Sleep Medicine 19 (2016) 69–74

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

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

Hassan A. Chami [a,b,*], Ramachandran S. Vasan [c,d], Martin G. Larson [e,f], Emelia J. Benjamin [c,d], Gary F. Mitchell [g], Daniel J. Gottlieb [h,i]

[a] Department of Medicine, American University of Beirut, Beirut, Lebanon
[b] The Pulmonary Center, Boston University School of Medicine, Boston, MA, USA
[c] Sections of Cardiovascular and Preventive Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA, USA
[d] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
[e] Department of Mathematics and Statistics, Boston University, Boston, MA, USA
[f] Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA
[g] Cardiovascular Engineering, Inc., Norwood, MA, USA
[h] VA Boston Healthcare System, Boston, MA, USA
[i] Departments of Medicine and Neurology, Brigham & Women's Hospital, Division of Sleep Medicine, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 24 August 2015
Received in revised form 20 October 2015
Accepted 12 November 2015
Available online 27 November 2015

Keywords:
Aortic stiffness
Sleep apnea
Epidemiology

ABSTRACT

Objective: 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, 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.

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

* Corresponding author. American University of Beirut, PO Box 11-0236 Riad El Solh, Beirut, Lebanon. Tel.: +961 1350000; fax: +961 1370814.
E-mail address: hchami@aub.edu.lb (H.A. Chami).

http://dx.doi.org/10.1016/j.sleep.2015.11.009
1389-9457/

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 CFWPV, 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 the 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, 5–14.9, and ≥15 events per hour. For CT90% we used the categories <0.4%, 0.4–3.9%, 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/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