Additive Effects of Obstructive Sleep Apnea and Hypertension on Early Markers of Carotid Atherosclerosis

Luciano F. Drager, Luiz A. Bortolotto, Eduardo M. Krieger, Geraldo Lorenzi-Filho

Abstract—Obstructive sleep apnea (OSA) has emerged as an independent risk factor for atherosclerosis. However, OSA is frequently associated with several risk factors for atherosclerosis, including hypertension (HTN). The impact of OSA and HTN alone compared with the association of both conditions on carotid atherosclerosis is not understood. We studied 94 middle-aged participants free of smoking and diabetes mellitus who were divided into 4 groups: controls (n=22), OSA (n=25), HTN (n=20), and OSA+HTN (n=27). All of the participants underwent polysomnography and carotid measurements of intima-media thickness, diameter, and distensibility with an echo-tracking device. Compared with controls, intima-media thickness and carotid diameter were similarly higher in OSA (713±117 and 7117±805 μm), and HTN groups (713±182 and 7191±818 μm), with a further significant increase in OSA+HTN patients (837±181 and 7927±821 μm, respectively; P<0.01). Carotid distensibility was significantly lower in HTN (P<0.05) and OSA+HTN subjects (P<0.001) compared with controls. In the OSA+HTN group, carotid distensibility was significantly lower than in the OSA group and controls (P<0.05 for each comparison). Multivariate analysis showed that intima-media thickness was positively related to systolic blood pressure and apnea-hypopnea index. Apnea-hypopnea index was the only factor related to carotid diameter. Age and systolic blood pressure were independently related to carotid distensibility. In conclusion, the association of OSA and HTN has additive effects on markers of carotid atherosclerosis. Because early markers of carotid atherosclerosis predict future cardiovascular events, including not only stroke but also myocardial infarction, these findings may help to explain the increased risk of cardiovascular disease in patients with OSA. (Hypertension. 2009;53:64-69.)

Key Words: obstructive sleep apnea • atherosclerosis • hypertension • stroke • cardiovascular disease

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep resulting in oxygen desaturation and arousal from sleep.1 More than a local obstructive phenomenon in the upper airway, evidence exists indicating that OSA is independently associated with increased cardiovascular risk, including myocardial infarction and stroke.2–6 Carotid atherosclerosis is an attractive mechanism to explain not only the link between OSA and stroke7 but also the link between OSA and myocardial infarction.8 Increased markers of atherosclerosis have been described in a subgroup of young and apparently healthy patients with OSA.9 Moreover, the treatment with continuous positive airway pressure decreased carotid intima-media thickness (IMT), a validated marker of atherosclerosis.10 This evidence suggests that OSA is an independent risk factor for atherosclerosis.11 However, in clinical practice, several comorbidities are commonly associated with OSA. OSA and hypertension (HTN) are tightly linked.12 In patients with OSA, the prevalence of HTN is ≈40%, and the presence of HTN could be the result of the interaction of environmental and genetic factors.13 HTN is a well-known condition associated with atherosclerosis,14 and the coexistence of OSA and HTN may have additive effects on the risk of atherosclerosis.

In the present study, we evaluated the impact of OSA and HTN alone compared with the association of both conditions on markers of early carotid atherosclerosis. To this end, we carefully selected a subgroup of participants with no history of smoking and diabetes mellitus. We hypothesized that OSA and HTN have additive effects on carotid atherosclerosis, which could contribute to increase the risk of myocardial infarction and stroke.

Methods

Subjects

During a period of 2 years, we recruited patients who were referred to our sleep laboratory with suspected OSA. In addition, we selected healthy people and patients with a diagnosis of established HTN at low risk for OSA by Berlin Questionnaire15 to undergo full polysomnography. We carefully matched the groups for age (±5 years), sex, and body mass index (±2 kg/m²). Thirty eight (40%) of the participants were involved in a previous study evaluating the impact of OSA on heart remodeling by echocardiography.16 The local ethics

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committee approved the protocol, and all of the participants gave written informed consent. After the sleep study, we only studied subjects with no OSA or moderate-to-severe OSA apnea-hypopnea index (AHI) <5 and >15 events per hour, respectively). OSA patients were recently diagnosed and not treated. The study design allowed us to define 4 groups, as follows: (1) volunteers without OSA and HTN (controls); (2) OSA patients without HTN (OSA); (3) non-OSA patients with HTN (HTN); and (4) OSA patients with HTN (OSA+HTN). We excluded participants who regularly took medications other than anti hypertensive agents. All of the participants with HTN were outpatients from the Hypertension Unit, Heart Institute (InCor), with a previous investigation for other causes of secondary HTN. HTN was previously diagnosed according to current guidelines. In addition, no patients had a history of the white-coat effect. Blood pressure measurements were determined on separate occasions by ≥3 readings of systolic and diastolic (phase V) blood pressures obtained at 5-minute intervals with a conventional mercury sphygmomanometer, after participants had been seated for ≥15 minutes. To classify each participant as normotensive or hypertensive, experienced physicians who were not involved in the study performed blood pressure measurements according standard measurements criteria. Further measurements were performed by the same researcher (L.F.D.) confirming the blood pressure levels. The cutoff point for HTN was 140/90 mm Hg. For ethical reasons, all of the hypertensive patients were on medications for blood pressure control. To avoid acute effects of anti hypertensive treatment, patients did not take medications on the day that vascular parameters were measured, as described previously from different groups.

Sleep Study
All of the participants underwent a standard overnight polysomnography (EMBLA - Flagra hf. Medical Devices), as described previously. Apnea was defined as complete cessation of airflow for ≥10 seconds, associated with oxygen desaturation of 3%. Hypopnea was defined as a significant reduction (>50%) in respiratory signals for ≥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.

Vascular Parameters
All of the participants had their vascular parameters evaluated by an experienced observer (L.A.B.), blinded to the clinical condition of each participant. All of the measurements were taken between 2 PM and 4 PM, with the patient in a recumbent position while awake. We used a high-resolution echo-tracking system (Wall Track System, Neurodata), which is based on the radio-frequency signal analysis that has been described, validated, and used in previous clinical studies. The accuracy of the system is 30 μm for the diastolic diameter measurement and <1 μm for the pulsatile change in diameter (difference between systolic and diastolic diameters). All of the measurements were performed on the right common carotid arteries 1 cm below the bifurcation at the site of the distal wall, as assigned in other studies using the same methodology.

Intima-Media Thickness
Carotid IMT was measured at the thickest point on the near and far walls with a specially designed computer program. A high rate of IMT reproduction has been demonstrated previously. Plaque was defined as a localized thickening >1.2 mm that did not uniformly involve the whole artery, and, if present, the measurements were taken ≥1 cm away from plaque.

Carotid Diameter
The high-resolution echo-tracking system determined the transcutaneous assessment of arterial wall displacement during the cardiac cycle and, hence, of the time-dependent changes in arterial diameter relative to initial diameter at the start of the cardiac cycle. The radio-frequency signal of 4 to 8 cardiac cycles was recorded, digitized, and temporarily stored in a large memory bank. We determined the signals corresponding with the proximal and the distal walls and, therefore, measured the posterior wall thickness and the internal diameter by positioning markers in the respective posterior and anterior wall signals. The system computed the successive values of internal end-diastolic diameter and stroke change in diameter and digitized the displacement waveform.

Carotid Distensibility
Carotid distensibility was calculated from the mean of 2 consecutive measurements in parallel with measurements from beat-to-beat blood pressure monitoring (Portapres, TNO Biomedical Instrumentation), which has been shown to accurately estimate intra-arterial blood pressure. Continuous blood pressure measurements were performed in a supine position. The mean values of arterial diastolic diameter (d), distension (Δd; defined as the difference between systolic and diastolic diameter during heart cycle), IMT, and carotid pulse pressure (ΔP; estimated as the difference between systolic and diastolic arterial pressure obtained by noninvasive beat-to-beat concomitant measurement by Portapres) were used for analysis. Distensibility was calculated by using the following equations: distensibility (D) = (2Δd + ΔP)/ΔP Δd). Results are expressed as ΔP/ΔΔd. Because systolic blood pressure has direct influence on carotid distensibility, we also adjusted carotid distensibility values for the mean systolic blood pressure in all of the groups using 2-way ANCOVA analysis.

24-Hour Blood Pressure Monitoring
To exclude masked HTN (ie, normal office with elevated ambulatory blood pressure monitoring), we performed 24-hour blood pressure monitoring with a SpaceLabs device (model 90207, SpaceLabs Medical, Inc) in the control and OSA groups. Blood pressure 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. Normal values were considered when systolic and diastolic blood pressures were <135 and 85 mm Hg for daytime and <120 and 70 mm Hg for nighttime.

Blood Samples
Venous blood was collected from all of the participants for the measurement of 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. Quantitative variables are expressed as means ± SDs. Comparisons between groups were made by 2-way ANOVA, and Bonferroni posthoc group comparisons (α=0.05 level of significance) were used to determine differences across the 4 groups. Linear regression models with vascular parameters, including carotid IMT, carotid diameter, and carotid distensibility as dependent variables and independent variables including age, body mass index, systolic and diastolic blood pressures, cholesterol, AHI, and minimal oxygen saturation, were constructed. Multiple regression analysis was used to identify variables that were independently associated with the vascular parameters and to adjust for possible confounding factors. A value of P<0.05 was considered significant.

Results
We initially selected 30 controls and 30 patients with HTN. In addition, from 100 patients with moderate and severe OSA, we initially selected only 60 patients because of the presence of ≥1 exclusion criteria, such as diabetes mellitus, smoking, or previous treatment for OSA. Ninety-four subjects (mean age: 46±6 years) were included in the final analysis (Figure 1). The 4 groups studied were similar in respect to several of
the well-known risk factors for cardiovascular diseases, including age, sex, body mass index, and cholesterol levels (Table). As expected, there were significant differences in sleep parameters and blood pressure values in OSA groups and HTN groups, respectively. In controls and OSA groups, systolic blood pressure and diastolic blood pressure during awake (systolic: 122.1±8.0 versus 122.5±6.8 mm Hg; diastolic: 77.8±6.5 versus 77.8±5.3 mm Hg) and sleep (systolic: 106.8±12.0 versus 110.1±9.4 mm Hg; diastolic: 65.1±5.3 versus 65.9±5.1 mm Hg) were similar, respectively. In HTN and OSA+HTN groups, the numbers of antihypertensive medications and the times from HTN diagnosis were similar (Table). In addition, the percentages of antihypertensive medications in HTN and OSA+HTN groups were similar, including diuretics (65% versus 56%), β-blockers (40% versus 37%), calcium channel blockers (25% versus 26%), angiotensin-converting enzyme inhibitors (40% versus 44%), and angiotensin II receptor antagonists (20% versus 22%), respectively.

IMT was 597±82 μm for controls, 713±117 μm for the OSA group, 713±182 μm for the HTN group, and 837±181 μm for the OSA+HTN group (P<0.0001; Figure 2). Carotid diameter was 6575±383 μm for controls, 7117±805 μm for the OSA group, 7191±818 μm for the HTN group, and 7927±821 μm for the OSA+HTN group (P<0.0001; Figure 3). Compared with controls, IMT and carotid diameter had similar increases in the OSA and HTN groups (P<0.05); a further significant increase was observed in OSA+HTN subjects (P<0.01). In percentage values, compared with the control group, carotid IMT and carotid diameter increased by 19.4% and 8.2% in the OSA group, 19.5% and 9.4% in the HTN group, and 40.3% and 20.6% in the OSA+HTN group, respectively.

According to Figure 4, carotid distensibility was 16.5±5.3 kPa⁻¹·10⁻³ for controls, 14.2±4.2 kPa⁻¹·10⁻³ for the OSA group, 13.1±3.6 kPa⁻¹·10⁻³ for the HTN group, and 10.4±3.8 kPa⁻¹·10⁻³ for the OSA+HTN group (P<0.01). Compared with controls, carotid distensibility was significantly decreased in HTN (P<0.05) and OSA+HTN subjects (P<0.001). In this last group, carotid distensibility was significantly lower than that in the OSA group (P<0.05). After adjustments for systolic blood pressure (mean systolic blood pressure of the entire group: 129.9 mm Hg), carotid distensibility was significantly decreased in OSA+HTN compared with that in controls (11.7±0.8 versus 15.1±0.9 kPa⁻¹·10⁻³; P=0.03). In our study, we did not detect carotid plaques in healthy controls. This vascular finding was verified in 2 normotensive patients with OSA (8%), in 1 hypertensive patient without OSA (5%), and in 4 patients with both conditions (15%).

In the multivariate analysis performed on the whole study sample, IMT was positively related to systolic blood pressure and AHI (P<0.05). The only variable independently associated with carotid diameter was AHI (P<0.05). Age (P<0.05) and systolic blood pressure (P<0.01) were independently related to carotid distensibility.

**Discussion**

The new findings in this study are as follows: (1) carotid IMT and diameter are associated with a similar increase in OSA and HTN groups, with a further significant increase observed when both conditions coexist; (2) after blood pressure adjustment, carotid distensibility is significantly decreased in OSA+HTN subjects compared with that in controls; and (3) multivariate analysis showed that carotid IMT is positively related to systolic blood pressure and AHI, whereas carotid diameter is related to AHI. Age and systolic blood pressure are independently related to carotid distensibility but not to AHI. Together, our results suggest that the frequent observed association of OSA and HTN has additive effects on the progression of carotid atherosclerosis.

Atherosclerosis is the leading cause of coronary heart disease, stroke, and peripheral vascular disease. Stroke and coronary disease are the leading causes of death around the world, including in developing countries. Although distinct artery-dependent patterns of atherosclerosis exist, sub-
activation, increased lipid lowering in macrophages, lipid peroxidation, high-density lipoprotein dysfunction, and endothelial dysfunction. Recent evidence in rabbits suggests that snoring promotes energy transmission to the carotid artery that could also be involved in atherosclerosis progression. In addition, the association between OSA and atherosclerosis could be mediated by the presence of HTN, a condition that is also associated with proatherogenic factors, such as endothelial dysfunction and inflammation. Typical patients with OSA share several risk factors for cardiovascular disease, including obesity and HTN, well established causes of atherosclerosis. In the present study, we characterized not only the relative impact of OSA on validated markers of early atherosclerosis but also the impact of the concomitant HTN, a very common condition associated with OSA. We described previously that severe OSA and HTN are associated with arterial stiffness and heart structure abnormalities of clinical carotid atherosclerosis is reported to have a good correlation with coronary and intracranial atherosclerosis. In addition, the detection of early markers of atherosclerosis is a predictor of future cardiovascular events. For instance, OSA is associated with increased risk of stroke and myocardial infarction. In parallel with these studies, evidence is growing that OSA is an independent risk factor for atherosclerosis. The mechanisms whereby OSA may contribute to atherosclerosis are multiple and include systemic inflammation, oxidative stress, vascular smooth cell activation, increased adhesion molecule expression, lymphocyte

Table. Patients Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=22)</th>
<th>OSA (n=25)</th>
<th>HTN (n=20)</th>
<th>OSA+HTN (n=27)</th>
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<tr>
<td>Age, y</td>
<td>45±7</td>
<td>46±5</td>
<td>44±4</td>
<td>47±5</td>
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<td>Male, %</td>
<td>68</td>
<td>80</td>
<td>80</td>
<td>81</td>
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<td>White subjects, %</td>
<td>82</td>
<td>76</td>
<td>80</td>
<td>74</td>
</tr>
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<td>Body mass index, kg/m²</td>
<td>30.0±3.6</td>
<td>29.4±3.2</td>
<td>30.0±3.4</td>
<td>30.7±3.6</td>
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<td>Waist circumference, cm</td>
<td>98.2±7.6</td>
<td>99.3±7.7</td>
<td>99.2±8.4</td>
<td>101.7±8.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>116±12</td>
<td>118±13</td>
<td>143±23†</td>
<td>143±17†</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>61±9</td>
<td>62±11</td>
<td>82±17†</td>
<td>82±14†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73±8</td>
<td>78±9</td>
<td>77±11</td>
<td>78±10</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>96±8</td>
<td>94±11</td>
<td>95±7</td>
<td>96±13</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>206±48</td>
<td>230±37</td>
<td>210±21</td>
<td>216±34</td>
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<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>131±37</td>
<td>143±37</td>
<td>134±21</td>
<td>133±33</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>45±11</td>
<td>48±10</td>
<td>44±10</td>
<td>45±13</td>
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<tr>
<td>Triglycerides, mg/dL</td>
<td>148±91</td>
<td>175±94</td>
<td>161±78</td>
<td>174±88</td>
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<td>Metabolic syndrome diagnosis, %*</td>
<td>41</td>
<td>40</td>
<td>45</td>
<td>52</td>
</tr>
<tr>
<td>AHI, events per hour</td>
<td>3±1</td>
<td>50±26‡</td>
<td>3±2</td>
<td>51±23‡</td>
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<td>Antihypertensive drugs, No.</td>
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<td>...</td>
<td>1.9±1.4</td>
<td>1.8±1.2</td>
</tr>
<tr>
<td>Time from HTN diagnosis, y</td>
<td>...</td>
<td>...</td>
<td>6±2</td>
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<tr>
<td>Awake oxygen saturation, %</td>
<td>96±1</td>
<td>95±2</td>
<td>95±1</td>
<td>95±2</td>
</tr>
<tr>
<td>Minimal oxygen saturation, SatO₂min</td>
<td>90±3</td>
<td>75±11‡</td>
<td>90±3</td>
<td>73±9‡</td>
</tr>
</tbody>
</table>

Values are mean±SD or No. *Metabolic syndrome was diagnosed according to the National Cholesterol Education Program, Adult Treatment Panel III, if 3 of 5 factors were present as follows: (1) waist circumference ≥102 cm in men and ≥88 cm in women; (2) triglycerides ≥150 mg/dL or patient on specific drug treatment; (3) high-density lipoprotein cholesterol <40 mg/dL, in men and <50 mg/dL, in women or when on specific drug treatment; (4) arterial blood pressure ≥130 or 85 mm Hg for systolic and diastolic blood pressure, respectively, or patient on antihypertensive drug treatment; and (5) fasting glucose ≥100 mg/dL or patient on specific drug treatment. †Data are different from controls and OSA groups (P<0.001). ‡Data are different from controls and HTN groups (P<0.01), and the remaining variables were nonsignificant (P>0.05).
similar magnitude, with additive effects when both conditions coexist. However, to the best of our knowledge, the effects of OSA and HTN in isolation and the impact of the association of OSA and HTN on carotid atherosclerosis were not described previously. In the present study, we found that, compared with controls, IMT and carotid diameter had a similar increase in OSA and HTN groups, and a further significant increase was observed in OSA+HTN subjects. Further indicating the relative role of OSA, AHI was independently associated with carotid IMT and diameter in the multivariate analysis.

Our study has some strengths and limitations. The strengths include the availability of polysomnography data, which is the gold standard for OSA diagnosis, and the careful selection of matched controls and hypertensive patients at low risk for OSA, further confirmed by polysomnography. We also excluded masked HTN in the control and OSA groups, a clinical situation that seems not to be uncommon in apparently normotensive patients with OSA. The limitation is the fact that the direct comparison of the effects of 2 distinct conditions (OSA and HTN) must be made with caution. All of the OSA patients had moderate-to-severe disease that was not being treated, whereas all of the HTN patients were receiving treatment (although their mean systolic blood pressure was not fully controlled, remaining in stage 1 HTN). However, it is well recognized that HTN patients receiving optimal treatment have higher IMT and are at increased risk for cardiovascular disease than are normotensive subjects. Therefore, our study design corresponds with what is commonly seen in clinical practice. Another important point is that patients with OSA and HTN had a significantly greater increase in IMT and carotid diameter than did patients with HTN, despite taking similar antihypertensive medications. This fact reinforces the relative role of OSA in atherosclerosis. Second, although finger blood pressure accurately estimates intra-arterial blood pressure, an estimation of carotid blood pressure is preferred. Third, we did not perform 24-hour blood pressure monitoring in the HTN and OSA+HTN groups. Patients with OSA+HTN may have a higher nighttime blood pressure than patients with OSA or HTN alone, and this fact could be involved in the vascular damage promoted by this common association. Finally, our study was not designed to evaluate more advanced atherosclerotic lesions, such as carotid plaques. Future studies should be performed to explore the additive effects of OSA and HTN on atherosclerotic plaques in comparison with each condition alone.

**Perspectives**

The clinical implication of the present study is the demonstration of additive effects on markers of atherosclerosis in patients with OSA and HTN. These findings could be implicated in the rate of progression of carotid atherosclerosis in these patients, which could further contribute to increase the risk of stroke. Considering that the underdiagnosis of OSA in patients with HTN is still common and that continuous positive airway pressure therapy in patients with OSA has beneficial effects on blood pressure and early markers of atherosclerosis and decreases fatal and nonfatal cardiovascular events (including stroke), our results reinforce the importance of OSA in patients with HTN.

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**Disclosures**

None.

**References**


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