Diurnal and Obstructive Sleep Apnea Influences on Arterial Stiffness and Central Blood Pressure in Men

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Study Objectives: Nocturnal and early morning elevation of blood pressure are common acute manifestations of obstructive sleep apnea (OSA) that do not always carry over into a sustained daytime hypertension. Using pulse wave analysis, we examined the effect of OSA on arterial stiffness and central aortic blood pressure to assess whether each would be elevated independent of diurnal changes in peripheral blood pressure.

Design: Cross-sectional sleep laboratory cohort study.

Setting: Two university teaching hospitals.

Patients: 57 male nonsmokers referred for suspected OSA and free of known cardiovascular disease or blood-pressure and lipid-lowering medications.

Measurements and Results: The augmentation index, a quantification of augmentation of central aortic pressure due to the reflected component of the pulse pressure waveform, and brachial and aortic blood pressure were determined in the evening and early morning. The augmentation index consistently increased from evening to morning (P < .001) and was accompanied by an increase in central systolic blood pressure (P = .007) and a decrease in pulse pressure amplification (P < .001). However, these changes were unaccompanied by any changes in peripheral blood pressure.

Conclusions: Systemic arterial stiffness is positively correlated with OSA severity and, in addition, is increased in magnitude in the early morning independent of OSA severity.

Key Words: Obstructive sleep apnea; arterial stiffness; augmentation index


INTRODUCTION

RECENT STUDIES HAVE ESTABLISHED A LINK BETWEEN OBSTRUCTIVE SLEEP APNEA (OSA) AND INCREASED CARDIOVASCULAR MORBIDITY. In particular, robust evidence now clearly demonstrates a strong causative link between OSA and systemic hypertension.1,2 An association has also been demonstrated between OSA and the long-term sequelae of hypertension, such as an increased incidence of coronary artery disease3 and stroke.4

Mechanistic studies have focused on how the repetitive hypoxic insult or other changes associated with OSA may disturb hemodynamic homeostasis and vascular function. These disturbances include autonomic imbalance associated with excessive sympathetic activation,5,6 alterations to baroreflex control of blood pressure,7 endothelial dysfunction,8,9 and vascular inflammation.10 Several studies have now implicated oxidative stress associated with the repetitive hypoxia/reoxygenation that occurs during apneas as a key mechanism associated with endothelial dysfunction and vascular inflammation.11

Hypertension is an important predictor of cardiovascular risk. Studies using populations in which OSA status is unknown have demonstrated that different blood pressure indexes improve the prediction of cardiovascular risk, depending upon age. For example, data from the Framingham Study have shown that as age increases, the strength of prediction of cardiovascular risk gradually shifts from diastolic to systolic blood pressure and then to pulse pressure.12 Arterial stiffness has been identified as another important vascular property that increases both with age and in certain disease states that are typically associated with increased cardiovascular risk. Methods for determining arterial stiffness include techniques that measure pulse wave velocity in the descending aorta13 and the aortic augmentation index. This latter measure is a quantification of augmentation of central aortic pressure due to the reflected component of the pulse pressure waveform.14 In young subjects with compliant arteries, the aortic augmentation index is negative because the reflected pressure wave arrives during diastole and helps to improve coronary perfusion. In older subjects with less-compliant arteries, the reflected pressure wave arrives much earlier during systole, causing an increase in peak systolic pressure, thereby increasing left ventricular workload. Pulse wave analysis (PWA) is a technique that allows the noninvasive assessment of the aortic augmentation index and central aortic pressure using applanation tonometry of the radial artery.15 The assessment of central arterial pressure allows for the quantification of the ratio of peripheral to central pulse pressure or pulse pressure amplification, a well-established hemodynamic phenomenon in cardiovascular physiology that is negatively correlated with age and positively correlated with heart rate.16 The measurement of the aortic augmentation index and aortic pre-
sures may be superior predictors of cardiovascular risk, since they are correlated with indexes of left ventricular hypertrophy, the incidence and extent of coronary artery disease, and several established cardiovascular risk scores.

Given that early-morning peripheral blood pressure is often elevated in subjects with OSA, with a subsequent return to normal levels during the day, we aimed to assess arterial stiffness by PWA, at 2 time points that would coincide with periods of elevated or normal peripheral blood pressure. We hypothesized that OSA severity, as measured by the respiratory disturbance index (RDI), would be associated with increased levels of arterial stiffness and central aortic blood pressure independent of any diurnal fluctuation in peripheral blood pressure. Furthermore, this effect would be independent of other known or potential confounders such as age, heart rate, body mass index, and cholesterol.

METHODS

Study Population

Fifty-seven subjects were recruited from a population of patients referred for a routine diagnostic sleep study at 2 university teaching hospitals affiliated with the Woolcock Institute of Medical Research—Royal North Shore Hospital and Royal Prince Alfred Hospital. Inclusion criteria were male sex, age 17 to 65 years, and no medical history of cardiovascular disease or diabetes. Subjects were required to be lifelong nonsmokers with alcohol consumption not exceeding 40 grams per day and not taking antihypertensive, lipid-lowering or beta agonist agents. The human research ethics committees from both hospitals approved the study. Written informed consent was obtained from each subject prior to study participation.

Study Protocol

Subjects underwent a PWA study both in the evening (5-7 PM) prior to sleep and in the morning (5-6am) following their overnight sleep study. The morning study was conducted within 15 minutes after awakening, with the subjects remaining in bed until completion of measurements. In order to avoid any confounding influence of meal or posture on arterial stiffness, both PWA studies were conducted in the supine and fasted state. Hence, on the scheduled date for the sleep study, subjects were asked to withhold all food and drink (other than water) for at least 5 hours prior to the evening PWA study. In addition, subjects were required to be supine for at least 20 minutes prior to PWA measurements. Evening and morning sessions followed an identical procedure. Following the morning PWA readings, subjects had blood taken for fasting cholesterol, glucose, and insulin measurements.

Pulse Wave Analysis

PWA of the radial artery waveform was performed on the nondominant arm using the technique of applanation tonometry (Sphygmocor, Atcor Medical, Sydney, Australia). The arm was immobilized in a cradle, and, following the location of a good-quality signal, the pressure tonometer probe was placed in a probe holder to enable a hands-free measurement and thus avoid any operator-induced error. PWA readings were performed in triplicate and were preceded by a single blood pressure calibration reading from brachial artery pressures in the dominant arm with the use of an oscillometric blood pressure device (Omron T5 blood pressure monitor—Omron Healthcare Inc, Japan). The choice of blood pressure cuff size varied according to arm circumference, as recommended by the manufacturer. Testing was performed at least 3 times, resulting in a minimum of 9 PWA readings and 3 blood pressure readings for each (evening or morning) session. PWA readings were pooled to calculate a mean (evening or morning) result for each subject.

The PWA technique allows for the noninvasive assessment of central aortic pressures using a transfer algorithm that assumes a similar mean arterial pressure throughout the arterial system. Augmentation pressure is defined as the pressure difference between the late systolic peak, augmented by the peripherally reflected wave and the early systolic peak caused mainly by left ventricular ejection in the pulse. The aortic augmentation index is defined as the ratio of augmentation pressure and aortic pulse pressure expressed as a percentage. Pulse pressure amplification is subsequently calculated as the ratio of peripheral (brachial) to central (aortic) pulse pressure.

Sleep Studies

All sleep recordings (S-Series, Compumedics, Melbourne, Australia) included electroencephalography, electrooculography, submental electromyography, oxygen saturation (pulse oximetry), respiratory movements (inductance plethysmography), nasal and oral airflow (thermistor), and nasal pressure (nasal cannulae and pressure sensor). Sleep staging and sleep-disordered breathing were subsequently scored using standard techniques but with all apneas and hypopneas inclusive of a mandatory minimum 4% oxygen desaturation.

Statistics

All evening-to-morning changes in PWA indexes were compared using paired t tests. A multiple linear regression model was used to investigate factors that could potentially influence the magnitude of both the static (evening or morning) and the overnight change (evening to morning) in the aortic augmentation index. Age, height, heart rate, mean arterial pressure, RDI, body mass index, and total cholesterol were entered into the model (SPSS statistical software version 11.5; SPSS, Inc., Chicago, Ill). Outcome variables in the regression model were normally distributed. Univariate analysis of variance was used to explore the covariate-adjusted effects of OSA severity on arterial stiffness. A probability value < .05 was considered to be statistically significant, and all tests were 2-tailed.

RESULTS

The demographic, biochemical, and sleep-disordered breathing data for the study group are presented in Table 1. Based upon evening measurements, 6 subjects in the group (N = 57) had hypertension defined as a blood pressure above 140/90 mm Hg. Two of these subjects had no OSA (RDI < 5), 2 had mild OSA (5 < RDI > 10), and 2 had severe OSA (RDI > 30). Based on the same RDI cutpoints, there were 22 subjects in the entire group who did not have OSA, 10 subjects had mild OSA, and 25 had moderate-to-severe OSA.

Evening-to-Morning Hemodynamic Changes
There was a small increase in mean arterial pressure (94.0 ± 1 vs 96.3 ± 1 mm Hg; \( P = .018 \)) and a small fall in heart rate (67 ± 1 vs 64 ± 1 beats per minute; \( P < .001 \)) from evening to morning, respectively. The remaining evening and morning peripheral and central hemodynamics are presented in Table 2. Peripheral systolic and diastolic pressures did not change significantly. Despite this, there was a significant rise in early morning aortic systolic pressure and augmentation pressure. This coincided with a marked increase in the aortic augmentation index and a significant decrease in pulse pressure amplification from the aorta to the brachial artery as assessed by the ratio of peripheral to central pulse pressure. Nonaugmented central systolic blood pressure did not change (107.0 ± 1 vs 107.3 ± 1 mm Hg; \( P = .78 \)). With few exceptions, Figure 1 illustrates that the morning measures of the aortic augmentation index were consistently higher than the evening measures. The data presented in Figure 2 show typical evening and morning pulse wave recordings from a patient and demonstrate the divergence between peripheral and central systolic blood pressure.

### Regression Analysis

The regression analysis results for evening and morning aortic augmentation indexes are presented in Table 3. Age, heart rate, and mean arterial pressure were all significant independent predictors for both evening and morning aortic augmentation index. In addition, RDI had a significant (albeit smaller) independent effect at both time points. Body mass index, height, and total cholesterol had no significant effects. In a separate analysis (results not shown), changes in heart rate and mean arterial pressure were the only significant predictors of the magnitude of the overnight change in the aortic augmentation index; however, they only accounted for a third of the variance (\( R^2 = 0.339, P = .002 \)).

### Arterial Stiffness and Blood Pressure in Relation to OSA Severity

A further analysis of the aortic augmentation index between different OSA severity groups is presented in Figure 3. After adjusting for significant covariates (age, heart rate, and mean arterial pressure), the RDI severity group was significantly associated with an increase in the augmentation index at both time points (\( P = .003 \)). In this predominantly normotensive cohort, however, RDI severity group did not correlate with central aortic systolic blood pressure at either time point (\( P = .65 \) evening) and (\( P = .061 \) morning).

### DISCUSSION

This study has demonstrated 2 main findings in a carefully selected group of predominantly normotensive subjects referred for investigation of OSA. Firstly, there was an overnight change in arterial stiffness that was independent of OSA severity. In effect, there was a marked increase in early morning arterial stiffness relative to evening measures. Secondly, sleep apnea severity was positively correlated with arterial stiffness at both measurement times. Hence, sleep apnea appears to predispose subjects to increased arterial stiffness, but it does not influence the magnitude of the overnight change.

### Overnight Changes in Arterial Stiffness

To our knowledge, this is the first study to suggest that systemic arterial stiffness determined by PWA is systematically modified across the sleep period. The increase in early morning arterial stiffness resulted in a divergence between overnight changes in peripheral and central systolic blood pressure. Early morning peripheral systolic pressure did not change, whereas central systolic pressure increased.

From a hemodynamic perspective, an increase in augmentation pressure (due to an increase in arterial stiffness) will increase central systolic pressure if there is no compensatory fall in nonaugmented systolic pressure, as was the case in this study. In contrast, these central pressure changes will not necessarily influence pressures measured in the periphery.

From a mechanistic perspective, the lack of change in peripheral systolic (and diastolic) pressure may relate to the fact that all study subjects were awake during evening and morning blood pressure measurements. The influence of wakefulness on blood pressure is supported by recent evidence suggesting that the 24-hour blood pressure profile has no endogenous circadian component but is more closely controlled by environmental and behavioral factors such as sleep itself. Although the presence of OSA could have masked any early morning dip in peripheral blood pressure, this is less likely because there was also no blood pressure increase.
pressure change among the 22 subjects with no sleep-disordered breathing (results not shown).

In contrast to peripheral pressure, central systolic pressure increased, suggesting that this change was independent of wakefulness. This increase was due to an increase in augmentation pressure associated with an increase in arterial stiffness and resulted in a decrease in pulse pressure amplification. While we did not perform PWA during sleep, these early morning central hemodynamic changes may actually represent a carry-over effect of sleep. Evidence for this comes from single-vessel studies that have demonstrated a generalized nocturnal decrease in arterial distensibility. Possible mechanisms to explain nocturnal changes in arterial distensibility and stiffness may relate to a circadian variation in both nitric oxide production and endothelial-mediated dilatation, with a decline in both during nocturnal hours.

Regardless of the mechanism, any sleep-related increase in arterial stiffness may cause a divergence between peripheral and central systolic blood pressure. In some cases, this could result in peripheral dippers becoming central nondippers. This may be important in the context that while current evidence supports a cardioprotective role of nocturnal (peripheral) blood pressure dipping, the assessment of central blood pressure may be a superior predictor of risk. Central blood pressure would, however, need to be more extensively examined over 24 hours and in non-OSA populations where dipping is less likely to be influenced by the acute effects of apnea. In this study, the dipping status of patients during sleep was not assessed; however, recent evidence suggests a high prevalence of nondipping even in normotensive OSA patients.

**Sleep Apnea Influences on Arterial Stiffness**

In addition to the finding of a systematic modification of arterial stiffness across the sleep period, this is the first study to our knowledge that demonstrates an increase in arterial stiffness in relation to the severity of sleep-disordered breathing in otherwise healthy patients with OSA. The increase in the aortic augmentation index of 8% at the evening time point in the highest RDI severity group, when compared to the lowest, is equivalent to approximately 8 years of aging. There are a number of mechanisms that could explain this finding. OSA is a condition associated with considerable blood pressure swings coinciding with apneas during sleep. Apneas lead to surges in sympathoadrenergic traffic, promoting persistent sympathetic activation and baroreceptor reflex adaptation. In addition, hypoxemia or other components of the apnea may induce a compromised nitric oxide production and exacerbate endothelial dysfunction. Emerging evidence now supports a key role for hypoxia/reoxygenation-induced oxidative stress in promoting vascular inflammation, potentially leading to further deterioration of endothelial function. The elimination of OSA with nasal continuous positive airway pressure has been shown to reverse these effects and reduce blood pressure; however, it remains to be established whether reductions in arterial stiffness parallel these changes.

Interestingly, in relation to OSA severity, the increase in arterial stiffness did not result in a generalized increase in central systolic pressure at either time point. The reasons for this may relate to the fact that the study group members as a whole were predominantly normotensive, relatively young, and without a history of cardiovascular disease. However, the findings from this study suggest that the development of overt hypertension may well be preceded by an increase in arterial stiffness.

**Study Limitations**

While the study excluded women because their shorter stature predisposes them to increased augmentation of central systolic pressure, it also excluded patients who were on antihypertensive or lipid-lowering medications. We chose to do this because anti-hypertensive medications have unequal effects in reducing arterial stiffness and the effect from lipid lowering medications is still unknown. Despite these strict selection criteria, we were still able to demonstrate a small yet significant contribution by OSA severity to arterial stiffness even in the absence of overt hypertension.

In this study, the detailed circadian pattern of arterial stiffness was not systematically assessed, and it is possible that changes may have occurred during both the sleep and wake period. Continuous arterial tonometry was not deemed practical during sleep due to the constraints of performing manual measurements over the radial artery. Furthermore, confounding influences from meal intake and posture may have limited the value of such assessments during the day, but these were minimized by performing studies in the fasted and supine state. However, it remains un-
Amada T, Ren Z-Y, Zimmerman MB. Our concern regarding the validity of the technique using PWA has not been without criticism. Much of the debate concerning the aortic augmentation index and central systolic blood pressure were accounted for by changes induced by sleep and sleep related phenomena.

Although the PWA technique has been shown to be highly reproducible, the use of a generalized transfer function to calculate the aortic augmentation index and central systolic blood pressure using PWA has not been without criticism. Much of the debate concerning the validity of the technique relates to the specifications of catheters used in validation studies and to central blood pressure inaccuracies arising from calibration inaccuracies of the cuff sphygmomanometer. In the present study, multiple calibration readings were performed to minimize calibration error. In addition, if the transfer function introduces errors, then these errors will presumably be consistent within a test subject. As such, the overnight change in the aortic augmentation index should reflect a true finding. Furthermore, given the significant association between PWA indexes and hard cardiovascular outcomes, our finding of a positive association between OSA severity and the aortic augmentation index adds to the understanding of cardiovascular risk in these patients.

CONCLUSIONS

This study highlights the need to more extensively examine factors that may influence the magnitude of the divergence between peripheral and central aortic blood pressure in relation to nocturnal dipping. It also highlights the need for conducting intervention studies in patients with OSA to more clearly delineate the relative influence treatment may have in reducing arterial stiffness and central systolic blood pressure when compared to the modest reductions that are already known to occur in peripheral blood pressure. This may be especially relevant for OSA patients with refractory hypertension in whom treatment has been shown to have a particularly powerful blood pressure-lowering effect. Given that this study has demonstrated an increase in arterial stiffness with OSA in a predominantly normotensive cohort, treatment of OSA may well reduce the degree of stiffness and retard the progression of overt hypertension and subsequent morbidity and mortality associated with cardiovascular disease.

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