Published in final edited form as:

Sleep Med. 2016 March ; 19: 69–74. doi:10.1016/j.sleep.2015.11.009.

The association between sleep-disordered breathing and aortic stiffness in a community cohort

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Abstract

Background—Sleep-disordered breathing is associated with hypertension and cardiovascular disease. Increased aortic stiffness is one possible linking mechanism. We evaluated the association between sleep-disordered breathing and aortic stiffness in a community-based sample.

Methods—Our community-based cross-sectional observational study included 381 participants from the Framingham Heart Study (55% women, mean age 58.0 S.D.=9.4 years, 51% ethnic minorities). Polysomnographically derived apnea–hypopnea index and CT90% (cumulative % sleep time with oxyhemoglobin saturation <90%) quantified sleep-disordered breathing severity. Carotid-femoral pulse wave velocity, the gold-standard measure of aortic stiffness, was calculated using arterial applanation tonometry-derived waveforms and body surface measured transit distance. We assessed associations between sleep-disordered breathing and carotid-femoral pulse wave velocity using multivariable regression. We adjusted for age, sex, race, body mass index, diabetes, alcohol consumption, hormone replacement therapy, cholesterol/high-density lipoprotein,

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Conflicts of Interest: RSV, MGL and DJG reported no conflicts of interest related to this work.

lipid-lowering therapy, anti-hypertensive medication, smoking, hypertension, and prevalent cardiovascular disease.

Results—After multivariable adjustment, carotid-femoral pulse wave velocity was associated with both apnea–hypopnea index ($\beta = 0.03$, 95% CI: 0.002–0.07, $p = 0.04$) and CT90% ($\beta = 0.05$, 95% CI: 0.005–0.1, $p = 0.03$). The adjusted mean carotid-femoral pulse wave velocity was 9.43 (95% CI: 9.12–9.74), 9.76 (95% CI: 9.25–10.26), and 10.15 (95% CI: 9.37–10.92) m/s, respectively, in subjects with apnea–hypopnea index <5, 5–14.9, and ≥ 15 events/h.

Conclusions—In a community-based sample of middle aged and older men and women, sleep-disordered breathing was associated with increased carotid-femoral pulse wave velocity, a strong predictor of cardiovascular risk.

Keywords

Aortic stiffness; Sleep apnea; Epidemiology

1. Introduction

Sleep-disordered breathing (SDB) is associated with hypertension [1] and cardiovascular disease, including coronary artery disease [2], and stroke [3]. Multiple mechanisms linking SDB and cardiovascular disease have been proposed. Increased aortic stiffness is one possible mechanism. Increased aortic stiffness may precede the onset of systemic hypertension [4], and is a marker of subclinical atherosclerosis [5], coronary artery disease [6], and a strong predictor of cardiovascular risk in multiple populations [7–14].

Relative wave reflection as measured by the augmentation index has been found to increase acutely during apnea [15]. The association of SDB with measures of aortic stiffness has been evaluated in multiple small-clinic-based studies [16–25] that predominantly included men, and only two community-based studies [26,27]. SDB was associated with increased augmentation index [16,17] and carotid femoral pulse wave velocity (CFPWV) [20–22] in clinic-based studies, and both measures decreased with continuous positive airway pressure (CPAP) therapy [18,19,23,24]. However, in community-based studies, the association of SDB with augmentation index was demonstrated in men only [26], whereas the association of SDB with CFPWV was not replicated [27].

In the present study we primarily examined the cross-sectional associations of SDB with aortic stiffness, as assessed by the gold standard measure CFPWV, a predictor of hypertension [4] and cardiovascular risk [7–14], in a larger sample from the community-based Framingham Heart Study. We also explored the association of SDB with other hemodynamic measures including forward wave amplitude, and wave reflection, assessed by augmentation index. We hypothesize that SDB is associated with increased CFPWV, accounting for other risk factors.

2. Material and methods

2.1. Sample

The study sample included Framingham Heart Study Offspring and Omni (multiethnic) cohort participants who underwent polysomnography as part of the Sleep Heart Health Study (SHHS). The design of the Framingham Heart Study Offspring and Omni cohorts and the SHHS have been described [28,29]. Of 2640 participants in the Framingham Heart Study who had tonometry between 1998 and 2001, 407 had polysomnography data. Twenty-six participants were excluded for smoking within 6 h before undergoing tonometry, resulting in 381 participants for the main analysis. Included participants were less likely to smoke and were primarily Caucasians otherwise there were no systematic differences in the characteristics of included participants and those who were excluded (characteristics given in Supplementary Material). Participants signed informed consent. The Framingham Heart Study and SHHS were approved by the Boston University Medical Center Institutional Review Board (respective approval numbers H32132 and H22384).

2.2. Polysomnography

Participants underwent home-based polysomnography using previously published SHHS methods, scoring guidelines, and quality-assurance procedures [29–31]. Apnea–hypopnea index (AHI) was calculated as the number of apneas plus hypopneas per hour of sleep. The scoring of SDB events was based on the requirement of a 4% or greater decrease in oxyhemoglobin saturation. The CT90% was calculated as cumulative per cent sleep time spent at saturation less than 90%. The high reliability of the AHI and sleep stage scoring in the SHHS was previously reported [31,32].

2.3. Tonometry

Participants underwent tonometry as described in previously published methods [33]. Briefly, tonometry was obtained from brachial, carotid, femoral, and radial arteries using the SPT-301 tonometer (Millar Instruments, Houston, Texas) with simultaneous electrocardiography. Tracings were obtained in the supine position after 5 min of rest. Transit distances were assessed by body surface measurements from the suprasternal notch to each pulse-recording site. Supine brachial systolic and diastolic blood pressures were obtained using an oscillometric device (Dinamap, Critikon Inc, Tampa, FL, USA). The digitized tonometry data were analyzed in a core laboratory (Cardiovascular Engineering, Inc, Norwood, MA) blinded to all clinical data. CFPWV, forward wave pressure amplitude, augmentation index, and mean arterial pressure were calculated using previously described methods [34]. CFPWV was used as a measure of distal aortic stiffness whereas forward wave amplitude was used as a measure of proximal aortic stiffness. Augmentation index, which represents the percentage of the central pressure waveform amplitude (central pulse pressure) that is attributable to late pressure augmentation, was used as a measure of relative wave reflection. Finally, mean arterial pressure was used as a measure of steady-flow load on the heart and arteries.

2.4. Statistical analyses

Descriptive statistics of the study sample are presented stratified by clinical sleep apnea categories of AHI <5, 5–14.9, and ≥15 events/h. AHI was the main exposure variable; hypoxemia index and arousal index were also examined. CFPWV, the gold standard measure of aortic stiffness, was the a priori primary dependent variable. Other hemodynamic measures were assessed in secondary exploratory analyses including forward wave amplitude, augmentation index, and mean arterial pressure.

Multiple regression analysis (PROC REG and GLM in SAS 9.1 SAS Institute Inc. Cary, NC, USA) was used to evaluate the association of aortic stiffness and other hemodynamic measures with measures of SDB (AHI or CT90%) and with the arousal index. AHI and CT90% were treated as continuous variables in the main analysis and as categorical variables in alternative analyses for the purpose of presentation. For AHI we used the common clinical categories <5, 5–15, and >15 events per hour. For CT90% we used the categories <0.4%, 0.4–4%, and >4% of sleep time to approximate the frequency distribution of AHI clinical categories. To verify the robustness of the regression models, measures of CFPWV were transformed in alternative analyses to ensure near-normal distribution of the dependent variables using the formula: transformed CFPWV = $-1000/\text{CFPWV}$. Other hemodynamic measures were transformed using a natural logarithm. For ease of interpretation, we present the results of analyses performed without transformation.

Analyses were adjusted for age, sex, and race (defined as White, Black, Asian, and Hispanic) in the ‘demographic’ model. The multivariable model further adjusted for body-mass index (BMI), hormone replacement therapy, alcohol consumption, smoking, prevalent diabetes, total cholesterol/high-density lipoprotein ratio, lipid-lowering and anti-hypertensive therapy. The multivariable-cardiovascular disease model further adjusted for prevalent hypertension and cardiovascular disease, including coronary heart disease, heart failure, stroke, transient ischemic attacks, and claudication, which are conditions associated with both SDB and aortic stiffness.

To explore potential pathways mediating the association of SDB and aortic stiffness, models further adjusted for heart rate obtained during tonometry as a measure of sympathetic activation. Analyses were stratified by sex and age group (above/below median) and effect modification by these variables was tested by adding interaction terms to the regression models. Results with two-sided *p*-value <0.05 were considered statistically significant.

3. Results

Characteristics of the study sample are presented in Table 1 stratified by AHI categories. The severity of SDB in this sample was mild with a median AHI of 2.6 events/h (25th and 75th percentiles 0.6, 7.9). Sixty-six per cent of participants had AHI <5 and 11% of participants had AHI ≥15 events/h. On average, participants with more severe SDB were older, heavier, and more likely to be men, report antihypertensive therapy use, and to have hypertension, diabetes, and cardiovascular disease.

CFPWV was significantly associated with AHI in models that adjusted for demographic variables (Table 2). The association was attenuated with further adjustment for potential confounders including BMI but remained statistically significant (Table 2, Models 2–4). Findings were similar in analyses using hypoxemia index as a measure of SDB (Table 2). The associations of CFPWV with AHI and CT90% were significantly attenuated and became statistically non-significant in models further adjusting for heart rate ($\beta = 0.02$ 95% CI, -0.01 to 0.05 , $p = 0.13$ and $\beta = 0.04$ 95% CI, -0.08 to 0.08 , $p = 0.14$, respectively). There was no association between arousal index and CFPWV in any model (Table 2). Results were similar in analyses using transformed CFPWV.

In analyses that treated AHI and CT90% as categorical variables, CFPWV was progressively higher in categories with increased SDB severity (Figs 1 and 2). Formal test of interaction was significant for median age with AHI (older*AHI, $\beta = -0.09$ 95% CI -0.16 to -0.02 , $p = 0.007$; older = 1 if age > 57 years) but not for sex with AHI (sex*AHI $\beta = 0.019$ 95% CI -0.04 to 0.08 , $p = 0.55$). In analyses stratified by median age the association was observed in individuals younger than the median age of 57 years (Table 3). There was no association between AHI or CT90% and other hemodynamic measures (Table 4).

4. Discussion

In our community-based study, aortic stiffness as measured by CFPWV was associated with measures of SDB after adjustment for multiple potential confounders including age, sex, race BMI, hormone replacement therapy, alcohol consumption, smoking, diabetes, cholesterol, lipid lowering, anti-hypertensive therapy, hypertension, and cardiovascular disease. This finding is clinically relevant, as increased CFPWV is a precursor of future hypertension [4], and is associated with increased cardiovascular risk after adjusting for blood pressure and multiple other cardiovascular risk factors in multiple populations [7–14]. Furthermore, arterial stiffening increases left ventricular load and is associated with impaired cardiac systolic and diastolic function [35–37].

The difference of approximately 0.8 m/s in adjusted CFPWV between individuals with moderate-to-severe SDB and those with no SDB (Fig. 1) is nearly identical to the previously reported difference in CFPWV between smokers and non-smokers [38], and to the difference in CFPWV associated with a 10-year age difference [39]. Furthermore a 1-m/s increase in CFPWV was associated with a 14% increase in age, sex and risk factors adjusted cardiovascular event risk and a 15% increase in adjusted mortality [13].

To our knowledge, this is the first community-based study that demonstrates an association between SDB and CFPWV. Multiple prior clinic-based studies have shown an association between SDB and CFPWV [20–23,40], including a small randomized controlled trial and a meta-analysis of two trials that reported improved CFPWV with CPAP therapy [23,24]. While this trial suggests a causal association between SDB and aortic stiffness [23], the trial only included men with severe SDB. Another small randomized controlled trial that included individuals with moderate and severe SDB free of cardiovascular disease did not show a significant improvement in CFPWV with CPAP therapy [25]. In contrast to these clinic-based studies, the severity of SDB in our community-based sample is rather mild, and

our sample was multiethnic and included similar numbers of men and women, thereby extending the findings of clinic-based studies to the severity of SDB observed in the community in both men and women. A prior report from the smaller community-based Wisconsin Sleep Cohort ($N=153$) did not demonstrate such an association, possibly due to a smaller sample size [27].

We noted significant effect modification by age and in subgroup analyses, the association of SDB with aortic stiffness was primarily observed in younger participants. Although it is possible that age may influence the association of SDB and aortic stiffness, as it is an important determinant of aortic stiffness [39], the lack of association in older participants may be due to the smaller sample size. Alternatively, the comorbidities present in the older participants, including hypertension, diabetes and cardiovascular disease, may render it challenging to discern any potential association between mild SDB and aortic stiffness in older participants.

Multiple mechanisms may mediate the association of SDB and aortic stiffness, including sympathetic activation with baroreflex adaptation [41]. The lack of association between SDB and aortic stiffness in models adjusting for heart rate, a measure of sympathetic activation, is consistent with mediation of the effect of SDB on aortic stiffness by sympathetic activation. It has been demonstrated that apneas are associated with repetitive increases in vascular tone, occurring prior to blood pressure increase or electroencephalographic arousal [12]. These repetitive increases in vascular tone might lead to vascular remodeling and therefore to persistently increased vascular tone during wakefulness. In the present study, aortic stiffness was associated with hypoxemia index but not with arousal index, suggesting that hypoxia rather than arousal may mediate the association of SDB with aortic stiffness. Reduced levels of nitric oxide have been found in patients with SDB, which could lead to impaired vascular relaxation [42].

Furthermore recurrent hypoxemia is associated with markers of vascular inflammation [43,44], which have also been associated with increased vascular stiffness [45], likely bi-directionally. Finally, the negative intra-thoracic pressures generated by the attempts to breath against an obstructed upper airway during obstructive apneas, subject the thoracic aorta to dilatory forces [46] and stretches and thins the fixed pool of aortic wall elastin, which would stiffen the aortic wall [47].

This epidemiologic study has several limitations. Although the association between SDB and aortic stiffness is biologically plausible, the cross-sectional design does not allow us to draw firm conclusions on whether the association is causal, or on the direction of the association. Furthermore, we cannot exclude the possibility of residual confounding. In addition, tonometry was performed a median of 2.4 years (range 1.2–4.8 years) after polysomnography, raising concerns about interim changes in both the sleep and the tonometry measures. However, the stability of the AHI was previously documented in the SHHS participants over a 5-year follow-up period and only 1.5% of the SHHS participant received CPAP therapy [48]. It is therefore unlikely that interim changes in AHI or CPAP therapy would cause substantial misclassification, which would in any case bias us toward the null hypothesis. Our sample was moderate in size, and we tested several exposures and

dependent measures, raising the issue of multiple statistical testing; therefore, we cannot exclude the possibility of both false positive and false negative findings, although CFPWV, the gold standard measure of aortic stiffness, was chosen a priori as the primary dependent variable. Balancing these limitations are several strengths including the well-characterized community-based sample selected independent of risk factors for SDB or cardiovascular disease and the standardized polysomnography and aortic stiffness assessments following strict protocols and rigorous quality control measures.

5. Conclusions

In a community-based sample, AHI was associated with CFPWV, the gold-standard measure of aortic stiffness and an important predictor of cardiovascular risk. Our data support the hypothesis that SDB at a severity present in the community is associated with aortic stiffness. Numerous prior studies [7–11] and two meta-analyses [13–14] have shown that higher CFPWV is strongly associated with risk for future cardiovascular disease events. In addition, a genome-wide association study has shown that the lead genetic variant associated with higher CFPWV is also associated with higher risk for incident coronary heart disease and heart failure, consistent with the notion that CFPWV represents a true risk factor for incident cardiovascular disease [49]. Whether and to what extent aortic stiffness contributes to cardiovascular risk in individuals with SDB merits further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Sleep Heart Health Study (SHHS) acknowledges the Atherosclerosis Risk In Communities Study, the Cardiovascular Health Study, the Framingham Heart Study, the Cornell/Mt. Sinai Worksite and Hypertension Studies, the Strong Heart Study, the Tucson Epidemiologic Study of Airways Obstructive Diseases, and the Tucson Health and Environment Study for allowing their cohort members to be part of the SHHS and for permitting data acquired by them to be used in the study. SHHS is particularly grateful to the members of these cohorts who agreed to participate in SHHS as well. SHHS further recognizes all of the investigators and staff who have contributed to its success. A list of SHHS investigators, staff, and their participating institutions is available on the SHHS website (www.jhuccr.com/shhs).

This work was supported by the NHLBI, Framingham Heart Study, (NHLBI/NIH Contract HHSN268201500001I; N01-HC-25195) 1R01HL60040, 1R01HL70100 and the Boston University School of Medicine and by HL076784, G028321, HL070100, HL060040, HL080124, HL071039, HL077447, HL107385, and 2-K24-HL04334. It was also supported by the SHHS cooperative agreements U01HL53940 (University of Washington), U01HL53941 (Boston University), U01HL53938 (University of Arizona), U01HL53916 (University of California, Davis), U01HL53934 (University of Minnesota), U01HL53931 (New York University), U01HL53937 and U01HL64360 (Johns Hopkins University), U01HL63463 (Case Western Reserve University), and U01HL63429 (Missouri Breaks Research).

GFM is owner of Cardiovascular Engineering, Inc., a company that develops and manufactures devices to measure vascular stiffness, serves as a consultant to and receives honoraria from Novartis, Merck, and Servier, and is funded by research grants HL107385 and HL104184 from the National Institutes of Health. EJB is funded by research grants related to this work N01-HC 25195; 1HL60040 and 1HL70100 from the National Institutes of Health. HAC is funded by investigator initiated research grants unrelated to this work by Pfizer and Astra Zeneca.

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Highlights

- Sleep-disordered breathing in the community is linked to increased aortic stiffness.
- Aortic stiffness is a strong predictor of cardiovascular risk.
- The association persisted after adjustment for multiple potential cofounders.

Fig. 1.

Mean adjusted carotid-femoral pulse wave velocity (CFPMV) by apnea-hypopnea index (AHI) category. Demographic model: Adjusts for age, sex and race. Multivariable model: further adjusts for body mass index, hormone-replacement therapy, alcohol consumption, cigarette smoking, total serum cholesterol/high-density lipoprotein ratio, diabetes, and lipid-lowering and antihypertensive therapy. Multivariable + CVD model further adjusts for prevalent hypertension and cardiovascular disease (coronary heart disease, congestive heart failure, stroke, transient ischemic attacks, and claudication).

Fig. 2. Mean adjusted carotid-femoral pulse wave velocity (CFPMV) by hypoxemia index category. Demographic model: adjusts for age, sex and race. Multivariable model: further adjusts for body mass index, hormone-replacement therapy, alcohol consumption, cigarette smoking, total serum cholesterol/high-density lipoprotein ratio, diabetes, and lipid-lowering and antihypertensive therapy. Multivariable + CVD model further adjusts for prevalent hypertension and cardiovascular disease (coronary heart disease, congestive heart failure, stroke, transient ischemic attacks and claudication).

Table 1

Characteristics of the study sample.

Clinical characteristics	AHI <5 (N=247, 66%)	AHI 5–14.9 (N=93, 24%)	AHI 15 (N=41, 11%)
Women, %	65	41	32
Age years, mean (SD)	56.5 (9.1)	59.6 (9.5)	62.8 (9.0)
Race %			
White	45	58	51
Black	17	11	22
Hispanic	27	23	22
Asian	11	8	5
Body mass index (kg/m ²), mean (SD)	26.8 (4.4)	28.9 (4.4)	31.3 (6.5)
Alcohol drinks/week mean (SD)	3.2 (5.7)	3.6 (5.7)	4.4 (7.5)
Heart rate (b.p.m.), mean (SD)	62 (10)	64 (9)	65 (10)
Serum cholesterol (mg/dl), mean (SD)	198 (40)	199 (40)	201 (33)
Total cholesterol/high-density lipoprotein ratio, mean (SD)	3.9 (1.4)	4.4 (1.4)	4.7 (1.4)
Smoker %	6	2	2
Hypertension %	39	40	71
Antihypertensive therapy %	26	24	46
Cardiovascular diseases%	11	10	17
Diabetes %	11	17	27
Lipid-lowering therapy %	13	24	22
Hormone replacement, % of females	29	24	31
Sleep characteristics			
Apnea–hypopnea index events per hour, median (25–75%)	1.0 (0.3–2.4)	8.2 (6.6–11.3)	22.5 (18.3–28.7)
% Time with oxygen saturation <90%, median (25–75%)	0.0 (0–0.7)	0.5 (0.1–1.5)	3.3 (1.9–9.5)
Arousal index events/h, median (25–75%)	13.3 (9.7–17.8)	17.3 (13.6–21.9)	23.4 (14.5–29.4)

Table 2

The association of carotid-femoral pulse wave velocity and sleep-disordered breathing.

	Carotid-femoral pulse wave velocity β (95% CI) <i>p</i> -value		
	Demographic- adjusted model	Multivariable- adjusted model	Multivariable + CVD adjusted model
Apnea– hypopnea index (<i>N</i> =381)	$\beta=0.062$ (0.031–0.093) <i>p</i> =0.0001	$\beta=0.035$ (0.002–0.067) <i>p</i> =0.04	$\beta=0.035$ (0.003–0.067) <i>p</i> =0.03
Hypoxemia index (<i>N</i> =381)	$\beta=0.084$ (0.038–0.13) <i>p</i> =0.0004	$\beta=0.052$ (0.006–0.098) <i>p</i> =0.03	$\beta=0.056$ (0.01–0.10) <i>p</i> =0.01
Arousal index (<i>N</i> =378)	$\beta=0.006$ (–0.024–0.038) <i>p</i> =0.68	$\beta=0.002$ (–0.028–0.032) <i>p</i> =0.89	$\beta=0.003$ (–0.026–0.033) <i>p</i> =0.82

Demographic model: adjusts for age, sex and race. Multivariable model: further adjusts for body mass index, hormone-replacement therapy, alcohol consumption, cigarette smoking, total serum cholesterol/high-density lipoprotein, diabetes, and lipid-lowering and antihypertensive therapy.

Multivariable + CVD model: further adjusts for prevalent hypertension and cardiovascular disease (coronary heart disease, congestive heart failure, stroke, transient ischemic attacks, and claudication).

Table 3

The association of carotid-femoral pulse wave velocity and sleep-disordered breathing stratified by age group (below/above median age).

	Apnea–hypopnea index β (95% CI) <i>p</i> -value		Hypoxemia index β (95% CI) <i>p</i> -value	
	Age<57years <i>N</i> =188	Age ≥57years <i>N</i> =188	Age<57years <i>N</i> =188	Age ≥57years <i>N</i> =188
Demographic-adjusted model	$\beta=0.12$ (0.08–0.2) <i>p</i> <0.0001	$\beta=0.05$ (0.01–0.10) <i>p</i> =0.02	$\beta=0.13$ (0.05–0.2) <i>p</i> =0.0008	$\beta=0.07$ (0.006–0.13) <i>p</i> =0.03
Multivariable adjusted model	$\beta=0.08$ (0.03–0.14) <i>p</i> =0.001	$\beta=0.03$ (–0.01–0.07) <i>p</i> =0.20	$\beta=0.06$ (–0.01–0.13) <i>p</i> =0.11	$\beta=0.04$ (–0.02–0.10) <i>p</i> =0.22
Multivariable + CVD adjusted model	$\beta=0.09$ (0.04–0.14) <i>p</i> =0.0002	$\beta=0.03$ (–0.01–0.07) <i>p</i> =0.19	$\beta=0.07$ (–0.004–0.14) <i>p</i> =0.062	$\beta=0.17$ (–0.02–0.1) <i>p</i> =0.17

Demographic model: adjusts for age, sex and race. Multivariable model: further adjusts for body mass index, hormone-replacement therapy, alcohol consumption, cigarette smoking, total serum cholesterol/high-density lipoprotein ratio, diabetes, and lipid lowering and antihypertensive therapy. Multivariable + CVD model: further adjusts for prevalent hypertension and cardiovascular disease (coronary heart disease, congestive heart failure, stroke, transient ischemic attacks, and claudication).

Table 4

The association of sleep-disordered breathing with other hemodynamic measures.

	AHI β (95% CI) <i>p</i> -value		Hypoxemia index β (95% CI) <i>p</i> -value	
	Demographic-adjusted model	Multivariable-adjusted model	Demographic-adjusted model	Multivariable-adjusted model
Forward wave Amplitude (<i>N</i> =377)	β =0.03 (-0.11–0.18) <i>p</i> =0.65	β =-0.013 (-0.17–0.14) <i>p</i> =0.87	β =0.23 (0.01–0.44) <i>p</i> =0.04	β =0.14 (-0.08–0.36) <i>p</i> =0.22
Augmentation index [*] (<i>N</i> =377)	β =0.050 (-0.08–0.18) <i>p</i> =0.47	β =0.10 (-0.04–0.24) <i>p</i> =0.17	β =-0.003 (-0.015–0.008) <i>p</i> =0.58	β =-0.002 (-0.01–0.01) <i>p</i> =0.77
Mean arterial Pressure (<i>N</i> =377)	β =0.19 (0.05–0.3) <i>p</i> =0.071	β =0.11 (-0.04–0.25) <i>p</i> =0.14	β =0.21 (0.002–0.42) <i>p</i> =0.04	β =0.12 (-0.09–0.33) <i>p</i> =0.25

Demographic model: adjusts for age and race. Multivariable model: further adjusts for body mass index, hormone-replacement therapy, alcohol consumption, cigarette smoking, total serum cholesterol/high-density lipoprotein ratio, diabetes, and lipid-lowering and antihypertensive therapy.

^{*} Both models further adjusted for resting heart rate.