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Impacts of Comorbidities on the Association between Arterial Stiffness and Obstructive Sleep Apnea in the Elderly

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Key Words
Obstructive sleep apnea · Arterial stiffness · Elderly population · Pulse wave velocity · Lung

Abstract
Background: Although the impact of obstructive sleep apnea (OSA) on cardiovascular risk is reasonably well established in middle-aged patients, the debate persists as to whether OSA also increases this risk in the elderly. Arterial stiffness has been used as an early independent predictor of cardiovascular risk. **Study Objectives:** We sought to determine whether OSA has significant effects on the arterial stiffness in the elderly population and evaluate the impact of comorbidities on the association between arterial stiffness and OSA. **Methods:** We performed a cross-sectional study in a university hospital. Elderly participants (≥60 years) were invited to participate in our study between November 2010 and January 2013. OSA was diagnosed using gold standard polysomnography and arterial stiffness was assessed by brachial-ankle pulse wave velocity (baPWV), cardio-ankle vascular index (CAVI) and central systolic and diastolic blood pressure (cSBP and cDBP). The high-sensitivity C-reactive protein (hs-CRP) level was also measured. **Results:** We found no significant association between the severity of OSA and the arterial stiffness-related parameters cSBP, cDBP, baPWV, CAVI and hs-CRP. However, in patients with no comorbid medical conditions or use of medications (n = 101), we showed a modest association between OSA and arterial stiffness-related parameters and hs-CRP. **Conclusion:** We conclude that OSA is associated with increased arterial stiffness in an otherwise healthy elderly population, although the association was obviated by comorbidities and medications perhaps due to ceiling effects.

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Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive pauses in breathing during sleep resulting in an intermittent reduction in blood oxygen saturation. The prevalence of OSA is about 6–13% in the middle-aged population with higher values of up to 19–37% in older individuals [1–3]. In the era of population aging, OSA in older people might be a serious health threat, but the consequences of OSA in the elderly have been debated. OSA is known to increase the risk of mortality and cardiovascular diseases such as coronary artery disease, heart failure and stroke [4–7]. In older people, some authors have

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shown that OSA is also associated with increased blood pressure (BP) [8], high cardiovascular risk [4, 5] and high mortality [9]. On the other hand, others have shown that OSA in the elderly is not associated with either systolic/diastolic hypertension or mortality [10, 11].

Arterial stiffness has been implicated as an early independent predictor of cardiovascular risk in OSA patients [12, 13]. There are several indices for measuring arterial stiffness such as brachial-ankle pulse wave velocity (baPWV) and the cardio-ankle vascular index (CAVI). A substantial body of evidence shows that these measurements of arterial stiffness are increased in middle-aged patients with OSA [12], and our group has also shown an association of nocturnal hypoxemia and arterial stiffness in middle-aged male OSA patients [14]. However, there is a paucity of research addressing the association between arterial stiffness, an early marker of cardiovascular risk, and OSA in the elderly population. Considering the controversies regarding OSA in the elderly, we sought to test the hypothesis that elderly OSA patients would have greater vascular stiffness than matched individuals without OSA, independent of known comorbidities. Since the elderly frequently present with comorbid medical conditions, excluding those with comorbidities might only result in an artificially healthy group of the elderly. Conversely, the impact of comorbidities on vascular stiffness might lead to ceiling effects which would limit the ability to assess the impact of OSA. Moreover, certain comorbidities such as hypertension and diabetes may be causally linked to OSA, which further complicates the decision of whether to include or exclude these patients in rigorous analyses. Thus, we planned to assess elderly OSA patients with and without known comorbidities to allow determination of the impact of OSA on vascular stiffness and potential interactive effects with comorbidities.

Methods

Study Subjects

We conducted a cross-sectional observational study of 471 elderly individuals, at least 60 years of age, who were recruited by convenience sampling from the sleep laboratory of the Seoul National University Bundang Hospital, Seongnam-si (and adjacent communities), South Korea, by advertisement between November 2010 and January 2013. We excluded patients with a history of prior therapy for snoring or OSA, heart failure, cerebrovascular diseases with neurologic deficits, inflammatory diseases, chronic obstructive pulmonary disease, nocturnal asthma, Cheyne-Stoke respiration and other sleep disorders such as parasomnias and circadian rhythm disorders. All of the participants underwent nocturnal polysomnography and clinical evaluation. Our Institution-

al Review Board approved the study (B-1006/103-010), and a signed informed consent was obtained from all of the subjects or from their legal guardians.

Clinical Evaluation

Clinical data were collected using a standardized protocol, including questions about current medical conditions and medication use, the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale (ESS). Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg or the current use of antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dl or current use of antidiabetic medications. Metabolic dyslipidemia was considered to be present if subjects were taking lipid-lowering medications at recruitment or had a high level of serum triglyceride (≥150 mg/dl) or a low level of high-density lipoprotein cholesterol (≤50 mg/dl for men and ≤40 mg/dl for women) [15, 16]. Laboratory tests were carried out for measuring the lipid profile and levels of high-sensitivity C-reactive protein (hs-CRP), fasting blood sugar and insulin.

Nocturnal Polysomnography

We used the Embla N7000 (Embla, Reykjavik, Iceland) with standard electrodes and sensors. Electroencephalography electrodes were applied at C4/A1, C3/A2, O1/A2 and O2/A1, and two electrooculography electrodes were applied on the sides of both eyes to record horizontal and vertical eye movements. Electromyography electrodes were applied on the submentalis muscles and both anterior tibialis muscles. Strain gauges were used for recording chest and abdominal respiratory movements, and nasal pressure cannulae were used to record airflow. Oxygen saturation was measured using a pulse oximeter applied on the index finger. Based on the criteria of Rechtschaffen and Kales [17], sleep was scored at every 30-second epoch of the nocturnal polysomnography. Apnea was defined as complete cessation of airflow for at least 10 s. Hypopnea was defined as a discernible reduction in airflow for at least 10 s associated with electroencephalographic arousal or oxygen desaturation (≥4%) [18]. The apnea-hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of sleep, and the oxygen desaturation index (ODI) was calculated as the number of oxygen desaturations (≥4%) per hour of sleep. OSA was diagnosed if AHI was ≥15/h, and was divided into 2 groups, i.e. mild-to-moderate OSA (AHI between 15 and 29/h) and severe (AHI ≥30/h) OSA [9].

Assessment of Arterial Stiffness

Arterial stiffness was assessed by brachial-ankle pulse wave velocity (baPWV), cardio-ankle vascular index (CAVI) and central BP, both systolic (cSBP) and diastolic (cDBP). To evaluate baPWV, we measured electrocardiogram, phonocardiogram and oscillometric signals from 4 extremities and the ankles as well as tonometric signals from the right common carotid and right femoral arteries with a noninvasive vascular screening device system (VP-2000; Omron-Colin, Kyoto, Japan) [19]. The measurement of baPWV and CAVI was performed based on the literature [13, 20]. The time interval between the wave front of the brachial waveform and that of the ankle waveform was defined as the time interval between the brachium and ankle (ΔTba). The path length from the suprasternal notch to the brachium (Lb) and ankle (La) was obtained from superficial measurements and was calculated using the following equations: Lb = 0.2195 × height (in cm) – 2.0734; La =

Table 1. Clinical characteristics of the study population

Variable	Normal (AHI <15/h)	Mild-to-moderate (15≤ AHI <30/h)	Severe (AHI ≥30/h)	p value
Total number of subjects	226	127	118	
Males	66 (29.2)	77 (60.6)	85 (72.0)	<0.001[†]
Age, years	67.9±5.60	67.7±5.43	68.2±5.73	0.743
BMI, kg/m^2	23.3±2.47[a]	24.4±2.79[a]	25.5±3.17[a]	<0.001*
Current smokers	12 (5.4)	12 (9.5)	13 (12.4)	0.078
Hypertension	123 (54.4)	71 (55.9)	72 (61.0)	0.498
Diabetes	44 (19.5)	24 (18.9)	26 (22.0)	0.802
Dyslipidemia	98 (43.6)	53 (42.1)	52 (44.4)	0.930

Data are presented as n (%) or means ± SD. [†] $p < 0.05$, χ^2 test; * $p < 0.05$, ANOVA.
[a] A pairwise comparison was made between the means for each AHI subgroup with Bonferroni's correction ($p < 0.05$).

$0.8129 \times$ height (in cm) + 12.328. Finally, baPWV was calculated by the following equation: baPWV = (La – Lb)/ΔTba [20]. We measured baPWV after at least 5 min of rest, and then CAVI was calculated using the following equation: CAVI = $2\rho \times 1 / (Ps – Pd) \times$ ln (Ps/Pd) × baPWV^2, where ρ is the density of blood and Ps and Pd are the SBP and DBP, respectively [13]. cBPs were assessed non-invasively using an algorithm that derives the pressure wave at the ascending aorta from an external measurement taken at the radial artery (SphygmoCor; AtCor Medical, Itasca, Ill., USA).

Statistical Analysis

Subjects were divided into 3 subgroups based on the AHI, i.e. normal (AHI <15/h), mild-to-moderate (15≤ AHI <30/h), and severe OSA (AHI ≥30/h). We used an AHI cut-off value of 15 for making the diagnosis of OSA (control group) in the elderly [1]. Comparison between subgroups was done with analysis of covariance after adjusting for body mass index (BMI) and gender. Multiple linear regression analysis was used to determine the relationship between cardiovascular variables as dependent variables and polysomnographic and clinical variables as independent variables. All significance tests were 2-sided and $p < 0.05$ was considered statistically significant. Statistical analysis was done with SPSS version 18.0 for Windows (SPSS Inc., Chicago, Ill., USA).

Results

Clinical Characteristics of Subjects

Overall, 71.0% of male and 34.7% of female subjects were diagnosed as having OSA. Table 1 shows the clinical characteristics of the study population. Age did not differ across the 3 subgroups, i.e. normal (n = 226, 68.0 ± 5.6 years), mild-to-moderate OSA (n = 127, 67.7 ± 5.4 years) and severe OSA (n = 118, 68.2 ± 5.7 years). We found that the proportion of male subjects and BMI were different among subgroups ($\chi^2 = 67.34$, d.f. = 2, $p < 0.001$ and F = 26.21, d.f. = 2, $p < 0.001$, respectively). Hypertension, di-

abetes and dyslipidemia were equally distributed among the AHI subgroups ($p = 0.498$, $p = 0.802$ and $p = 0.930$, respectively). The proportion of medicated subjects with hypertension, diabetes and dyslipidemia in the comorbidity group was 80.4, 70.8 and 43.3%, respectively.

Polysomnographic Findings and Arterial Stiffness-Related Variables

We compared scales for sleep quality and sleepiness, polysomnographic findings and arterial stiffness-related variables among the 3 groups defined by AHI (table 2). As expected, subjective sleepiness measured by ESS was higher in the severe OSA group ($p = 0.001$ by ANOVA; $p = 0.001$ between the normal and severe OSA group by post hoc test with Bonferroni's method). Polysomnographic data showed significant group differences in AHI, the lowest oxygen concentration (% of sleep time), oxygen desaturation <90% (% of sleep time) and ODI ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). However, we could not identify any significant difference in cardiovascular variables such as cSBP, cDBP, baPWV, CAVI and hs-CRP ($p = 0.118$, $p = 0.159$, $p = 0.202$, $p = 0.062$ and $p = 0.154$, respectively).

Subgroup Analysis: Comorbidity and Healthy Groups

We stratified the subjects into 2 groups for subgroup analysis by design, i.e. the comorbidity group (n = 370) and the group with no comorbidities, i.e. the healthy group (n = 101). The AHI subgroups in the healthy group did not differ in the proportion of males and BMI but those in the comorbidity group did ($\chi^2 = 68.1$, d.f. = 2, $p < 0.001$ and F = 25.3, d.f. = 2, $p < 0.001$, respectively). Therefore, adjustment for gender and BMI was performed only for the comorbidity group. The healthy group revealed a significant

Table 2. Polysomnographic and cardiovascular variables of all subjects

	All subjects (n = 471)			p value
	normal (n = 226)	mild-to-moderate (n = 127)	severe (n = 118)	
PSQI	6.49 (0.27)	7.18 (0.34)	7.55 (0.39)	0.077
ESS	6.71 (0.32)[a]	7.31 (0.40)	8.16 (0.46)[a]	0.048*
AHI, events/h	6.79 (0.51)[a]	21.62 (0.65)[a]	46.56 (0.71)[a]	<0.001*
Lowest O_2[b], %	87.78 (0.39)[a]	84.24 (0.49)[a]	78.59 (0.53)[a]	<0.001*
Desat. <90%[c], %	1.20 (0.52)[a]	1.58 (0.66)	8.83 (0.72)[a]	<0.001[c]
ODI	5.02 (0.66)[a]	14.83 (0.84)[a]	36.01 (0.91)[a]	<0.001*
cSBP, mm Hg	115.4 (1.05)	118.6 (1.32)	118.5 (1.44)	0.118
cDBP, mm Hg	74.6 (0.63)	75.9 (0.80)	76.8 (0.87)	0.159
baPWV, cm/s	1,632.9 (19.6)	1,633.9 (248.0)	1,675.3 (282.7)	0.202
CAVI	5.64 (0.14)	5.79 (0.18)	6.25 (0.20)	0.062
hs-CRP, mg/l	1.04 (0.11)	1.31 (0.14)	1.39 (0.15)	0.154

Data are presented as means (SEM). PSQI = Pittsburgh Sleep Quality Index. * p < 0.05, gender- and BMI-adjusted ANCOVA.
[a] A pairwise comparison was made between the means of the subgroups with Bonferroni's correction (p < 0.05).
[b] Lowest O_2 saturation during sleep study.
[c] Percentage of sleep with a desaturation of O_2 <90%.

Table 3. Polysomnographic and cardiovascular variables of subjects in the comorbidity and healthy group

	Comorbidity group (n = 370)			p value	Healthy group (n = 101)			p value
	normal (n = 171)	mild-to-moderate (n = 103)	severe (n = 96)		normal (n = 55)	mild-to-moderate (n = 24)	severe (n = 22)	
Age, years	68.1 (5.65)	67.67 (5.46)	67.95 (5.95)	0.832	67.45 (5.49)	67.58 (5.44)	69.32 (4.62)	0.363
Males[a]	48 (28.1)	67 (65.0)	73 (76.0)	<0.001*	18 (34.5)	10 (41.7)	12 (54.5)	0.204
BMI, kg/m^2	23.39 (2.42)	24.51 (2.78)	25.84 (3.13)	<0.001*	22.85 (2.6)	24.08 (2.85)	23.85 (2.89)	0.124
PSQI	6.68 (3.82)	7.08 (3.71)	6.99 (3.82)	0.044*	7.29 (3.82)	6.42 (3.96)	7.52 (4.25)	0.583
ESS	6.35 (3.87)	7.57 (4.13)	8.32 (5.63)	0.144	6.98 (4.7)	6.79 (4.78)	9.05 (4.51)	0.187
AHI, events/h	6.06 (4.14)	22.13 (3.87)	47.16 (13.68)	<0.001*	6.77 (4.27)	20.73 (3.63)	42.89 (7.89)	<0.001*
Lowest O_2[b], %	88.26 (3.88)	83.81 (4.89)	78.44 (7.66)	<0.001*	86.94 (5.12)	85.92 (4.09)	78.00 (9.21)	<0.001*
Desat. <90%[c], %	0.48 (2.17)	1.56 (2.03)	10.33 (14.66)	<0.001*	1.41 (7.41)	2.53 (6.3)	6.41 (8.0)	0.013*
ODI	3.89 (3.39)	15.54 (4.74)	38.02 (16.21)	<0.001*	5.83 (13.41)	13.2 (5.59)	32.89 (11.88)	<0.001*
cSBP, mm Hg	114.99 (14.48)	119.64 (17.13)	119.24 (15.17)	0.268	112.93 (12.32)	116.38 (13.32)	122.09 (10.92)	0.014*
cDBP, mm Hg	73.02 (9.24)	76.99 (10.16)	78.43 (9.16)	0.447	73.8 (8.97)	75.25 (7.94)	79.5 (8.53)	0.037*
baPWV, cm/s	1,660.95 (305.45)	1,629.87 (259.07)	1,656.99 (288.97)	0.711	1,546.04 (189.67)	1,651.29 (197.18)	1,755.23 (243.78)	<0.001*
CAVI	5.89 (2.27)	5.68 (1.75)	5.96 (2.29)	0.537	5.23 (1.26)	6.05 (1.49)	6.9 (2.15)	<0.001*
hs-CRP, mg/dl	1.15 (1.3)	1.34 (1.89)	1.37 (1.82)	0.642	0.69 (0.67)	1.14 (1.9)	1.62 (1.83)	0.022*

Data are presented as means (SD), unless otherwise indicated. PSQI = Pittsburgh Sleep Quality Index. * p < 0.05, adjustment for gender and BMI for the comorbidity group.
[a] Number of subjects (% within each AHI group).
[b] Lowest O_2 saturation during sleep.
[c] Percentage of sleep with desaturation of O_2 <90%.

subgroup difference in cSBP, cDBP, baPWV, CAVI and hs-CRP (F = 4.460, p = 0.014; F = 3.408, p = 0.037; F = 8.703, p < 0.001; F = 9.554, p < 0.001; F = 3.953, p = 0.022, respectively; table 3; fig. 1). In figure 1, cSBP represents all cBPs because the results for cDBP were similar. In contrast, the comorbidity group did not show subgroup differences in any of cSBP, cDBP, baPWV, CAVI or hs-CRP (F = 1.320, p = 0.268; F = 0.808, p = 0.447; F = 0.341, p = 0.711; F = 0.623, p = 0.537; F = 0.443, 0.642, respectively). Within the comorbidity group, further subgroup analysis for the pa-
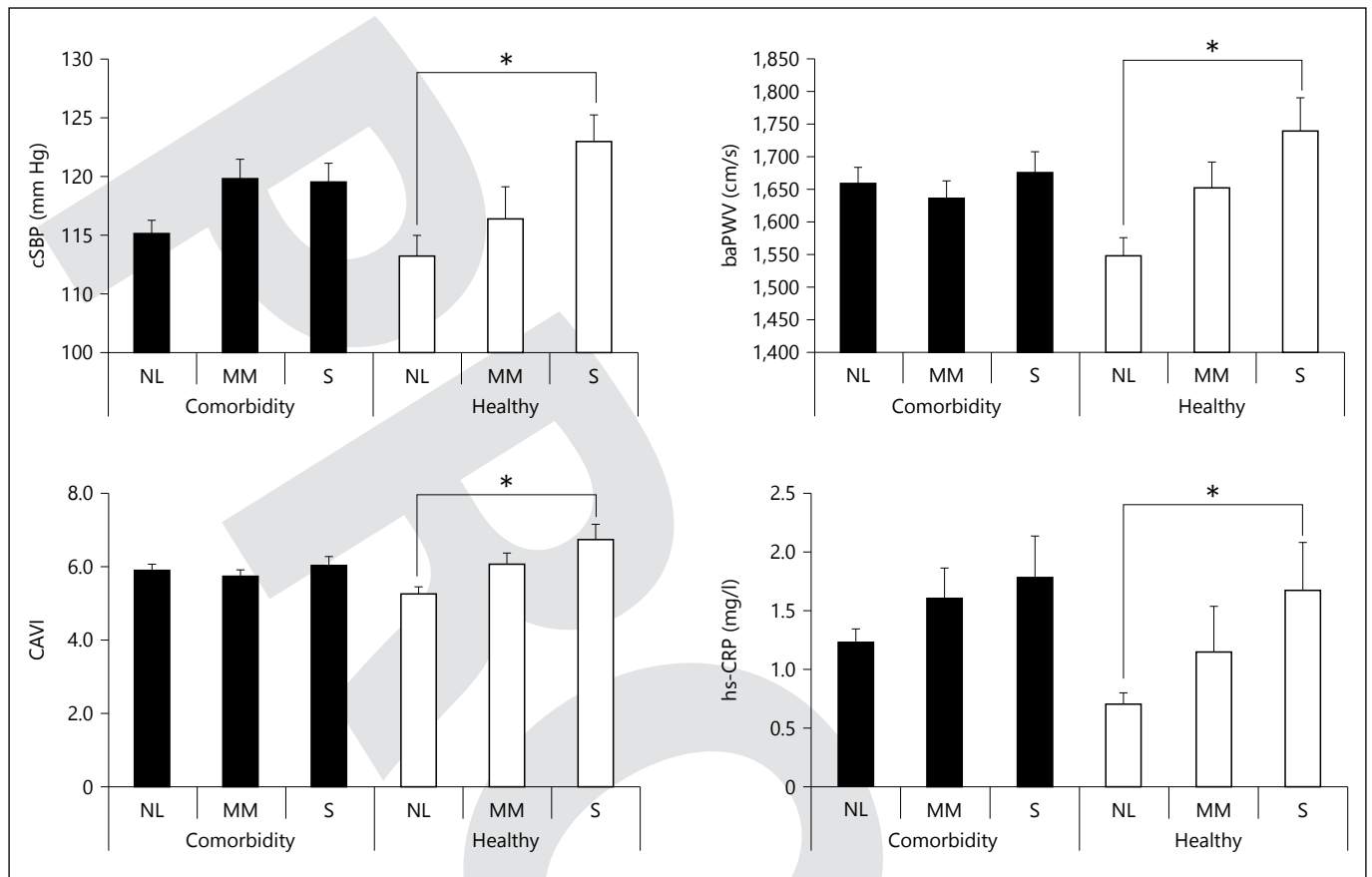
Fig. 1. The normal AHI and severe OSA subgroups of the healthy group showed differences in cSBP, baPWV, CAVI and hs-CRP. Black and white bars indicate the mean of the comorbidity and healthy groups, respectively, and the error bars show the SEM.

* p < 0.05, post hoc test by Bonferroni's method following ANOVA. NL = Normal group; MM = mild-to-moderate OSA group; S = severe OSA group.

tients with (n = 233) or without medication (n = 137), respectively, e.g. antihypertensive patients or antidiabetics, showed no difference of cSBP, cDBP, baPWV and CAVI across the AHI subgroups after adjusting for sex and BMI. To investigate the relationship between OSA and arterial stiffness in the healthy group, we first performed a univariate regression analysis; this showed a significant correlation between AHI and arterial stiffness-related variables (R = 0.308, p = 0.002 for cSBP; R = 0.251, p = 0.012 for cDBP; R = 0.355, p < 0.001 for baPWV; R = 0.354, p < 0.001 for CAVI; R = 0.322, p = 0.001 for hs-CRP). We also performed a multiple linear regression analysis for the arterial stiffness-related variables. These 5 variables were used as dependent variables and AHI, sex and BMI as independent variables. Central BPs, baPWV, CAVI and hs-CRP had a significant association with AHI (β = 0.286, p = 0.007; β = 0.232, p = 0.024; β = 0.326, p = 0.002; β = 0.326, p = 0.002; β = 0.333, p = 0.007, respectively; table 4).

Discussion

We studied the elderly population for assessing the relationship between OSA and arterial stiffness. The elderly patients with OSA did not show an association between AHI and arterial stiffness-related variables, but the subgroup without comorbidities revealed a modest association between AHI and the given variables, cSBP, cDBP, baPWV and CAVI and the systemic inflammatory marker hs-CRP.

Arterial stiffness is one of the important biological markers for arterial health at various sites in the arterial system and is caused by structural changes in the vascular wall including fibrosis, medial smooth-muscle cell necrosis, breaks in elastin fibers, calcification and diffusion of macromolecules into the arterial wall [21]. Greater arterial stiffness is associated with atherosclerosis [22], which increases the risk of cardiovascular diseases and events. PWV is the most thoroughly and clinically investigated

Table 4. Multiple linear regression analysis of arterial stiffness variables in the healthy group

Independent variables	Dependent variables				
	cSBP	cDBP	baPWV	CAVI	hs-CRP
AHI	0.286 (0.007)*	0.232 (0.024)*	0.326 (0.002)*	0.326 (0.002)*	0.333 (0.002)*
Sex	−0.103 (0.478)	−0.271 (0.061)	−0.119 (0.415)	−0.102 (0.486)	0.209 (0.152)
BMI, kg/m^2	0.113 (0.271)	0.080 (0.428)	−0.015 (0.882)	−0.029 (0.782)	0.045 (0.657)
Current smoker	−0.007 (0.960)	−0.010 (0.945)	−0.128 (0.381)	−0.154 (0.293)	0.092 (0.523)

Data are presented as a standardized β coefficient (p value). * $p < 0.05$, multiple linear regression.

measure of arterial stiffness, defined as the wave speed within a material (distance travelled/transit time) [12]. The association between OSA and arterial stiffness has been studied by many researchers; a review conducted by Philips et al. [12] summarized that 20 out of 28 cross-sectional studies on middle-aged patients found a significant difference in arterial stiffness between controls and patients with OSA. baPWV has been suggested as a predictor of the presence of coronary artery disease; however, in patients with OSA, it can be affected by changes in BP during measurement [22]. Thus, CAVI was an improved measurement obtained by adjusting peripheral BPs so that the effect of BP at the time of the measurement might be reduced [23]. Recently, good reproducibility of CAVI was validated in OSA [13]. It is also noteworthy that cBPs are closely related to arterial stiffness and are more relevant than peripheral BP in the pathogenesis of cardiovascular diseases [24].

After we demonstrated that nocturnal hypoxemia is associated with arterial stiffness and endothelial dysfunction in the middle-aged [14, 25], we questioned whether OSA in the elderly could also have an impact on arterial stiffness. Previous studies on the association between OSA and arterial stiffness were performed with middle-aged patients [12]. To the best of our knowledge, ours is the first cross-sectional study to investigate the association between OSA and arterial stiffness exclusively in an elderly population. Unlike the middle-aged population, the elderly with OSA did not show an association between OSA and arterial stiffness-related variables. Evaluation of endothelial dysfunction could yield positive results [26], but has been reported that in older adults, the measurements for both arterial stiffness and endothelial dysfunction are directly associated, thus providing similar information [27, 28]. On the other hand, as the elderly are prone to various diseases and consequently take more medications, we analyzed a subgroup without comorbidities. A relationship between OSA and arterial stiffness was found in

this healthy group. Our subgroup analysis based on medication status within the comorbidity group showed no worsening of arterial stiffness according to OSA in both the medication and nonmedication subgroups. For the nonmedication subgroup, medical conditions per se, like hypertension, diabetes and dyslipidemia, might aggravate arterial stiffness regardless of the presence of OSA [29, 30] whereas for the medication subgroup, antihypertensive and antidiabetic medications might improve arterial stiffness in OSA patients [31, 32]. Thus, it is plausible that the presence of these comorbidities and the use of medication may negate a possible relationship between OSA and arterial stiffness in the elderly via the mixture of a ceiling effect of increased stiffness and a medication effect of decreasing arterial stiffness. Although we found a modest but significant association between AHI and arterial stiffness after eliminating the potential confounding effects of medical conditions and medication use, we should be cautious about the interpretation of these results. The healthy OSA subgroup consisted of only a quarter of all the subjects, so whether they were representative is debatable. Still, we believe that our analyses are of value because we removed the confounding effects of comorbidities/medications in order to explore the isolated impact of OSA on cardiovascular risk in the elderly.

CRP is an important serum biomarker of inflammation that can predict cardiovascular risk in apparently healthy subjects [33] and in heart-failure patients with central sleep apnea [34]. However, the association between CRP and OSA is controversial [15, 35–37]. Previously, we showed that CRP was associated with obesity rather than with AHI [25]. It should be noted that the subjects of the previous study were middle-aged men (42.1 ± 8.7 years, n = 90) and not from the elderly population. In this context, the study of Roche et al. [15] in 2009 is relevant to this study because their subjects included the elderly who had OSA without cardiovascular morbidity. Their study population was similar to ours, especially

the healthy group, and they also showed a significant association between CRP and OSA. Therefore, the discovery of the association between CRP and OSA might indicate a characteristic of the elderly population without comorbidities.

The issue of potential ceiling effects deserves further comment. The patients with OSA and comorbidities did not have worse vascular stiffness than those with comorbidities only, so the possibility exists that a 'maximum' stiffness in elderly humans occurs, above which further worsening is unlikely. Both biological as well as methodological explanations could play a role here. For example, OSA and diabetes mellitus could work through autonomic, inflammatory or oxidative stress mechanisms such that the combination of diseases may not worsen risk, at least as assessed through vascular stiffness [38, 39]. The instrumentation required to measure PWV may also have reduced sensitivity at maximal values such that measurement of increased vascular stiffness may be problematic in some patients. As our patients with severe OSA and comorbidities did not have velocities greater than the other groups, we suggest that our findings are more likely to be driven by biological rather than methodological issues. However, further work is clearly needed in this area.

The main strengths of this study was the large number of subjects with laboratory polysomnographic data and the detailed medical evaluation, which enabled us to stratify the subjects based on the presence or absence of medical illness. However, we also acknowledge some limitations. First, the elderly without comorbidities comprised only a quarter of our subjects, which limited the statistical power. We could therefore parsimoniously suggest that comorbidities and their medications attenuate the impact of OSA on arterial stiffness. Second, we found modest correlations between AHI and cardiovascular variables, indicating that other factors might also influence these variables. Third, arterial stiffness is an early marker of atherosclerosis. This is a good cardiovascular marker for the middle-aged population, but may not be ideal for the elderly, because the ceiling effect of arterial stiffness might be present in this group, especially in the patients with comorbidities. Despite these limitations, we could conclude that OSA was associated with increased arterial stiffness in an otherwise healthy, elderly population. This association was obviated by comorbidities and medications perhaps due to ceiling effects.

Acknowledgement

Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest. Dr. Malhotra relinquished all outside personal sources of income in 2012.

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