Sleep Apnea and Markers of Vascular Endothelial Function in a Large Community Sample of Older Adults

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Clinical studies have suggested that sleep apnea is associated with impaired brachial artery flow-mediated dilation, a surrogate of endothelial dysfunction. We examined this question among older participants in the baseline examination of the Sleep Heart Health/Cardiovascular Health Study cohort (n = 1,037, age 68 years or older, 56% female). Indices of sleep apnea, derived from 12-channel home polysomnography, were the apnea–hypopnea index (average number of apneas/hypopneas per hour) and the hypoxemia index (percentage of time below 90% O_2 saturation). Baseline arterial diameter and percentage of flow-mediated dilation were measured by ultrasound. Sleep apnea measures were associated with baseline diameter and the percentage of flow-mediated dilation, although these associations were weakened after adjustment for other cardiovascular risk factors, particularly body mass index. However, a statistically significant linear association between the hypoxemia index and baseline diameter was observed even after adjustment for body mass index and other confounders ($p < 0.01$). The associations were stronger among participants who were younger than 80 years and among those who with hypertension. This study adds to the growing body of evidence linking sleep apnea with vascular dysfunction in older subjects. Whether these relationships are entirely independent of obesity is unclear. This association might be one of the mechanisms explaining the relationship between sleep apnea, hypertension, and cardiovascular disease.

Keywords: brachial artery ultrasonography; endothelium; hypertension; sleep apnea

Sleep apnea and related breathing disorders during sleep have been associated with hypertension and cardiovascular disease in both cross-sectional and prospective studies (1–3). Increased sympathetic activity and hypoxia associated with apneic episodes have been proposed as possible mechanisms explaining these associations (4), possibly through the induction of endothelial dysfunction, as suggested by studies finding an association between sleep apnea and abnormal vasodilatory responses to reactive hyperemia in the brachial circulation (5–8). These were all small case control studies in sleep clinic–based samples of patients and, thus, are potentially subject to random error, referral biases, and uncontrolled confounding. To our knowledge, there are no available studies addressing this question in a large, population-based sample of healthy older individuals.

If an association between sleep apnea and endothelial dysfunction is confirmed, this could provide insights into the pathophysiology underlying the cardiovascular consequences of sleep apnea. This study was designed to determine whether the degree of sleep apnea is associated with brachial artery diameter and vasodilatory response to reactive hyperemia in a large, community-based sample of older individuals and whether this association is modified by the presence of systemic hypertension and other host characteristics. Preliminary results of this study have been previously reported in abstract form (9).

METHODS

The study population is a subset of the Cardiovascular Health Study (CHS), composed of participants included in an ancillary study to measure brachial artery flow-mediated vasodilator responses at the 10th CHS annual cycle (1997–98) who also participated in the baseline exam of the Sleep Heart Health Study (SHHS) (1995–98).

CHS

The CHS was initiated in 1989 (10). A total of 5,201 individuals aged 65 years or more were recruited from Health Care Financing Administration Medicare eligibility lists in four communities of the United States: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA (11). An additional group of 687 African American participants was recruited and examined in 1992–1993. The CHS baseline examination included a variety of measures of clinical and subclinical cardiovascular disease and risk factors, including venipuncture, smoking history, physician's diagnosed history of diabetes or coronary heart disease, height, left ventricular mass (by echocardiography), ankle–arm index (12), and maximum intima-media thickness measured in the common carotid by ultrasound (10, 13, 14). CHS participants were examined annually.

As part of the 10th annual exam (1997–1998), brachial artery ultrasound measurements were conducted in surviving CHS participants who agreed to participate in this ancillary study. Exclusion criteria were (*1*) the presence of Raynaud's phenomenon or (*2*) in women a previous radical mastectomy on either side. The methods employed for measurement of brachial flow-mediated vasodilation have been described elsewhere (15–17). Briefly, all subjects were examined after an overnight fast. The examination began with a 15-minute rest period with the subject lying supine in a quiet, temperature-controlled room. A standard pediatric blood pressure cuff was placed 2 inches below the right antecubital fossa. Blood pressure and heart rate were recorded every 5 minutes using an automated sphygmomanometer on the left arm. The right brachial artery was identified approximately 7 cm proximal to the brachial bifurcation using a 10-MHz Biosound Phase 2 ultrasound system. The transducer was positioned to allow simultaneous viewing of the blood–intimal and medial–adventitial interfaces on the near and far walls. Imaging geometry was maintained throughout the procedure by

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monitoring the location of cursors on the screen placed in the lumen and on distinct perivascular anatomic landmarks at the beginning of the study.

Once the transducer position was established, baseline data were recorded for 2 minutes. After this 2-minute baseline period, the cuff was inflated to 50 mm Hg more than the subject's baseline systolic blood pressure for 4 minutes and then deflated. The brachial artery was continuously imaged during the period of cuff inflation and for 2 minutes immediately after cuff release. Nitroglycerin was not administered in this protocol to avoid the possibility of headaches and hypotension in these older, fasting, mostly nitroglycerin-naïve subjects.

Images were recorded on S-VHS tape and analyzed at the Wake Forest University Cardiology Image Processing Core Laboratory using a previously validated analysis system (15). The program determines baseline and maximum diameter, percentage change in diameter, and area under the diameter versus time curve and automatically stores these data in a database for future analysis. Data are reported as baseline diameter, absolute change in diameter (maximum − baseline), and percentage change in diameter (absolute change/baseline × 100), heretofore identified as percentage flow-mediated dilation (%FMD). Clinic sonographers were blinded as to the subjects' status regarding other risk factors; core laboratory technicians were also blinded as to the subjects' identities. Reproducibility of the method, including anatomic placement of the blood pressure cuff and the automated analyses, was tested with repeat examinations less than 1 week apart in a subset of 127 CHS participants and has been reported elsewhere (16). Briefly, the mean (SD) difference in percentage change in diameter was 0.02% (1.54%) in the paired sample, and the R^2 was 0.7.

Total and high-density lipoprotein serum cholesterol were measured with an Olympus Demand system (Olympus Corp., Lake Success, NY), standardized according to the Centers for Disease Control.

SHHS

The specific aims and major design features of the SHHS have been previously reported (18) (*see* http://www.jhucct.com/shhs/). In brief, SHHS participants were recruited from individuals 40 years old or more included in ongoing cohort studies of cardiovascular or respiratory disease (parent cohorts). Three of the subcohorts of the SHHS were recruited from CHS sites (Pittsburgh, PA; Sacramento County, CA; and Washington County, MD). Participants with history of treatment of sleep apnea with continuous positive airway pressure, tracheotomy, or current home oxygen therapy were excluded from the initial examination of the SHHS. A total of 6,441 SHHS participants were enrolled for the SHHS baseline sleep study conducted in the homes of the participants between November 1995 and January 1998. Of these, 1,250 participants were from CHS and had participated in the brachial ultrasound examination.

Enrolled participants completed a self-administered questionnaire on sleep habits. The home visit was conducted in the evening and included a brief health interview, assessment of current medication use (19), blood pressure and anthropometric measurements, and a 12-channel, unattended sleep study (polysomnographic study) (20).

Sitting blood pressure was measured in the right arm after a 5-minute rest using a conventional mercury sphygmomanometer. The first and last Korotkoff sounds were used to determine systolic and diastolic blood pressure, respectively. The average of the second and third of three consecutive measurements was used as the blood pressure value in this report. Hypertension was defined as systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 95 mm Hg or more, or current medical treatment for hypertension. This definition, previously used in analyses of data from the CHS study (21), was chosen a priori because of the age range of the study population; a more widely used definition (blood pressure of 140/90 mm Hg or more) resulted in such a high proportion of subject with hypertension (approximately 74%) that it would have limited the ability to conduct stratified analyses. Weight was measured with the participant wearing light clothes using a portable scale. Body mass index (BMI) was calculated as the ratio of weight (in kg) divided by height (in meters) squared.

Polysomnography (PSG) was conducted using a Compumedics PS-2 system (Compumedics Pty. Ltd., Abbotsford, Australia) with the following montage: two central electroencephalograms, a left and right electrooculogram, chin electromyogram, single bipolar electrocardiogram, finger pulse oximetry (NONIN, Minneapolis, MN), chest and abdominal excursion (by respiratory inductance plethysmography), airflow (by oronasal thermocouples; Protec, Woodenwille, WA), body position (by mercury gauge sensor), and ambient light (20). Sensors were placed and equipment was calibrated during the evening home visit by a team that included centrally trained and certified technicians following a common protocol, as described in detail in the study's manual of operations (http://www.jhucct.com/shhs/). Data were stored in real time on PCMCIA cards. The equipment was retrieved the next morning. PSG studies were downloaded into a personal computer and transmitted to the SHHS Reading Center (Case Western Reserve University, Cleveland, OH).

A detailed protocol for central scoring of sleep stages, arousals, and respiratory events has been described in detail elsewhere (20). Apneas were identified if airflow was absent or nearly absent (at least 75% below baseline values) for at least 10 seconds. Hypopneas were identified if discernible, discrete reductions in airflow or thoracoabdominal movement (at least 30% below baseline values) occurred for at least 10 seconds. An apnea–hypopnea index (AHI) was defined as the average number of apneas or hypopneas, each associated with a greater than or equal to 4% decrease in oxygen saturation, per hour of sleep. Additionally, apneas were further classified as "obstructive" if movement on either the chest or abdominal inductance channels was noted or as "central" if no displacement was observed on both of these channels, and the obstructive apnea index and the central apnea index were then calculated. Consistent with the strong correlations between these indexes in the SHHS (22), analyses based on alternative definitions of the AHI based on 2% and 3% desaturation yielded results virtually identical to the AHI based on 4% desaturation and thus are not presented here.

As reported elsewhere (23), the reliability of the scoring of the AHI was high, with interscorer intraclass correlation of 0.99. Likewise, a high degree of night-to-night reproducibility of the PSG measurements has been demonstrated in the study (24). As an additional indicator of the presence of sleep apnea, the percentage of sleep time with oxygen saturation below 90% (hypoxemia index) was also quantified.

Statistical Analyses

Of 3,030 participants who returned to the CHS 10th annual exam, 2,798 individuals (92%) completed the brachial ultrasound exam. Of these, 1,037 also completed the PSG exam in SHHS and had complete information on all key variables for these analyses (demographics, AHI, %FMD, BMI, and smoking). These individuals comprise the study sample for the present analyses. The average interval between the PSG exam and the brachial ultrasound exam was 1.1 years (range −0.6 to 2.25 years). The main independent variables of interest were baseline brachial artery diameter and %FMD.

The crude relationship between continuous variables was analyzed using the Spearman ordinal correlation coefficient (r_s). Analyses of variance and multiple regression analyses were used to assess the relationship between brachial artery ultrasound measures and the presence of certain demographic characteristics, markers of cardiovascular disease (clinical or subclinical), or risk factors, while adjusting for age (continuous), sex, and race. For these analyses, PSG measures (AHI, hypoxemia index) were categorized using previously defined categories (1). For variables defined with more than two ordinal categories, the presence of a statistically significant linear trend on the brachial artery ultrasound values was evaluated by the Wald test statistic of the corresponding single ordinal covariate in the regression model. The possible confounding or intermediary role of certain variables on the relationship between PSG and brachial artery ultrasound measures was evaluated by assessing the change in the regression coefficients for PSG parameters after entering each of these variables in the model.

Further analyses were conducted after stratification by demographic characteristics (age, sex), hypertension, and diabetes status. Analyses were also repeated after excluding participants currently taking medications that could affect endothelial function (nitrates, calcium antagonists, angiotensin-converting enzyme inhibitors, β-blockers, and estrogens) (25, 26).

RESULTS

Participants ranged in age from 68 to 96 years at the time of their PSG exam; 44% were male, and 61.4% had prevalent

hypertension. The mean AHI was 9.9 per hour (median 5.7; range 0–149 per hour). The mean brachial artery baseline diameter was 4.6 mm (range 2.3–7.0 mm); most of apnea–hypopnea events were obstructive in nature, as indicated by the similarity between the AHI and the obstructive apnea index. Central apnea events were rare; the mean central apnea index was 0.65 per hour, and only 3.5% participants had a central apnea index of more than 5. The mean %FMD was 3.0% (range −0.9% to 13%). Other descriptive statistics of the main study variables are presented in the online supplement.

As shown in Table 1, the baseline diameter was directly associated with BMI, diastolic blood pressure, fasting glucose, carotid intima-media thickness, ankle–arm index, and left ventricular mass and inversely associated with total and high-density lipoprotein cholesterols; %FMD was inversely correlated with BMI, carotid intima-media thickness, and left ventricular mass and directly with high-density lipoprotein cholesterol. AHI, obstructive apnea index, and hypoxemia index were correlated with both brachial ultrasound measures, with ordinal correlations of similar magnitude as those of established cardiovascular disease risk factors; the correlations for central apnea index were somewhat weaker. The correlation between AHI and hypoxemia index was $r_s = 0.67$ and that of baseline diameter and %FMD was $r_s = -0.34$ (both $p < 0.0001$).

Table 2 shows the age-, sex-, and race-adjusted mean baseline diameter and %FMD according to levels of risk factors, disease status, and sleep apnea variables. Compared with their corresponding counterparts, the baseline diameter was significantly higher in men, overweight/obese participants, those with hypertension, and those with prevalent coronary heart disease, and %FMD was significantly lower in the same groups. No statistically significant associations with smoking and markers of subclinical atherosclerosis (intima-media thickness, ankle–arm index) were evident. With respect to indices of sleep apnea, increasing levels of both AHI and hypoxemia index were associated with an increased baseline diameter and a decreased %FMD in a dose–response fashion. The association appeared to be particularly strong for baseline diameter (p for trend 0.003 and 0.0001 for AHI and hypoxemia index, respectively); interestingly, those in the top category of both AHI (30 or more per hour) and hypoxemia index (12% or more) had one of the highest mean baseline diameters (4.74 mm) of all the groupings in the table.

TABLE 1. ORDINAL (SPEARMAN) CORRELATION COEFFICIENTS BETWEEN MARKERS OF BRACHIAL ARTERY ENDOTHELIAL FUNCTION AND SELECTED VARIABLES

	Baseline Diameter	%FMD
Age	0.05	−0.02
BMI	0.13†	−0.10§
Total cholesterol	−0.21†	−0.02
HDL cholesterol	−0.33†	0.12†
Systolic blood pressure*	0.08	−0.02
Diastolic blood pressure*	0.11‡	0.01
Fasting glucose	0.25†	−0.06
Carotid intima-media thickness	0.16†	−0.12†
Ankle–arm index	0.15†	0.04
Left ventricular mass	0.55†	−0.22†
Apnea–hypopnea index	0.21†	−0.11†
Obstructive apnea index	0.20†	−0.11†
Central apnea index	0.15†	−0.04
Hypoxemia index	0.16†	−0.10§

Definition of abbreviations: BMI = body mass index; %FMD = percentage flow-mediated dilation; HDL = high-density lipoprotein.

* Among individuals not taking antihypertensive medications (n = 437).

† $p < 0.001$.

‡ $p < 0.05$.

§ $p < 0.01$.

As shown in Figure 1, with the exception of BMI, no other risk factor or clinical or subclinical measure of atherosclerosis appeared to confound the relationship between sleep apnea and baseline diameter to any meaningful degree. Adjustment for BMI consistently reduced the association between the brachial measurements and categories of AHI and hypoxemia index by 21% to 37% in comparison to the coefficients adjusted for only demographics. The associations of sleep apnea measures and %FMD seemed to be confounded by both BMI and serum cholesterol. Even after adjustment for BMI, a statistically significant association between baseline diameter and hypoxemia index was still present (increase in baseline diameter, 0.05 mm per unit increase in category of hypoxemia index, $p = 0.003$).

The demographics- and BMI-adjusted regression coefficients, both overall and after stratifying by sex, age, and hypertension status, are shown in Table 3. Associations tended to be stronger in women, participants younger than 80 years, and those with hypertension. Among subjects with hypertension, statistically significant linear associations between hypoxemia index and both baseline diameter ($p = 0.0014$) and %FMD ($p = 0.046$) were still present after adjustment for BMI in addition to demographic characteristics. The associations among women shown in Table 3 remained unchanged after excluding women taking estrogens (data not shown). Analyses in the group of individuals with hypertension were also conducted after excluding participants taking drugs that could potentially affect endothelial function (nitrates, calcium antagonists, angiotensin-converting enzyme inhibitors, β-blockers). In the remaining subgroup of 189 individuals with hypertension, associations for AHI were slightly weakened, whereas those for the hypoxemia index were slightly strengthened in comparison to those shown in Table 3 (data not shown).

The preceding results did not change in any meaningful way when the previously mentioned analyses were repeated using the obstructive apnea index; on the other hand, associations between endothelial measures and central apnea index were weaker than those presented here (results not shown).

DISCUSSION

To our knowledge, this is the first study showing that measures of sleep apnea are associated with indicators of vascular function (brachial artery baseline diameter and flow-mediated dilation) in a large community-based sample of generally healthy older individuals. Other than a partial confounding effect by BMI, results of this study appeared to be largely independent of other risk factors, particularly among younger individuals and subjects with hypertension (Table 3), and especially for baseline arterial diameter. Although stronger relationships were observed in analyses that did not adjust for BMI, it is unclear which sets of analyses may be most appropriate. Because sleep apnea may be one causal mechanism linking BMI and cardiovascular disease, adjusting for BMI may "overadjust" and mitigate biologically significant associations. Nonetheless, the reduction in the magnitude of the reported associations after BMI adjustment suggests the need for cautious interpretation of the extent to which sleep apnea is an independent risk factor for endothelial dysfunction.

Moreover, even though the associations were relatively weak, they were comparable in magnitude to those noted between these brachial artery measurements and other well-established cardiovascular risk factors. The associations between brachial artery ultrasound measures and cardiovascular risk factors in this study were weaker than those seen in previous studies. This could stem from (*1*) the advanced age of the study population

TABLE 2. ADJUSTED* MEAN LEVELS OF MARKERS OF ENDOTHELIAL FUNCTION ACCORDING TO CATEGORIES OF RISK FACTORS AND DISEASE STATUS

	Baseline Diameter			%FMD		
	Mean (%)	p (*ANOVA*)	p (*Trend*)	Mean (*mm*)	p (*ANOVA*)	p (*Trend*)
Sex						
Female	4.10			3.30		
Male	5.18	< 0.0001		2.60	< 0.0001	
Race						
White	4.53			3.11		
Black	4.81			2.43		
Other	4.26	0.0001		1.89	0.0001	
BMI						
< 25 kg/m^2	4.42			3.14		
25–29.9	4.60			2.98		
⩾ 30	4.73	< 0.0001	< 0.0001	2.79	0.06	0.02
Smoking						
Never	4.56			3.02		
Former	4.61			2.93		
Current	4.48	0.28	0.86	3.10	0.62	0.71
Hypertension						
No	4.49			3.23		
Yes	4.63	0.0006		2.83	0.0002	
Prevalent CHD						
No	4.53			3.06		
Yes	4.70	0.0003		2.80	0.028	
IMT 4th Quartile						
No	4.58			3.02		
Yes	4.58	0.96		2.92	0.47	
AAI 1st Quartile						
No	4.61			3.05		
Yes	4.54	0.14		2.83	0.08	
AHI (per hour)						
< 1.5	4.48			3.19		
1.5–4.9	4.57			3.07		
5.0–14.9	4.60			2.88		
15.0–29.9	4.61			2.82		
⩾ 30	4.74	0.039	0.003	2.89	0.20	0.026
Hypoxemia index (%)						
< 0.05	4.50			3.13		
0.05–0.49	4.48			3.17		
0.50–3.99	4.62			2.79		
4.00–11.9	4.73			2.87		
⩾ 12	4.74	0.0001	0.0001	2.84	0.041	0.015

Definition of abbreviations: AAI = ankle–arm index; AHI = apnea–hypopnea index; ANOVA = analysis of variance; BMI = body mass index; CHD = coronary heart disease; %FMD = percentage flow-mediated dilation; IMT = intima-media thickness.

* Adjusted for age, sex, and race.

resulting in smaller and a more restricted range of vasodilator responses and (*2*) more random variability in free-living healthy individuals than in clinical populations used in previous studies.

The association between brachial flow–mediated vasodilation and other measures of endothelial function in those with cardiovascular disease has been extensively reviewed (27). Impaired endothelial function, as measured by this and other techniques, is associated with cardiovascular risk factors and prevalent as well as incident cardiovascular disease (28–31). In addition, lipid-lowering and antihypertensive therapy, antioxidants, and hormone replacement are all known to have favorable effects on endothelial function (27).

Few reports have discussed the role of baseline brachial diameter as an additional metric of vascular health. One study found a small, nonstatistically significant difference in baseline brachial diameter in patients with coronary artery disease compared with control subjects (25), of remarkably similar relative and absolute magnitude to that seen in our study participants with and without prevalent coronary heart disease (4.7 and 4.5 mm, respectively). In another recent study among women undergoing angiographic examination (32), baseline brachial diameter, but not %FMD, was significantly associated with the presence of coronary artery disease. Others have reported that increases in carotid artery diameter are associated with cardiovascular risk factors (33). Increased baseline diameter may be the consequence of impaired endothelial production of endothelin and other autocrine or paracrine substances designed to maintain vascular tone (34). Thus, it is possible that baseline diameter might be an alternative indicator of endothelial function, perhaps more useful than %FMD in older populations, potentially explaining why we found more consistent associations between measures of sleep apnea with the former than with the latter measure. An alternative explanation for these findings is that baseline diameter, rather than a marker of endothelial dysfunction, is a marker of atherosclerosis and increased vascular stiffness (32), although this is not supported by the negligible change in the estimates after adjustment for ankle–arm index.

The association of endothelial function with sleep apnea observed in this study is consistent with previous studies in smaller samples of sleep apnea patients (5–8). They are also

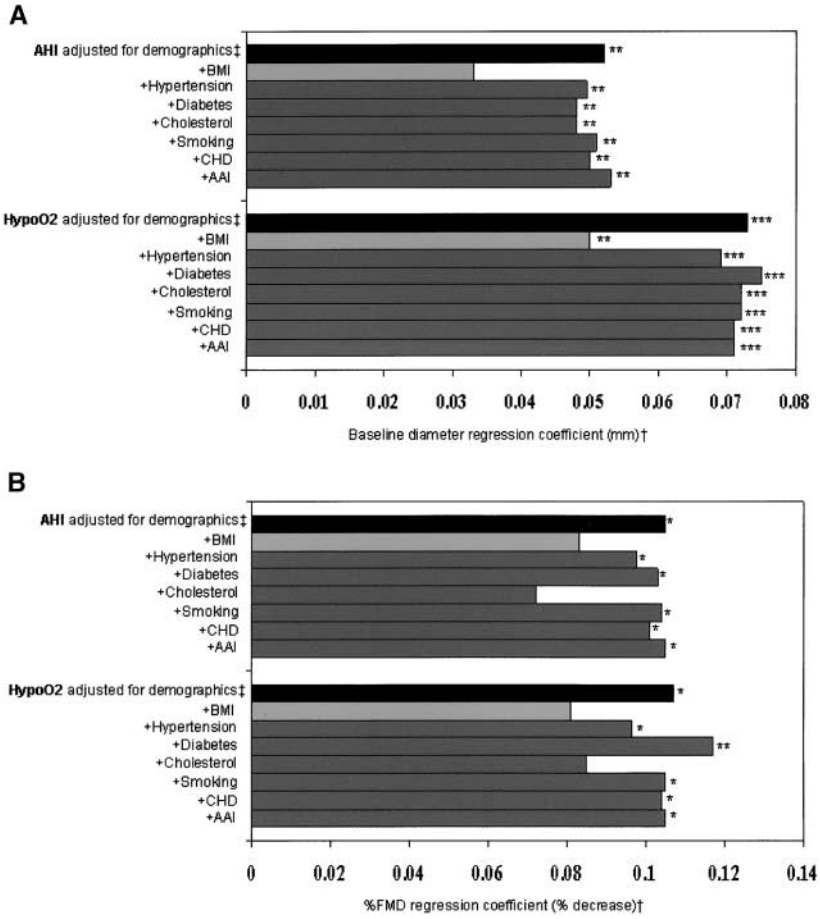

Figure 1. Linear regression analyses of the baseline diameter (*A*) and percentage flow-mediated dilation (%FMD) (*B*) in relationship to apnea–hypopnea index (AHI) or hypoxemia index, adjusted for demographic factors† and additional covariates. The *bars* in the figure represent the value of the regression coefficient, that is, the predicted increase in the dependent variable (baseline diameter or %FMD) per 1-unit increase in category of AHI or hypoxemia index,‡ after independently adding each of the variables to the model, including the demographic variables only. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. † Age (continuous), sex, and race. ‡ Categories of AHI and hypoxemia index as defined in Table 2. AAI = ankle–arm index; AHI = apnea–hypopnea index; BMI = body mass index; CHD = coronary heart disease.

consistent with studies showing an association of sleep apnea with other markers of endothelial dysfunction such as circulating levels of adhesion molecules (intercellular adhesion molecule-1, L-selectin) (35, 36), vascular endothelial growth factor (37), and how these changes improve after nasal continuous airway pressure therapy (36, 37). Sleep apnea patients have an increased expression of adhesion molecules and reactive oxygen species in leukocytes, effects that seem to be mediated by hypoxia and that can also be reversed by nasal continuous airway pressure therapy (38).

The hypothesis of a causal relationship between sleep apnea and endothelial dysfunction is pathophysiologically plausible and could explain in part the etiopathogenic role of sleep apnea in hypertension and cardiovascular disease. The fact that flow-mediated changes in brachial diameter was more strongly related to sleep apnea among those with hypertension is consistent with results from a previous study showing that endothelium-independent dilation (brachial artery reactivity following infusion of sodium nitroprusside, a vasodilator substance) was reduced among patients with hypertension but not among patients without hypertension (5). This suggests the possibility of more structural and permanent vascular changes in subjects with hypertension with sleep apnea.

TABLE 3. STRATIFIED ANALYSES: ADJUSTED* LINEAR REGRESSION COEFFICIENTS FOR MEASURES OF ENDOTHELIAL FUNCTION PER UNIT INCREASE IN CATEGORIES SLEEP APNEA MEASURES

		Baseline Diameter (*mm*)		%FMD	
	n	AHI	Hypoxemia Index	AHI	Hypoxemia Index
All	1,037	0.033	0.050†	−0.083	−0.081
Females	579	0.038	0.055‡	−0.115	−0.099
Males	458	0.022	0.035	−0.049	−0.062
Age					
< 80 yr	720	0.045	0.058†	−0.067	−0.082
⩾ 80 yr	317	0.007	0.029	−0.120	−0.055
Subjects without hypertension	400	0.019	0.013	−0.038	−0.003
Subjects with hypertension	637	0.036	0.064†	−0.095	−0.107‡

Definition of abbreviations: AHI = apnea–hypopnea index; %FMD = percentage flow-mediated dilation.
* Adjusted for age (continuous), sex, race, and BMI (continuous).
† $p < 0.01$.
‡ $p < 0.05$.

We speculate that the stronger association between sleep apnea measures and endothelial function in subjects with hypertension may be evidence that susceptibility to sleep apnea–mediated high blood pressure may vary in the population; those individuals who have both hypertension and elevated AHI levels may be those in whom sleep apnea induces endothelial dysfunction.

The putative association between sleep apnea and endothelial dysfunction could be explained by sleep-associated intermittent hypoxemia and reoxygenation associated with enhanced generation of superoxide free radicals, sympathetic nervous system stimulation, augmented systemic inflammation, or enhanced expression of adhesion molecules. These effects may reduce the availability of endothelial nitric oxide (39), a potent vasodilator, as well as enhance vascular shear stress and/or alter vascular tone and structure. In our data, as also shown by Kraiczi and colleagues (7), brachial reactivity was better correlated with a measure of hypoxemia than by the AHI, supporting the potential pathophysiologic role for hypoxemic stress.

As a limitation of this study, we were not able to measure non–endothelium-dependent vascular dilation (e.g., in response to nitroglycerin). The possibility of selection biases because of the volunteer character of the sample (surviving participants in an ongoing cohort study who agreed to undertake the brachial ultrasound and home PSG exams) needs to be considered as well. However, we consider it unlikely that these biases will affect the internal validity of the results (i.e., the association between sleep apnea and brachial ultrasound measures). Strengths of this study include its large sample size, the community-based character of our sample, the wealth of high-quality information on cardiovascular risk factors and disease status that allowed for effective control of potential confounders and modifiers (e.g., BMI, hypertension), and the standardized methods for brachial ultrasound and PSG measurements, both conducted by certified technicians and using centralized reading in core laboratories and subject to extensive quality control procedures.

In summary, these results are consistent with previous observational evidence, suggesting that sleep apnea–associated hypoxemia might be associated with endothelial dysfunction. These findings suggest potential mechanisms explaining the putative association between sleep-disordered breathing and hypertension and cardiovascular disease.

Conflict of Interest Statement: F.J.N. has no declared conflict of interest; D.M.H. has no declared conflict of interest; S.R. has no declared conflict of interest; E.J.B. has no declared conflict of interest; J.A.R. has no declared conflict of interest.

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References

1. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study: Sleep Heart Health Study. *JAMA* 2000;283:1829–1836.
2. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378–1384.
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002; 165:1217–1239.
4. Bonsignore MR, Marrone O, Insalaco G, Bonsignore G. The cardiovascular effects of obstructive sleep apnoeas: analysis of pathogenic mechanisms. *Eur Respir J* 1994;7:786–805.
5. Carlson JT, Rangemark C, Hedner JA. Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. *J Hypertens* 1996; 14:577–584.
6. Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, Somers VK. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000;102:2607–2610.
7. Kraiczi H, Caidahl K, Samuelsson A, Peker Y, Hedner J. Impairment of vascular endothelial function and left ventricular filling: association with the severity of apnea-induced hypoxemia during sleep. *Chest* 2001; 119:1085–1091.
8. Imadojemu VA, Gleeson K, Quraishi SA, Kunselman AR, Sinoway LI, Leuenberger UA. Impaired vasodilator responses in obstructive sleep apnea are improved with continuous positive airway pressure therapy. *Am J Respir Crit Care Med* 2002;165:950–953.
9. Nieto FJ, Herrington DM, Robbins JA, O'Connor GT, Redline S. Sleep apnea and endothelial function in a large community-based sample of elderly adults. American Heart Association EPI Asia Pacific; 2002. Available from http://aha.agora.com/abstractviewer/default.asp.
10. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, *et al.* The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991; 1:263–276.
11. Tell GS, Fried LP, Hermanson B, Manolio TA, Newman AB, Borhani NO. Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. *Ann Epidemiol* 1993;3:358–366.
12. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, Wolfson SK. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study: Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation* 1993;88:837–845.
13. Kuller L, Borhani N, Furberg C, Gardin J, Manolio T, O'Leary D, Psaty B, Robbins J. Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. *Am J Epidemiol* 1994;139:1164–1179.
14. O'Leary DH, Polak JF, Wolfson SK Jr, Bond MG, Bommer W, Sheth S, Psaty BM, Sharrett AR, Manolio TA. Use of sonography to evaluate carotid atherosclerosis in the elderly: the Cardiovascular Health Study: CHS Collaborative Research Group. *Stroke* 1991;22:1155–1163.
15. Herrington DM, Werbel BL, Riley WA, Pusser BE, Morgan TM. Individual and combined effects of estrogen/progestin therapy and lovastatin on lipids and flow-mediated vasodilation in postmenopausal women with coronary artery disease. *J Am Coll Cardiol* 1999;33:2030–2037.
16. Herrington DM, Fan L, Drum M, Riley WA, Pusser BE, Crouse JR, Burke GL, McBurnie MA, Morgan TM, Espeland MA. Brachial flow-mediated vasodilator responses in population-based research: methods, reproducibility and effects of age, gender and baseline diameter. *J Cardiovasc Risk* 2001;8:319–328.
17. Herrington DM, Espeland MA, Crouse JR III, Robertson J, Riley WA, McBurnie MA, Burke GL. Estrogen replacement and brachial artery flow-mediated vasodilation in older women. *Arterioscler Thromb Vasc Biol* 2001;21:1955–1961.
18. Quan SF, Howard BV, Iber C, Nieto FJ, Rapoport DM, Redline S, Sanders M, Young T, Sleep Heart Health Study (SHHS) Research Group. The Sleep Heart Health Study: design, rationale, and methods. *Sleep* 1997;20:1077–1085.
19. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study: the Cardiovascular Health Study Collaborative Research Group. *J Clin Epidemiol* 1992;45:683–692.
20. Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smith PL, Kiley JP. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study: Sleep Heart Health Research Group. *Sleep* 1998;21:759–767.
21. Howard G, Manolio TA, Burke GL, Wolfson SK, O'Leary DH. Does the association of risk factors and atherosclerosis change with age? An analysis of the combined ARIC and CHS cohorts: the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) investigators. *Stroke* 1997;28:1693–1701.
22. Redline S, Kapur VK, Sanders MH, Quan SF, Gottlieb DJ, Rapoport DM, Bonekat WH, Smith PL, Kiley JP, Iber C. Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. *Am J Respir Crit Care Med* 2000;161:369–374.
23. Whitney CW, Gottlieb DJ, Redline S, Norman RG, Dodge RR, Shahar E, Surovec S, Nieto FJ. Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep* 1998;21:749–757.
24. Quan SF, Griswold ME, Iber C, Nieto FJ, Rapoport DM, Redline S, Sanders M, Young T, Sleep Heart Health Study (SHHS) Research

Group. Short-term variability of respiratory and sleep during unattended non-laboratory polysomnography: the Sleep Heart Health Study. *Sleep* 2002;25:843–848.
25. Schroeder S, Enderle MD, Ossen R, Meisner C, Baumbach A, Pfohl M, Herdeg C, Oberhoff M, Haering HU, Karsch KR. Noninvasive determination of endothelium-mediated vasodilation as a screening test for coronary artery disease: pilot study to assess the predictive value in comparison with angina pectoris, exercise electrocardiography, and myocardial perfusion imaging. *Am Heart J* 1999;138:731–739.
26. Lieberman EH, Gerhard MD, Uehata A, Walsh BW, Selwyn AP, Ganz P, Yeung AC, Creager MA. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann Intern Med* 1994;121:936–941.
27. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, *et al.* Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;39:257–265.
28. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;340:1111–1115.
29. Corretti MC, Plotnick GD, Vogel RA. Technical aspects of evaluating brachial artery vasodilatation using high-frequency ultrasound. *Am J Physiol* 1995;268:H1397–H1404.
30. Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, Deanfield JE. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993;88:2149–2155.
31. Heitzer T, Yla-Herttuala S, Luoma J, Kurz S, Munzel T, Just H, Olschewski M, Drexler H. Cigarette smoking potentiates endothelial dysfunction of forearm resistance vessels in patients with hypercholesterolemia: role of oxidized LDL. *Circulation* 1996;93:1346–1353.
32. Holubkov R, Karas RH, Pepine CJ, Rickens CR, Reichek N, Rogers WJ, Sharaf BL, Sopko G, Merz CN, Kelsey SF, *et al.* Large brachial artery diameter is associated with angiographic coronary artery disease in women. *Am Heart J* 2002;143:802–807.
33. Crouse JR, Goldbourt U, Evans G, Pinsky J, Sharrett AR, Sorlie P, Riley W, Heiss G. Risk factors and segment-specific carotid arterial enlargement in the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke* 1996;27:69–75.
34. Mathew V, Hasdai D, Lerman A. The role of endothelin in coronary atherosclerosis. *Mayo Clin Proc* 1996;71:769–777.
35. Ohga E, Nagase T, Tomita T, Teramoto S, Matsuse T, Katayama H, Ouchi Y. Increased levels of circulating ICAM-1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. *J Appl Physiol* 1999; 87:10–14.
36. Chin K, Nakamura T, Shimizu K, Mishima M, Miyasaka M, Ohi M. Effects of nasal continuous positive airway pressure on soluble cell adhesion molecules in patients with obstructive sleep apnea syndrome. *Am J Med* 2000;109:562–567.
37. Lavie L, Kraiczi H, Hefetz A, Ghandour H, Perelman A, Hedner J, Lavie P. Plasma vascular endothelial growth factor in sleep apnea syndrome: effects of nasal continuous positive air pressure treatment. *Am J Respir Crit Care Med* 2002;165:1624–1628.
38. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med* 2002;165:934–939.
39. Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC, Lam WK. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2000;162:2166–2171.