Arterial Stiffness Increases During Obstructive Sleep Apneas

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INTRODUCTION

Obstructive sleep apnea (OSA) appears to be an independent risk factor for diurnal systemic hypertension, but the specific biologic markers for this association have not been well established. Increased arterial stiffness is an important measure of increased left ventricular load and a predictor of cardiovascular morbidity and may precede the onset of systemic hypertension in humans. However, arterial stiffness has not been measured in association with obstructive apneas in patients with OSA, nor related to systemic blood pressure (BP) activity in this setting. Our objective was to test the hypothesis that arterial stiffness may be utilized as a sensitive measure of arterial vasomotor perturbation during obstructive events in patients with OSA, by demonstrating that (1) arterial stiffness increases acutely in association with obstructive apnea and hypopnea, and that (2) such increased stiffness may occur in the absence of acute BP increase.

Study Objectives: Obstructive sleep apnea (OSA) appears to be an independent risk factor for diurnal systemic hypertension, but the specific biologic markers for this association have not been well established. Increased arterial stiffness is an important measure of increased left ventricular load and a predictor of cardiovascular morbidity and may precede the onset of systemic hypertension in humans. However, arterial stiffness has not been measured in association with obstructive apneas in patients with OSA, nor related to systemic blood pressure (BP) activity in this setting. Our objective was to test the hypothesis that arterial stiffness may be utilized as a sensitive measure of arterial vasomotor perturbation during obstructive events in patients with OSA, by demonstrating that (1) arterial stiffness increases acutely in association with obstructive apnea and hypopnea, and that (2) such increased stiffness may occur in the absence of acute BP increase.

Study Methods: A tertiary-care university-based sleep and ventilatory disorders center.

Patients: Forty-four normo- and hypertensive adult patients (11 women, 33 men) with polysomnographically diagnosed moderate to severe OSA.

Interventions: N/A.

Measurements and Results: Beat-to-beat BP was recorded from the radial artery by applanation tonometry during nocturnal polysomnography. Arterial augmentation index (AAI), a measure of arterial stiffness, was calculated as the ratio of augmented systolic BP (SBP) to pulse pressure and expressed as a percentage for the following conditions: awake, the first 10 (“early apnea”) and last 10 (“late apnea”) cardiac cycles of obstructive events, and the first 15 cardiac cycles following apnea termination (“post apnea”). Mean AAI (±SD) for the group was significantly increased during NREM sleep from early apnea to late apnea (12.02 ± 2.70% vs 13.35 ± 3.54%, p<0.05, ANOVA). During REM (analyzed in 20 patients), AAI again significantly increased from early apnea to late apnea (11.75 ± 2.81% vs 13.43 ± 4.97%). Conversely, neither mean SBP nor mean arterial BP was significantly increased from early apnea to late apnea (11.75 ± 2.81% vs 13.43 ± 4.97%). Arterial stiffness increases acutely during obstructive apneas in both NREM and REM sleep, in the absence of measurable BP change. These data suggest that arterial stiffness may be a sensitive measure of acute arterial vasomotor perturbation in this setting and may have implications concerning cardiovascular sequelae in patients with OSA.

Key Words: Arterial augmentation index; blood pressure; sleep apnea

METHODS

Subjects

All adult patients referred to the Columbia University Cardiopulmonary Sleep and Ventilatory Disorders Laboratory between October 2000 and December 2001 with a presumptive diagnosis of OSA, and without prior treatment for OSA, were consecutively recruited for this study. Patients other than those who did not meet these eligibility requirements included adult patients referred primarily with other forms of sleep-disordered breathing (COPD, hypoventilation related to neuro-muscular disorders, nocturnal asthma, and patients with congestive heart failure with a primary referral for Cheyne-Stokes respiration) and patients referred primarily for insomnia, circadian rhythm disorders, and excessive daytime sleepiness unrelated to OSA. The study was approved by the Institutional Review Board of the New York Presbyterian Hospital (Columbia Presbyterian Medical Center), and all subjects gave informed consent before participating. All patients who agreed to participate were studied during a night of standard clinical diagnostic

Disclosure Statement

This work was presented in part at the Associated Professional Sleep Societies’ annual meetings in Chicago, IL, June 2001.

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MEASUREMENTS

Nocturnal polysomnography

Sleep was recorded using standard polysomnographic measurements including central and occipital referential electroencephalography (EEG; C4/A1, O2/A1, C3/A2, O1/A2), right and left electrooculography, submental and anterior tibialis electromyography (EMG), electrocardiography with precordial surface electrodes, nasal and oral airflow measured by thermistors and nasal pressure transducers, respiratory movements of the rib cage and abdomen with piezo sensor bands, and arterial oxyhemoglobin saturation (SaO2) with a finger pulse oximeter (Embla, type XN). Data were collected and stored on an Embla signal recording system with Somnologica Window NT Software (Flaga hf. Medical Devices). An obstructive apnea was defined as a cessation of upper airway flow in association with continued respiratory effort of at least 10 seconds. Obstructive hypopnea was defined according to American Academy of Sleep Medicine clinical research criteria. EEG arousal was defined as an abrupt and discrete change in EEG frequency, with or without increased EMG activity. Apnea plus hypopnea index (AHI) was defined as the number of apnea plus hypopnea episodes per hour of sleep. OSA was defined as the presence of more than 10 obstructive apneas or hypopneas per hour of sleep. Sleep staging was performed according to standard criteria by a board-certified sleep specialist.

Figure 1—Calculation of the arterial augmentation index (AAI) in a representative subject. The top tracings represent the superimposition of a series of 10 sequential arterial pulse waveforms during late apnea. The bottom tracings represent the average of the superimposed arterial waveforms (upper tracing) and the fourth derivative of the waveform (lower tracing). The AAI is found as the derived waveform intercepts the X-axis at the systolic peak to pulse pressure and expressed as a percentage.

AAI

Continuous beat-to-beat BP was recorded from the radial artery by applanation tonometry using a noninvasive wrist oscillometric device (Model 7000, Colin Medical Instruments Corp., San Antonio, TX). The pressure transducer was placed over the radial artery and gently depressed against the underlying bone in a standard fashion. The bone provides a contact force between the skin and the sensor approximating intraarterial pressure. The contact force is converted to an electrical signal by the transducer, providing a continuous beat-to-beat recording. A wrist brace with velcro straps wrapped around the wrist and hand firmly secured the pressure transducer. The signal was sampled at 200 Hz/channel with an analog-to-digital converter (DAQ-700, National Instruments, Austin, TX) and channeled into a Dell Pentium Computer. The digitized arterial pressure waveform was analyzed using customized LabView software. An algorithm detects the waveform’s inflection point on the upstroke, which signals the onset of the reflected wave and thus divides the arterial pressure wave into an early and late systolic peak. As a measure of arterial stiffness, the AAI, a time domain estimate of the contribution of arterial pressure wave reflection to pulse pressure, was calculated through the superimposition of a series of sequential arterial pulse waveforms, which was averaged. The fourth derivative of the waveform was then taken, and the AAI found as the derived waveform intercepts the X-axis at the systolic shoulder. The AAI was calculated as the ratio of augmented systolic blood pressure (SBP) to pulse pressure and expressed in this manner as a percentage (Figure 1).

Study procedure

All subjects reported to the sleep laboratory at 8pm and underwent standard nocturnal polysomnography until 7am the following morning. Subjects continued clinically prescribed medication regimens, including antihypertensive medications. Subjects were prepared for baseline polysomnography in the standard manner and allowed to get into bed supine by 9:30pm. The applanation tonometer device and brachial BP cuff were then applied. The arm with the tonometer was placed flat, at the approximate level of the right atrium, with the palm of the hand facing up. The BP recordings were begun when a reproducible signal from the oscillometric device was accurately calibrated to the ipsilateral brachial cuff BP measurement. After all calibrations were performed, a 5-minute period of supine awake data was recorded. All subjects were able to stay awake for this recording. Lights out was at 11pm. As per laboratory clinical protocol, patients underwent a baseline sleep recording period of 2 to 3 hours followed by positive airway pressure titration; only data from the baseline period were analyzed for this study. Recalibration of the arterial tonometer was performed during the study if the radial artery SBP differed more than 5 mmHg from brachial cuff SBP recording.

Data analysis

For purposes of this study, we analyzed obstructive hypopneas as well as apneas and did not discriminate between these in the data analysis.

The first 10 successive cardiac cycles beginning at the onset of obstructive apnea or hypopnea ("early apnea"), the last 10 cardiac cycles during the apnea or hypopnea ("late apnea"), and the first 15 cardiac cycles immediately following the obstructive event ("post apnea") were analyzed and averaged for arterial augmentation index (AAI), systolic blood pressure (SBP), and mean arterial blood pressure (MAP) for each obstructive event in each patient. The mean of 5 epochs of 10 successive cardiac cycles during the last 5 minutes of the supine relaxed awake state prior to lights out ("awake") was similarly analyzed in each subject. The early apnea segment was chosen as most representative of a "baseline" associated with obstructive events during sleep. The late apnea segment was chosen as the most representative of the accumulated mechanical and chemical effects of the obstructive event prior to arousal. The post-
apnea segment was likewise chosen as most representative of the effect of arousal following resumption of ventilation and with resolving asphyxia. We recognize that none of these segments conform to a pure physiologic state given the unstable environment each period represents. We chose 10 successive cardiac cycles as the minimal unit of time allowing for a meaningful averaging of response, while allowing enough time for dividing the analysis into early and late apneic response. We chose to analyze 15 cardiac cycles following the arousal based on previous work, which found that autonomic and baroreceptor response to abrupt arousal from sleep in normal humans was affected maximally at cardiac cycles 5 to 15 following such arousal.

We analyzed every obstructive event that was free of motion artifact, that had radial artery BP well correlated with brachial cuff measurement (±5 mmHg), that had no awakening after the event (as opposed to transient arousal), and which fulfilled our requirement for significant hypoxemia (a nadir SaO2 of ≤ 89%). Further, based on our need for at least 10 consecutive cardiac cycles for representative averaging of the AAI over the periods of early and late apnea, we analyzed only those obstructive events that were of at least 20 cardiac-cycle duration. For all such apneas and hypopneas in each sleep stage (NREM and REM), the mean of AAI, SBP, and MAP was calculated in each patient. For each subject, the mean absolute value for all AAI, SBP, and MAP measurements awake, in NREM sleep, and in REM sleep was entered into the data analysis such that each subject contributed one data point each for awake, NREM, and REM state regardless of how many obstructive events were analyzed. Comparisons among awake state and early-apnea, late-apnea, and post-apnea data were made by repeated measures analysis of variance (ANOVA). All posthoc pairwise multiple comparison procedures utilized the Student-Newman-Keuls method (SigmaStat, Jandel, San Rafael, CA). Statistical significance for this procedure was considered at p<0.05. We performed identical analyses for these absolute data normalized as a percentage of awake values and normalized as a percentage of early apnea values.

To assess whether specific demographic or physiologic variables were correlated with AAI, correlational analysis (Pearson product moment correlation) was performed with changes in AAI as the dependent variable and the following as independent variables: age, gender, ethnicity, body mass index, SaO2 nadir, duration of analyzed obstructive events, AHI, history of hypertension, family history of hypertension, history of diabetes, history of smoking, and use of antihypertensive medications.

**RESULTS**

A total of 64 patients with suspected OSA consecutively recruited for this study met prospective eligibility requirements; all consented to participate in this research. Of these, 5 patients did not go on to fulfill criteria for OSA on their diagnostic polysomnography. Six patients were excluded postpolysomnography because of cardiac arrhythmia that interfered with wave form analysis; 9 patients were excluded because of inability to obtain a sufficient amount of artifact-free BP recordings. Thus, 44 patients are included in the data analysis. The age range of these participants was 27 to 77 years. There were 11 women and 33 men. Twenty participants were Caucasian, 11 were African-American, 12 were Hispanic, and 1 was Asian-American. The body mass index of these participants was 35±2 (mean±SD, range 25-60) kg/m². The AHI, calculated from the baseline polysomnographic recording, was 63±32 (mean±SD; range, 15-130) events per hour. The SaO2 nadir during scored obstructive events was 83±7 (mean±SD, range, 61%-89%). Twenty-seven participants had been diagnosed with systemic hypertension and treated: 7 were taking β-blockers, 9 calcium-channel antagonists, and 15 angiotensin converting enzyme inhibitors. Twenty-six of the participants had a family history of systemic hypertension. Ten had a diagnosis of diabetes mellitus; six were current smokers, while 5 had a history of past but not current cigarette smoking (none within the last 3 years).

**AAI**

A total of 284 NREM obstructive events (apneas and hypopneas) were analyzed among these participants. The number of scored events in each participant ranged from 6 to 10. A total of 136 REM obstructive events were analyzed for 20 out of the 44 patients with sufficient artifact-free REM data (mean of 6.8 REM events/subject).

For all obstructive events during both NREM and REM sleep, repeated measures ANOVA found significant differences in AAI among awake, early apnea, late apnea, and postapnea conditions (p=0.03). Posthoc multiple comparison procedures revealed that mean AAI was significantly increased (p<0.05) for the group during NREM sleep from awake to late apnea (12.09% ± 3.93% vs 13.35% ± 3.54%, all data mean ± SD) and from early apnea to late apnea (12.02% ± 2.70% vs 13.35% ± 3.54%). There was no significant change in AAI from early apnea to postapnea, nor from late apnea to postapnea. During REM AAI, significantly increased from early apnea to late apnea (11.75% ± 2.81% vs 13.43% ± 4.97%), and from early apnea to postapnea (11.75% ± 2.81% vs 13.15% ± 3.73%). These data are shown in Figure 2, top. There were no significant differences between awake and early apnea AAI in these subjects, so that normalizing the late apnea and postapnea AAI changes as percent change of awake AAI was virtually identical to analyzing them as a percent change from early apnea AAI. The major findings regarding change in AAI from awake and early apnea to late apnea and postapnea were virtually identical whether analyzed as change in the absolute value of AAI, or as a percent change of the absolute value. Mean (±SD) pulse pressure (PP) did not significantly change from awake or early apnea to late apnea (60 ± 6 mmHg awake, 58 ± 7 mmHg in early apnea, 58 ± 6 mmHg late apnea). However, PP significantly increased from awake, early, and late apnea to postapnea (64 ± , p<0.05,

![Figure 2](image-url)
ANOV A). Thus, while changes in PP followed changes in SBP and MAP, the PP changes remained discordant with changes in AAI. Thus, the change in PP did not appear to be responsible for the change in AAI. Further, the small decreases in arterial pressure from early to late apnea was a representative finding, such that the AAI changes were averaged over similar arterial pressure changes for the group.

No significant correlations were found among absolute AAI and any of the demographic and physiologic variables entered, including no significant correlations between mean AAI changes and apnea or hypopnea duration (mean ± SD = 22 ± 6 seconds), or presence/absence of vasoactive medications or hypertension. However, when AAI was normalized as a percentage of awake and early apnea values, male gender was significantly and positively correlated with change in AAI from early to late apnea (r = 0.31, p = 0.03), while nadir SaO2 during apneas was significantly and negatively correlated with the AAI change from early to late apnea (r = -0.33, p = 0.03).

When the subset of 17 normotensive patients (on no vasoactive medications) was compared with the 27 hypertensive patients using such medications, the changes in AAI from early to late apnea were statistically significant for both groups but were more prominent for the patients on no vasoactive medications. The patients on vasoactive medications showed an increase in AAI from early to late apnea of 11.68 ± 2.72% to 12.98% ± 3.86%, while the patients on no vasoactive medications showed an increase in AAI from awake to late apnea of 11.08% ± 2.23% to 15.03% ± 2.60 (mean ± SD). These data are shown in Figure 3.

Blood pressure

The SBP was significantly different among awake, early apnea, late apnea, and post apnea (p < 0.001, repeated measures ANOVA) during NREM sleep. However, SBP behavior differed from that of AAI: mean SBP in NREM was significantly decreased (p < 0.05) from awake (130 ± 15 mmHg) to both early apnea (120 ± 14 mmHg; all data mean ± SD). There was no significant change in SBP from early to late apnea. The SBP postapnea (139 ± 16 mmHg) was significantly increased from awake (133 ± 15 mmHg), early apnea (130 ± 14 mmHg), and late apnea (129 ± 14 mmHg). In REM, SBP changed in the same fashion as NREM: mean SBP was significantly decreased (p < 0.05) from awake (130 ± 15 mmHg) to both early apnea (128 ± 22 mmHg) and late apnea (127 ± 21 mmHg; all data mean ± SD). There was no significant change in SBP from early to late apnea. SBP post-apnea (141 ± 24 mmHg) was significantly increased from awake (133 ± 15 mmHg), early apnea (128 ± 22 mmHg), and late apnea (127 ± 21 mmHg). These data are shown in graphic form in Figure 2, bottom.

We did separate analyses using MAP rather than SBP and found that MAP changed in statistically identical fashion as SBP. Therefore, only the SBP data are presented here. Expressing and analyzing the data as a percentage of awake and early apnea values rather than in absolute values yielded identical results for BP (both SBP and MAP) as those noted above.

DISCUSSION

This study of arterial stiffness associated with obstructive apnea and hypopnea during sleep in patients with OSA yields two major and novel findings. First, arterial stiffness appears to increase acutely and transiently during obstructive events in both normotensive and hypertensive patients with OSA in NREM and REM sleep. Second, these changes in arterial stiffness are discordant with BP activity: arterial stiffness increases during the late phase of the apnea, prior to any discernible alteration in BP or EEG arousal.

The major import of these findings pertains both to the acute modulation of arterial vasomotor function and to possible long-term vascular outcome in patients undergoing obstructive apneas during sleep. Increased arterial stiffness may reflect acutely impaired vascular endothelial relaxation. An acute increase in arterial stiffness, as measured in the current study, appears to be a transient (and thus potentially reversible) phenomenon in patients with moderate to severe OSA and may represent a sensitive noninvasive physiologic marker of vascular endothelial dysfunction in this setting. Alternatively, the increased AAI during the apnea may reflect a homeostatic baroreceptor response aimed at preserving arterial pressure during increasing left ventricular afterload. The current findings add to, and are compatible with, the growing data concerning perturbed vascular distensibility in OSA patients. Abnormal vascular and autonomic responses may in fact precede the development of systemic hypertension or clinical evidence of cardiovascular disease in OSA patients. Normotensive patients with OSA have a greater pressor response to hypoxia than do age-matched, normotensive control subjects and do not vasodilate when exposed to isocapnic hypoxia as do normotensive controls. Further, endothelium-dependent vascular relaxation has been shown to be impaired in awake normotensive patients with OSA. The current data demonstrate, for the first time, acute vasomotor dysfunction in resistance arteries during obstructive sleep apneas in patients with OSA, in contrast to previous studies that have demonstrated peripheral arterial (finger-tip) vasoconstriction and increased limb vascular resistance only in the immediate postapnea period.

The magnitude of the increases in arterial stiffness (as measured by AAI) found in the current data set may be put into biologic perspective: for example, in patients with renal failure, after adjustment for all confounding factors, the risk ratio for each 10% increase in resting AAI was 1.51 (95% CI, 1.23 to 1.86, p < 0.0001) for all-cause mortality and 1.48 (95% CI, 1.16 to 1.90, p < 0.0001) for cardiovascular mortality. While the current data suggest that radial-artery stiffness measurement is a reproducible marker of vascular perturbation during obstructive apnea, we cannot be certain of the sensitivity of this measurement as an indicator of vasomotor function in this setting.

Increasing heart rate, and associated shortening of systolic duration and ejection time, will tend to reduce the augmentation of the arterial PP and thus the measurement of early wave reflection. In our subset, mean (± SD) heart rate did not significantly change for the group from early apnea to late apnea (74 ± 12 vs 73 ± 15), the period for which we report an increase in AAI. At the same time, mean heart rate did increase post apnea (88 ± 19) compared with awake (76 ± 17), early apnea (74 ± 12), and late apnea (73 ± 15), (p < 0.05, ANOVA). Thus, while the increase in AAI from early to late apnea does not appear to be related to a change in heart rate, the lack of a significant increase in AAI from late apnea to post apnea may well be related to the increase in heart rate that occurred in that time.

While beat-to-beat changes in both BP and AAI occurred in these patients both awake and during sleep, BP (SBP and MAP) averaged over the representative segments (awake, early apnea, late apnea, and postapnea) was not significantly different among awake, early apnea, and late...
apnea, the period in which AAI was significantly increasing. Thus, for this period, it appears that we were able to compare AAI using segments of BP that were relatively similar regarding BP change. At the same time, BP in the postapnea period was significantly increased from these other segments, so that we cannot be sure that the lack of AAI change between late apnea and post apnea we found was not due to dissimilar arterial pressures between these periods.

The patients we studied had, as per our design, moderate to severe OSA, and therefore AAI during sleep, but unrelated to the onset of obstructive hypopnea or apnea, could not be reliably determined; all of these subjects began with hypopnea and arousals during sleep wake transitions. Thus, we cannot compare apnea- and nonapnea-related changes in AAI related to sleep in these patients, although such a comparison would be of great interest. Similarly, mean SBP showed a mild but statistically significant decrease from awake data to early apnea data (133 ± 15 vs 130 ± 14, mean ±SD, p<0.05, ANOVA). We cannot tell from these data whether this decrease was due to the obstructive event, or to the effects of sleep itself, or a combination of these.

Because the physiologic data in these patients were collected early in the course of the study, as per the split-night protocol, we cannot rule out the possibility that AAI changes may show a circadian effect and may have differed over a longer course of study or later in the night. Similarly, it is possible that longer apneas, as may have occurred later in the study, might have changed the AAI responses. We found no significant correlation between AAI changes and obstructive-event duration (mean ±SD =22±6 seconds). However, this does not rule out the possibility of such an effect over the course of the night. Further, as we had only a subset of patients with sufficient analyzable REM data, we note that the lack of a significant difference between NREM and REM AAI response in these patients does not definitively rule out finding such a difference in a larger set of patients.

The current protocol was not designed to determine the specific pathogenesis of the reversible increases in arterial stiffness associated with obstructive apneas and hypopnea in sleep. The timing of the major increase in arterial stiffness, during late apnea but before EEG arousal, suggests that the asphyxia of the obstructive event, or the mechanical stimulus of increasingly negative intrathoracic pressure, are likely to be contributors to this change. It has been suggested that the chronic intermittent hypoxia associated with obstructive apneas during sleep may contribute to arterial endothelial damage and dysfunction, leading to reversible perturbations in vascular tone and blood flow. In the current study, the severity of SaO2 decrease associated with the obstructive events was significantly correlated with the degree of AAI increase, suggesting that the hypoxia of the obstructive event played a significant role in the increased arterial stiffness. However, increased arterial stiffness during the late phase of obstructive apnea is unlikely to reflect a response to hypoxia alone in these patients. Increased sympathetic activity accruing from absent lung-inflation reflexes during the apnea may alter the vasomotor responses compared with hypoxic subjects who breathe spontaneously. Further, were hypoxia alone mediating the increase in AAI, the maximal stimulation for either a reflex or a direct hypoxic effect would be expected to be seen later than at the point of resumption of ventilation, where AAI was not increasing in NREM, although it did show a small but statistically significant increase in REM sleep from early apnea to post apnea. It is similarly unclear from these data whether the arterial-stiffness changes we found are influenced by the hypercapnia that typically attends obstructive apneas. In rats, exposure to intermittent hypoxia for 30 days results in increased BP that is similarly elevated with and without the addition of CO2.

We chose obstructive events with prominent oxygen desaturation of hemoglobin for three major reasons: first, expecting that hypoxemia may be a major factor in increasing arterial stiffness prior to arousal (late apnea), we wished to maximize this effect; second, because we expected that increased arterial stiffness would be primarily affected by hypoxemia, we wished to offer a look at the physiology of events typical of more severe OSA; and third, we were looking for hypoxemia compara-

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