGROUND

Obstructive sleep apnea (OSA) is an established cause of hypertension. However, it is not clear whether the frequency of masked hypertension in patients with OSA and whether OSA have an independent role on arterial stiffness taking into account ambulatory blood pressure (BP) monitoring (ABPM).

METHODS

We evaluated 61 male normotensive participants as determined by casual clinic BP level <140/90 mm Hg without clinical evidence of cardiovascular disease and on no medications (43 patients with moderate-to-severe OSA (apnea–hypopnea index (AHI) ≥15 events/hour by polysomnography) and 18 age- and body mass index–matched controls without OSA (AHI <5 events/hour)). Pulse wave velocity (PWV), an index of arterial stiffness, and 24-h ABPM were performed in a blinded fashion. Masked hypertension was defined when abnormal daytime ABPM was ≥135 or ≥85 mm Hg.

RESULTS

The AHI and lowest oxygen saturation were 2.6 ± 1.6 and 90 ± 2 vs. 52.8 ± 21.0 events/hour and 75 ± 10% for controls and OSA patients, respectively; $P < 0.001$. Compared with controls, patients with OSA had higher office systolic BP (113 ± 9 vs. 118 ± 10 mm Hg; $P = 0.05$) and a higher unadjusted proportion of masked hypertension (2 controls (11.1%) vs. 13 patients (30.2%); $P < 0.05$). PWV was 8.7 ± 0.7, 9.4 ± 1.0, and 10.6 ± 1.1 m/s in the control, OSA without and with masked hypertension groups, respectively ($P < 0.01$ for each comparison). Multiple regression showed that systolic daytime ABPM and the lowest oxygen saturation were independently related to PWV (adjusted $R^2 = 0.34$; $P < 0.01$).

CONCLUSIONS

Patients with OSA presented a higher unadjusted rate of masked hypertension than matched controls. Lowest oxygen saturation has an independent association with arterial stiffness.

Keywords: *arterial stiffness; blood pressure; cardiovascular disease; hypertension; masked hypertension; sleep apnea*

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Obstructive sleep apnea (OSA) is a common condition characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep.[1] Repetitive obstructive respiratory events promote intermittent hypoxia and frequent microarousals that contribute to sympathetic activation and release of vasoactive factors, such as endothelin.[2] These phenomena directly influence hemodynamic behavior during sleep in patients with OSA, contributing to impaired blood pressure (BP) control.[3]

There is compelling evidence that OSA is a secondary cause of hypertension.[4] One recent study showed a large proportion of masked hypertension as determined by ambulatory BP monitoring (ABPM) in patients with OSA that were otherwise considered normotensive.[5] However, because a control group was not included,[5] it is not clear whether OSA is independently associated with an increased rate of masked hypertension. Both masked hypertension and OSA are independently associated with increased markers of atherosclerosis and target organ damage.[6–12] These evidences raise the possibility that the mechanisms linking OSA to vascular damage may be mediated by the presence of masked hypertension.

Therefore, the aims of this study were as follows: (i) to determine the frequency of masked hypertension in apparently normotensive OSA patients compared with proper controls with similar demographics but no OSA; (ii) to determine the dependent and independent BP effects of OSA on arterial stiffness, a marker of premature coronary artery disease, atherosclerosis, stroke, and cardiovascular mortality.[13–15]

METHODS

Subjects. We recruited consecutive men patients from the Sleep Laboratory, Heart Institute (InCor), University of São Paulo Medical School, who had a recent diagnosis of moderate-to-severe OSA (apnea–hypopnea index (AHI) ≥15 events/hour by polysomnography). At the same time, we selected men

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from staff and their relatives subjects with a low risk for OSA evaluated by Berlin questionnaire[16] who had a subsequent sleep study showing an AHI <5 events/hour (control group). OSA and controls were matched for age and body mass index. We excluded subjects with mild OSA, smoking history, hypertension, diabetes, heart failure, renal diseases, and patients using any medication. The local ethics committee approved the protocol, and all participants gave written informed consent. All patients with OSA were naive to treatment.

BP. All participants (controls and patients with OSA) had no previous history of high BP. BP measurements were determined in the same medical evaluation by the mean of three readings of systolic and diastolic (phase 5) BP obtained at 5-min intervals with a conventional mercury sphygmomanometer, after participants had been seated for at least 15 min. Clinical normotension was defined when the mean clinical systolic and diastolic BP were below 140 and 90 mm Hg, respectively.[4]

24-h ABPM. We performed 24-h ABPM with a SpaceLabs device (model 90207; SpaceLabs, Redmond, WA) in the control group and in the OSA group. All BP analyses were blinded to the presence or absence of OSA. BP was measured every 10 min during the day (8 AM to 11 PM) and every 20 min 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 in their diaries. We evaluated daytime and night time BP. 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 ABPM (≥135 or ≥85 mm Hg).[17,18]

Sleep evaluation. All patients underwent a standard overnight polysomnography (Embla–Flaga 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.[9] 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 AHI was calculated as the total number of respiratory events (apneas plus hypopneas) per hour of sleep. In addition, we evaluated subjective daytime sleepiness by using the Epworth Sleepiness Scale. A total score >10 was considered excessive daytime sleepiness.[19]

Arterial stiffness. As we had previously described,[9] arterial stiffness was determined by carotid–femoral pulse wave velocity (PWV) using a noninvasive automatic device, Complior (Colson, Garges les Gonesses, France). Briefly, common carotid artery and femoral artery pressure waveforms were recorded noninvasively by using a TY-306-Fukuda pressure-sensitive transducer (Fukuda, Tokyo, Japan). The distance between the recording sites (D) was measured, and PWV was automatically calculated as PWV = D/t, whereas (t) means pulse transit time.[20] Measurements were repeated over 10 different cardiac cycles, and the mean was used for the final analysis. A same experienced observer (L.A.B.), blinded to the polysomnographic data, performed all measurements.

Blood samples. Venous blood was collected from all participants for the measurement of fasting glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, and red blood cell count.

Statistical analysis. Data were analyzed with SPSS 10.0 statistical software (SPSS, Chicago, IL). The comparison of continuous variables between patients with and without OSA was performed using the Student's *t*-test or Wilcoxon, when appropriate. Categorical variables were expressed by frequency distribution and were compared using the χ^2 or Fisher's exact test. Comparisons between groups were made by one-way analysis of variance. The Bonferroni correction was used for multiple comparisons. A multiple regression analysis was used to identify variables that are independently associated with PWV via stepwise elimination. Only variables with $P < 0.1$ in bivariate analyses were included in the model. A value of $P < 0.05$ was considered significant.

RESULTS

We initially recruited 50 patients with moderate-to-severe OSA and 25 controls. The final analysis comprised 43 patients with OSA and 18 controls. Five patients with OSA had already initiated CPAP (continuous positive airway pressure) therapy before vascular measurement and two refused to perform 24-h ABPM. Five controls had mild OSA by polysomnography and two refused to perform 24-h ABPM, therefore being ineligible for the study.

Controls and patients had similar demographic characteristics including age, sex, body mass index, and waist circumference (**Table 1**). We observed that patients with OSA had a lower percentage of slow wave sleep and higher number of arousals indicating a significant impairment in sleep architecture in this group (**Table 1**). Although in the normal range, office systolic BP was higher in patients with OSA than in controls ($P = 0.05$). There was no difference in office diastolic BP values between groups (**Table 1**). All BP measurements derived from 24-h ABPM were similar in controls and in patients with OSA (**Table 1**). Compared with controls, patients with OSA had a higher unadjusted percentage of masked hypertension (2 controls (11.1%) vs. 13 patients (30.2%); $P < 0.05$). OSA patients with masked hypertension had a trend for higher levels of low-density lipoprotein-cholesterol and significant higher levels of office systolic BP than OSA patients without masked hypertension (**Table 2**).

Table 1 | Participants characteristics

	Controls ($n = 18$)	OSA ($n = 43$)	*P* value
Age (years)	43 ± 6	45 ± 7	0.38
Caucasians (%)	83	81	1.0
Body mass index (kg/m^2)	28.2 ± 2.9	29.0 ± 2.9	0.32
Fasting glucose (mg/dl)	93 ± 6	93 ± 9	0.98
Total cholesterol (mg/dl)	213 ± 88	212 ± 42	0.89
LDL-cholesterol (mg/dl)	137 ± 27	136 ± 36	0.94
HDL-cholesterol (mg/dl)	48 ± 14	43 ± 11	0.15
Triglycerides (mg/dl)	143 ± 81	162 ± 64	0.37
Heart rate (bpm)	78 ± 5	80 ± 10	0.45
Office systolic BP (mm Hg)[a]	113 ± 9 (range 90–126)	118 ± 10 (range 96–136)	0.05
Office diastolic BP (mm Hg)[a]	71 ± 8 (range 60–84)	73 ± 8 (range 60–88)	0.33
ABPM			
24-h Systolic BP (mm Hg)	118 ± 8	120 ± 8	0.55
24-h Diastolic BP (mm Hg)	75 ± 9	77 ± 6	0.28
Daytime systolic BP (mm Hg)	122 ± 9	124 ± 9	0.47
Daytime diastolic BP (mm Hg)	79 ± 10	81 ± 7	0.38
Night time systolic BP (mm Hg)	108 ± 11	109 ± 9	0.51
Night time diastolic BP (mm Hg)	66 ± 8	67 ± 8	0.49
Epworth Sleepiness Scale	8 (6–9)	12 (10–15)	<0.001
Polysomnography data			
Total sleep time (min)	379 ± 70	400 ± 73	0.30
Sleep efficiency (%)	86 ± 11	88 ± 8	0.29
% Stage 2 (%)	62 ± 8	63 ± 14	0.78
% Stage 3–4 (%)	18 ± 8	12 ± 6	0.002
% REM (%)	17 ± 5	15 ± 9	0.32
Arousals (*n*)	71 (45–109)	228 (168–310)	<0.001
AHI (events/hour)	2.6 ± 1.6	52.8 ± 21.0	<0.001
Awake oxygen saturation (%)	96 ± 2	95 ± 2	0.20
Lowest oxygen saturation (%)	90 ± 2	75 ± 10	<0.001
Total sleep time oxygen saturation <90% (%)	0 (0–0.2)	8 (3.4–22.6)	<0.001

Values are mean (± s.d.).
[a]Mean of three blood pressure readings. Variables with skewed distribution are presented as median (interquartile range).
ABPM, ambulatory blood pressure monitoring; AHI, apnea-hypopnea index; BP, blood pressure; bpm, beats/min; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OSA, obstructive sleep apnea; REM, rapid eye movement.

Regarding arterial stiffness, patients with OSA had a higher PWV (9.8 ± 1.2 vs. 8.7 ± 0.7 m/s; $P < 0.001$). Interestingly, we observed that OSA patients with masked hypertension had a significantly higher PWV (10.6 ± 1.1 m/s) compared with OSA patients without masked hypertension (9.4 ± 1.0 m/s; **Figure 1**). However, even when excluding subjects with masked hypertension, patients with OSA had higher PWV than controls had (9.4 ± 1.0 vs. 8.7 ± 0.7 m/s; $P = 0.004$).

Univariate analysis between PWV and anthropometric, BP and OSA variables from the entire sample are presented in **Table 3**. Multiple regression (**Table 4**) showed that systolic daytime ABPM and the lowest oxygen saturation during sleep were independently related to PWV (adjusted $R^2 = 0.34$; $P < 0.01$).

DISCUSSION

The main findings of this study are as follows: (i) Among apparently normotensive male OSA patients, masked hypertension is present in one-third of patients and in unadjusted analysis significantly less common among proper matched controls; (ii) There is a progressive impairment in arterial stiffness (evaluated by PWV) when we compared individuals with no OSA, and OSA patients without and with masked hypertension; (iii) Systolic daytime ABPM and the lowest oxygen saturation during sleep were the only factors independently associated with PWV in this sample. Together, these results suggest that the diagnosis of masked hypertension could be underestimated in OSA and that OSA has an association with arterial stiffness independent of masked hypertension.

Table 2 | Demographic data, laboratory, blood pressure, and sleep parameters in OSA patients with and without masked hypertension

	OSA with MH ($n = 13$)	OSA without MH ($n = 30$)	*P* value
Age (years)	47 ± 7	43 ± 7	0.09
Body mass index (kg/m^2)	28.9 ± 2.5	29.1 ± 3.2	0.86
Glucose (mg/dl)	93 ± 11	93 ± 8	0.99
Total cholesterol (mg/dl)	224 ± 44	205 ± 40	0.13
LDL-cholesterol (mg/dl)	153 ± 37	130 ± 34	0.06
HDL-cholesterol (mg/dl)	43 ± 10	42 ± 11	0.83
Triglycerides (mg/dl)	156 ± 50	165 ± 70	0.68
Office systolic BP (mm Hg)	123 ± 10	116 ± 9	0.02
Office diastolic BP (mm Hg)	76 ± 10	72 ± 7	0.11
24-h Systolic BP (mm Hg)	127 ± 6	117 ± 7	<0.001
24-h Diastolic BP (mm Hg)	84 ± 3	74 ± 5	<0.001
Daytime systolic BP (mm Hg)	132 ± 6	121 ± 7	<0.001
Daytime diastolic BP (mm Hg)	89 ± 4	77 ± 5	<0.001
Night time systolic BP (mm Hg)	115 ± 7	107 ± 8	0.002
Night time diastolic BP (mm Hg)	74 ± 6	64 ± 7	<0.001
Epworth Sleepiness Scale	12 ± 4	12 ± 4	0.99
Polysomnography data			
Arousals	238 (166–240)	235 (197–309)	0.74
AHI (events/hour)	52 ± 25	53 ± 19	0.67
Awake oxygen saturation (%)	94 ± 2	94 ± 2	0.62
Lowest oxygen saturation (%)	70 ± 12	78 ± 7	0.04
Total sleep time oxygen saturation <90% (%)	14.6 (5.3–33.2)	7.9 (3.5–14.9)	0.22

Values are mean (± s.d.). Variables with skewed distribution are presented as median (interquartile range).
ABPM, ambulatory blood pressure monitoring; AHI, apnea-hypopnea index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MH, masked hypertension; OSA, obstructive sleep apnea.

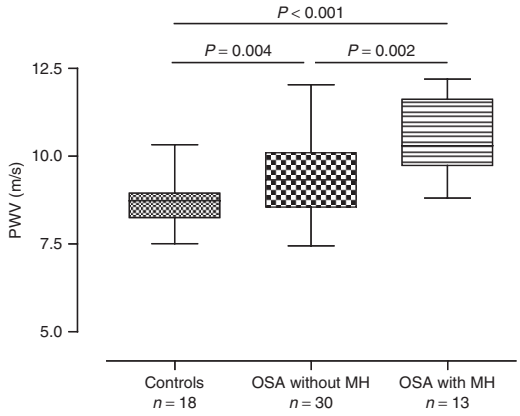

Figure 1 | Pulse wave velocity (PWV) in controls and in patients with obstructive sleep apnea (OSA) according to the presence or absence of masked hypertension (MH).

Table 3 | Correlations between pulse wave velocity (PWV) with anthropometric, laboratory, blood pressure, and sleep parameters

Variables	*R*	*P*
Age	0.32	0.01
Body mass index	0.18	0.16
Glucose	0.02	0.89
Total cholesterol	0.32	0.02
LDL-cholesterol	0.32	0.02
HDL-cholesterol	−0.01	0.96
Triglycerides	0.16	0.68
Office systolic BP	0.29	0.02
Office diastolic BP	0.22	0.09
Heart rate	0.17	0.20
ABPM		
24-h Systolic BP	0.31	0.02
24-h Diastolic BP	0.36	0.005
Daytime systolic BP	0.30	0.02
Daytime diastolic BP	0.31	0.02
Night time systolic BP	0.25	0.05
Night time diastolic BP	0.33	0.009
AHI	0.37	0.003
Arousals	0.25	0.05
Lowest oxygen saturation	−0.54	<0.001
Total sleep time oxygen saturation <90%	0.25	0.05

ABPM, ambulatory blood pressure monitoring; AHI, apnea-hypopnea index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

In our study, 30% of apparently normotensive patients with OSA and 11% of matched controls had masked hypertension. The overall prevalence of masked hypertension in apparently normotensive subjects drawn from the general population varies from 8 to 20%.[18] Despite the fact that cardiovascular prognosis of masked hypertension is not fully elucidated, previous studies have suggested that advanced target organ damage, such as left ventricular mass and urinary albumin excretion, is often present both in untreated and treated subjects with masked hypertension.[5–8,21] In the present investigation, we not only determined the proportion of OSA patients with masked hypertension, but we also evaluated the vascular impairment in these subgroups of patients. PWV, a noninvasive marker of arterial stiffness, was higher in OSA patients with than without masked hypertension. However, even OSA patients without masked hypertension had higher levels of PWV than controls (Figure 1). To the best of our knowledge, the only study until now that evaluated masked hypertension in OSA found a similar percentage of masked hypertension in patients apparently free of recognized cardiovascular disease.[5] However, contrary to our findings, they did not find significant alterations in PWV among OSA patients with and without

Table 4 | Multivariate regression model predicting pulse wave velocity (PWV)

Variables	Coefficient (β)	95% CI		*P*
Age	0.027	−0.025	0.079	0.30
Total cholesterol	0.014	−0.007	0.035	0.20
LDL-cholesterol	−0.012	−0.037	0.014	0.37
ABPM				
Daytime systolic BP	0.058	0.019	0.098	0.005
AHI	0.013	−0.003	0.030	0.11
Arousals	0.000	−0.004	0.002	0.71
Lowest oxygen saturation	−0.051	−0.094	−0.007	0.02
Total sleep time oxygen saturation <90%	−0.014	−0.036	0.008	0.21

ABPM, ambulatory blood pressure monitoring; AHI, apnea-hypopnea index; BP, blood pressure; CI, confidence interval; LDL, low-density lipoprotein.

masked hypertension.[5] The precise reasons that could justify these differences are not clear. The present results are in agreement with a previous study that evaluated vascular damage in untreated masked hypertensive subjects detected by home BP measurement.[8] After adjustment for covariates, we found that carotid intima-media thickness and brachial–ankle PWV were significantly higher in patients with masked hypertension than in normotensive controls and patients with white coat hypertension.[8] However, this study and the great majority of those that evaluated the impact of masked hypertension did not consider OSA as a potential confounding factor.

In our study, a marker of OSA severity, namely lowest oxygen saturation, was one of the factors independently associated with PWV in this sample. These data suggest that OSA may have an independent BP role on vascular damage. In addition, an effect of OSA dependent of BP was also observed. Supporting the present findings, we have shown additive effects on markers of subclinical atherosclerosis when OSA and hypertension coexist in the same patient.[10,11] The present study shows a similar scenario in the subset of patients with OSA and masked hypertension. Interestingly, our data reinforce the concept that masked hypertension may be an intermediary state between normotension and sustained hypertension because the PWV observed in OSA patients with masked hypertension was significantly higher than in controls and OSA patients without masked hypertension but lower than in OSA patients with established hypertension, as we had previously described.[10] However, repetitive surges in BP during each respiratory event may play an important role in vascular damage even in normotensive patients.[22] These BP oscillations occur in concert with respiratory events (in our study ~53 times/hour of sleep) and may not be detected by 24-h ABPM (3 BP measurements/hour during night time).[23] Therefore, we cannot exclude the role of BP oscillations on vascular damage in truly normotensive patients with OSA.

Our study has some strengths and limitations. The strengths of our study include the availability of polysomnography data, considered the "gold standard" for the diagnosis of OSA. Second, our study involved a matched control group. Third, our data are based on 24-h ABPM using actual sleep and wake times recorded by participants and not arbitrary preset times. Limitations: first, we included a relatively small sample of controls and OSA patients with and without masked hypertension. Therefore, the study may be underpowered to detect differences in some of the variables. Particularly, the process of including age- and body mass index–matched subjects without OSA to achieve the purpose of the present study was very arduous. Second, we only involved male patients with moderate-to-severe OSA. Therefore, these results could not be extrapolated to females and patients with mild forms of OSA. On the other hand, oral contraceptives, menopause, and hormone replacement therapy may have influences on BP variability.[24,25] The cross-sectional design did not allow inferring a cause-effect relationship between OSA and masked hypertension. Finally, this study was not designed to explore the precise mechanisms by which OSA is associated to higher rate of masked hypertension. Potential candidates included increased sympathetic activity,[26] endothelial dysfunction,[27] and activation of the renin–angiotensin–aldosterone system.[28]

In conclusion, the present study adds to the current knowledge by showing that masked hypertension is common in apparently normotensive male patients with OSA. Lowest oxygen saturation has an independent association with arterial stiffness. To clarify the cause-effect relationship between OSA and masked hypertension, future studies should be performed to evaluate the impact of CPAP on BP values in patients with masked hypertension.

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