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Correlates of Endothelial Function in Older Adults with Untreated Obstructive Sleep Apnea and Cardiovascular Disease

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Abstract

Background: Obstructive sleep apnea (OSA) is a highly prevalent and consequential sleep disorder in older adults. Untreated moderate to severe OSA substantially increases the risk for hypertension and cardiovascular disease (CVD), which can be attributed to the accelerated progression of atherosclerosis and endothelial dysfunction.

Objective: The aim of this study was to identify factors that can function as correlates of endothelial function in older adults with untreated, moderate to severe OSA and CVD or CVD risk factors.

Methods: A subsample (N = 126) of adults aged 65 years and older from the HeartBEAT study were included in the analyses. Univariate analyses and multiple linear regression models were conducted to establish which demographic and CVD risk factors were the best correlates of endothelial function.

Results: In the univariate analyses, sex, employment status, body mass index, waist circumference, hip-to-waist ratio, neck circumference, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, total cholesterol to high-density lipoprotein cholesterol ratio, plasminogen activator inhibitor-1, calcium channel blocker use, and beta-blocker use were associated with endothelial function at a level of $P < .10$. In the most parsimonious model, male sex ($b = -0.305$, $P < .001$), calcium channel blocker use ($b = -0.148$, $P < .019$), and body mass index ($b = -.014$, $P < .037$) were negatively associated with endothelial function after adjusting for the other covariates.

Conclusions: The authors identified the correlates of endothelial function in older adults with untreated OSA and CVD or CVD risk factors, which are different than the correlates in middle-aged adults with the same conditions.

Keywords

Endothelial function; obstructive sleep apnea; older adults; vascular health

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Conflicts of interest

The authors have no conflicts of interest.

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Obstructive sleep apnea (OSA) is a highly prevalent and consequential sleep disorder in older adults that affects approximately 7–56% of females and 18–70% of males, a tenfold increase compared to middle-aged persons.[1] OSA is characterized by the narrowing or complete obstruction of the upper airway during sleep, which causes a decrease (i.e., hypopneas) or cessation (i.e., apneas) of airflow. Furthermore, it is estimated that up to 80% of those with moderate to severe OSA are undiagnosed by their health care providers.[2] Despite being diagnosed with OSA, many patients do not accept treatment for OSA, in particular positive airway pressure (PAP) therapy, or are non-adherent to PAP treatment, thus leaving their OSA untreated.[3]

The resultant sympathetic activation, sleep fragmentation, and intermittent hypoxia from OSA can lead to a variety of adverse symptoms in older adults, including excessive daytime sleepiness, depression, and cognitive decline.[4–6] Untreated moderate to severe OSA substantially increases the risk for hypertension and cardiovascular disease (CVD), which can be attributed to the accelerated progression of atherosclerosis[7,8] Alterations to the normal endothelium, known as endothelial dysfunction, is one of the earliest markers of atherosclerosis and potential key mechanism linking OSA to CVD.[9,10] Apnea-related sleep fragmentation promotes oxidative stress, systemic and vascular inflammation, apoptosis, and reductions in nitric oxide availability and repair capacity, which further contributes to endothelial dysfunction.[11]

While continued study is needed to improve diagnosis and adherence to treatment of OSA, it is imperative to recognize that many persons with OSA remain untreated, increasing their risk for CVD. Endothelial function can be improved by lifestyle modifications, including exercise training and increased intake of n-3 fatty acids and antioxidants, and certain medications such as statins, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers, certain beta-blockers, and oral hypoglycemics.[12–14] Thus, evaluation of endothelial function in patients with untreated OSA is important to help guide treatment decisions.

The available methods for assessing endothelial functioning are either invasive (i.e., coronary angiography) or require specialized equipment (i.e., flow-mediated dilation), precluding their use in daily clinical practice. Identifying an alternative method for estimating endothelial function could provide a more streamlined evaluation of cardiovascular risk in patients with untreated OSA. The objective of this study was to examine the associations between demographic and CVD risk factors and endothelial function in a sample of older adults with untreated, moderate to severe OSA and CVD or CVD risk factors.

Methods

Design

This study was a secondary analysis of baseline data from the *Heart Biomarker Evaluation in Apnea Treatment* (HeartBEAT) study.[15] HeartBEAT was a multi-center, randomized clinical trial that evaluated the effects of supplemental nocturnal oxygen or PAP therapy versus optimal medical treatment on blood pressure outcomes among participants with CVD

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and moderate to severe OSA.[16] HeartBEAT data is available by request from the National Sleep Research Resource website (http://sleepdata.org/datasets/heartbeat), which is supported by the National Heart, Lung, and Blood Institute and the National Center for Research Resources.[15] Primary outcomes and details of the study have been fully described.[16]

Sample

The sample (N = 126) consisted of adults aged 65 years and older who exhibited stable coronary artery disease or multiple risk factors for CVD (i.e., hypertension, diabetes, body mass index [BMI] > 30, or dyslipidemia) and moderate to severe OSA (i.e., apnea hypopnea index [AHI] = 15–50). Potential HeartBEAT participants were screened for OSA with the Berlin Questionnaire.[17] Those with scores that indicated a high risk for moderate to severe OSA were evaluated with a home sleep study. Exclusion criteria included: (1) recent cardiovascular event, (2) severe congestive heart failure, (3) pathological daytime sleepiness (i.e., score of ≥ 16 on the Epworth Sleepiness Scale[18]), (4) current oxygen use, (5) previous treatment of OSA with PAP therapy, (6) short sleep duration, (7) hypoxia at rest (i.e., O_2 saturation < 90%), (8) poorly controlled hypertension, and/or (9) pregnant or planning to become pregnant.

Data Collection

According to the HeartBEAT research protocol, during the baseline visit, demographic information and medical histories were collected and physical examinations were conducted. Race, ethnicity, and sex were self-reported. The physical examination included a measurement of blood pressure (BP) and anthropometric measures of body fat distribution. Height and weight were collected to calculate BMI. All procedures were guided by detailed instructions to ensure the consistency of the measures conducted—and the data collected—among the four clinical evaluation sites featured in the HeartBEAT study.[16]

Anthropometric measures comprised of waist, hip, and neck circumference. The waist-to-hip ratio was calculated by dividing waist circumference by hip circumference.

Sleep apnea was assessed with the use of a portable monitor (Embletta Gold, Embla Systems, Broomfield, CO) in the homes of the participants. Parameters evaluated by the monitor comprised airflow detection and limitation, thoracic and abdominal movement, oxygen saturation, and body movement. Guidelines from the American Academy of Sleep Medicine were used to score the studies.[19] An apnea was defined as a decrease of 90% or more in airflow from baseline for 10 seconds or more. A hypopnea was defined as a decrease of 50% or more in airflow from baseline for 10 seconds or more, with an associated 3% or greater desaturation. A normal AHI is less than 5 events/hour.[20] OSA classifications based on AHI are: mild (AHI of 5 to 14 events/hour), moderate (AHI of 15 to 29 events/hour), and severe (AHI of more than 30 events/hour.[20] Moderate to severe OSA was an inclusion criterion for HeartBEAT participants. AHI was included in the analysis to control for OSA severity.

Endothelial function was assessed by determining the reactive hyperemia index (RHI) using the EndoPAT device (Itamar Medical, Caesarea, Israel). Using EndoPAT, fingertip probes

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were placed on both index fingers of participants and a BP cuff was placed on the non-dominant arm. The assessment consisted of a 5-minute baseline recording, followed by 5 minutes of occlusion via inflation of the BP cuff, and then rapid deflation of the BP cuff and recording of arteriolar pulse volume. RHI was calculated as the mean increase from baseline in pulse volume in the occluded hand following cuff deflation after adjusting for changes in the non-occluded hand. The Framingham-reactive hyperemia index (F-RHI), which uses the natural logarithmic transformation of the 90 to 120 second post-deflation interval of the RHI, was calculated and used as the dependent variable in our analyses.[21] A lower F-RHI represents worse endothelial function. The F-RHI has superior reproducibility compared to RHI and is associated with CVD risk factors.[21,22]

Blood was obtained from participants after fasting 12 hours to generate lipid profiles that comprised of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum glucose levels. Laboratory assays that were attained for systemic and vascular inflammatory cytokines included high sensitivity C-reactive protein (hs-CRP) and plasminogen activator inhibitor-1 (PAI-1). The protocol for obtaining, processing, and shipping specimens for analysis was standardized for all four sites. Laboratory procedures were conducted at the Laboratory for Clinical Biochemistry Research at the University of Vermont, College of Medicine.

Statistical Analysis

In this study, SPSS version 22.0 and SAS version 9.4 were used to perform the quantitative data analysis. The level of statistical significance was set at 0.05 (two-tailed). The demographic and clinical characteristics of the sample were examined using descriptive statistics. Continuous variables were reported as means and standard deviation, and categorical variables were reported as frequencies and percentages. Univariate association between each of demographic and clinical characteristics selected a priori and F-RHI were examined initially. The variables that were potentially correlated with F-RHI ($p < 0.10$) in the univariate analyses were considered for inclusion in the multiple regression model. Multiple linear regression models were conducted to establish which variables (independent variables) are the best predictors of F-RHI (the dependent variable).

Results

The sub-sample (N = 126) of participants older than age 65 from the HeartBEAT study was predominantly male (74.6%) and Caucasian (70.2%), with a mean (± SD) age of 70.2 ± 2.9 years. The majority of participants did not work (68.3%). Nearly 40% of the participants reported yearly household incomes of $30,000–$74,999 while 26% reported incomes over $75,000. The sample had a mean BMI of 32.7 ± 5.5 kg/m^2 and a mean AHI of 26 ± 9. Most of the participants had hypertension (90.5%) and hyperlipidemia (89.7%), and 42% had diabetes.

The univariate association analyses found 13 variables that were associated with F-RHI with a generalized linear model (GLM) p-value <.10 (Table 2). In order to test a parsimonious model with variables easily obtained in a clinical setting, we further reduced the number of variables included in the models. BMI, waist circumference, hip-to-waist ratio, and neck

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circumference were all highly correlated. BMI was selected as it is most frequently assessed in a clinical setting and the least likely to be measured incorrectly. Total cholesterol to HDL-C ratio, total cholesterol, and HDL-C also were also highly correlated. Total cholesterol to HDL-C ratio was chosen because it is the more informative of overall lipid status. Other covariates included in the models were male sex, calcium channel blocker (CCB) usage, employment status, beta-blocker usage, diastolic BP, and AHI. PAI-1 is not routinely measured in the clinical setting. As a result, we chose to conduct two separate models, one that included PAI-1 (Table 3) and one that excluded PAI-1 (Table 4).

In the model that includes PAI-1 (Table 3), male sex ($b = -0.306$, $p < .001$) and CCB usage ($b = -0.169$, $p < .019$) were negatively associated with F-RHI after adjusting for covariates. In the most parsimonious model without PAI-1 (Table 4), male sex ($b = -0.305$, $p < .001$), CCB usage ($b = -0.148$, $p < .019$), and BMI ($b = -.014$, $p < .037$) were negatively associated with F-RHI after adjusting for covariates.

Discussion

The results of this secondary data analysis of 126 middle-aged older adults with OSA and CVD or CVD risk factors identified several correlates of endothelial function. The best correlates for endothelial function when including PAI-1 in the model were male sex and CCB usage. In a model that excluded PAI-1, BMI became significantly associated endothelial function. Furthermore – and perhaps most interestingly – we found no difference in endothelial function across OSA severity, as measured by AHI.

In both models, we found that male sex was associated with a lower F-RHI after adjusting for AHI. Our findings are similar to the findings of Hamburg et al.[21] and Truschel et al.[23] However, Randby and colleagues[24] and Faulx and colleagues[25] found that OSA was an independent predictor of a low RHI in females but not in males. Notably, our study focused on older adults while the other studies focused on middle-aged adults. Although females continue to be underrepresented in OSA research, several sex differences have been identified in the literature, which include differences in the chemical factors that affect respiratory stability, Mallampati scores, airway size, hormonal factors, and body fat distribution.[26] In cases in which males and females exhibit the same BMI, males present with greater disease severity. Consequently, at the same AHI, females exhibit higher BMI than males; central adiposity is thought to contribute to this effect. Menopause, which is not associated with BMI or age, is considered an independent risk factor for OSA.[27]

Endothelial function can be improved through lifestyle modification and pharmacologic interventions.[12–14] Numerous medications, including CCBs, beta-blockers, ACEI, statins, and peripheral dilators, have been shown to improve endothelial function and cardiovascular outcomes.[28] However, in our sample of older adults, only CCBs were associated with F-RHI. Furthermore, we found that CCB usage was associated with lower F-RHI after adjusting for covariates. CCBs are generally safe and effective at lowering BP in older adults. In fact, CCBs may be superior to ACEIs in the prevention of stroke, whereas ACEIs may be superior to CCBs in the prevention of CHD.[29,30] The efficacy of CCBs may be sex-dependent.[31] Our finding that F-RHI was lower among male older adults prescribed CCBs

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supports a potentially clinically important sex difference. These findings suggest that more work in this area is needed.

In the model without PAI-1, a higher BMI was associated with a lower F-RHI after adjusting for other factors. Obesity, as defined by BMI, has been shown to be associated with endothelial dysfunction in individuals without OSA.[32] However, among individuals with OSA, the association between BMI and endothelial dysfunction is less clear. Several studies have reported an association between the presence and/or severity of OSA and endothelial dysfunction that is independent of not only BMI, but also traditional cardiovascular risk factors including smoking, BP, lipids, and diabetes.[21,33,34] Nonetheless, other studies found the opposite. For example, in a recent study of 53 obese adults with OSA, the severity of OSA was not significantly associated with endothelial dysfunction, even after adjustment for age, sex, BMI, waist circumference, alcohol intake, and physical activity.[35] Furthermore, in a study comparing 83 overweight patients with mild OSA and 46 weight-matched, non-OSA individuals, endothelial function was found to be well-preserved.[36] Once again, it is important to point out that these studies focused more on middle-age adults while our study was among older adults. Since men are likely to have more severe OSA at the same BMI as women, it is important to delineate other covariates besides BMI that lead to endothelial dysfunction in both men and women with OSA.

Previous studies have identified other predictors or correlates of endothelial function including LDL-C levels, hypertension, and CRP which were not significant in our models.[37–40] The very high prevalence of hyperlipidemia and hypertension (90% for both) and obesity in our sample may explain our results.

While AHI remains the basis for the diagnoses and management of OSA, it is not without limitations or controversy.[41–43] Specifically, AHI does not correlate well with excessive daytime sleepiness (EDS) and, when adjusted for other variables, certain clinical manifestations.[42,43] Our finding that AHI was not associated with endothelial function in older adults after adjusting for covariates supports this finding. The use of new approaches to assess the severity of OSA, such as the utilization of measures other than AHI like oxygen-desaturation index and the examination of accompanying symptoms and comorbid conditions, may result in improved OSA phenotypes to guide treatment.[41–43] For example, growing evidence supports a no-EDS OSA phenotype.[43] Furthermore, individuals with the no-EDS OSA phenotype may have a different response to PAP compared to individuals with the EDS phenotype.[43] Future studies exploring different OSA phenotypes should include older adults.

Study Limitations

A major limitation of this study was the truncated range of OSA severity (15–50) that precluded evaluation of endothelial dysfunction in persons with normal or mild OSA. The cross-sectional design does not allow for causal relationships between OSA, CVD disease and CVD risk factors, CVD treatment and endothelial function to be determined. As such, longitudinal studies are necessary to examine the causal relations. Nevertheless, a case for the generalizability of the results of this secondary analysis can be made owing to (1) its moderately large sample of individuals with moderate to severe OSA and coexisting risk

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factors for CVD, (2) the detailed procedures used to maintain protocol fidelity in the parent multi-site study, and (3) the validated objective measures deployed to determine OSA severity and endothelial dysfunction.

Conclusions

In this secondary analysis, the statistical model identified a negative association between endothelial function and male sex, CCB usage, and BMI. These findings suggest that the correlates of endothelial function in older adults with untreated OSA and CVD or CVD risk factors are different than the correlates in middle-aged adults with the same conditions. In the clinical context, focus should be on weight loss which could reduce not only OSA severity but also additional CVD-related risk factors that contribute to endothelial dysfunction. Evidence against prescribing CCBs in older adults is lacking, but additional work examining endothelial function in older adults taking these medications is warranted. Although both women and men with untreated OSA have an increased risk for endothelial dysfunction versus individuals with treated OSA, clinicians should consider potential sex differences in risk factors. Future prospective studies among older adults with OSA are needed to examine whether or not weight loss—and the resultant decrease in BMI—not only reverses abnormal vaso-reactivity, but also lowers CVD risk.

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References

1. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5(2): 136–143. doi: 10.1513/pats.200709-155MG. [PubMed: 18250205]
2. Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of obstructive sleep apnea: A population-based perspective. Expert Rev Respir Med 2008;2(3):349–364. [PubMed: 19690624]
3. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: The challenge to effective treatment. Proc Am Thorac Soc 2008;5(2):173–8. doi: 10.1513/pats.200708-119MG. [PubMed: 18250209]
4. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. Sleep 1991;14(6):486–495. [PubMed: 1798880]
5. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017;13(3):479–504. doi:10.5664/jcsm.6506. [PubMed: 28162150]
6. Mathieu A, Mazza S, Décary A, et al. Effects of obstructive sleep apnea on cognitive function: A comparison between younger and older OSAS patients. Sleep Med 2008;9(2):112–120. doi: 10.1016/j.sleep.2007.03.014. [PubMed: 17513171]
7. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 2005;172:613–618. [PubMed: 15901608]

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8. Savransky V, Nanayakkara A, Li J, et al. Chronic intermittent hypoxia induces atherosclerosis. Am J Respir Crit Care Med 2007;175:1290–7. [PubMed: 17332479]
9. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23:168–175. [PubMed: 12588755]
10. Hoyos CM, Melehan KL, Liu PY, Grunstein RR, Phillips CL. Does obstructive sleep apnea cause endothelial dysfunction? A critical review of the literature. Sleep Med Rev 2015:15–26. doi: 10.1016/j.smrv.2014.06.003.
11. Atkeson A, Yeh SY, Malhotra A, Jelic S. Endothelial function in obstructive sleep apnea. Prog Cardiovasc Dis 2009;51:351–362. doi: 10.1016/j.pcad.2008.08.002. [PubMed: 19249441]
12. Brown AA, Hu FB. Dietary modulation of endothelial function: Implications for cardiovascular disease. Am J Clin Nutr 2001;73(4):673–86. [PubMed: 11273841]
13. Higashi Y, Yoshizumi M. Exercise and endothelial function: Role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients. Pharmacol Ther 2004;102(1):87–96. doi:10.1016/j.pharmthera.2004.02.003. [PubMed: 15056500]
14. Lee PSS, Poh KK. Endothelial progenitor cells in cardiovascular diseases. World J Stem Cells 2014;6(3):355–366. doi:10.4252/wjsc.v6.i3.355. [PubMed: 25126384]
15. Dean DA, Goldberger AL, Mueller R, et al. (2016) Scaling up scientific discovery in sleep medicine: The National Sleep Research Resource. Sleep 39:1151–1164. doi: 10.5665/sleep.5774. [PubMed: 27070134]
16. Gottlieb DJ, Punjabi NM, Mehra R, et al. CPAP versus oxygen in obstructive sleep apnea. N Engl J Med 2014;370:2276–2285. doi: 10.1056/NEJMoa1306766. [PubMed: 24918372]
17. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 1999;131:485–491. [PubMed: 10507956]
18. Johns MW. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep 1991;14:540–545. [PubMed: 1798888]
19. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. J Clin Sleep Med 2007;3:737–747. [PubMed: 18198809]
20. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017;13(3):479–504. doi: 10.5664/jcsm.6506 [PubMed: 28162150]
21. Hamburg NM, Keyes MJ, Larson MG, et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. Circulation 2008;117:2467–2474. doi: 10.1161/CIRCULATIONAHA.107.748574. [PubMed: 18458169]
22. Selamet Tierney ES, Newburger JW, Gauvreau K, et al. Endothelial pulse amplitude testing: Feasibility and reproducibility in adolescents. J Pediatr 2009;154(6):901–5. doi: 10.1016/j.jpeds.2008.12.028. [PubMed: 19217124]
23. Truschel E, Jarczok MN, Fischer JE, Terris DD. High-throughput ambulatory assessment of digital reactive hyperemia: Concurrent validity with known cardiovascular risk factors and potential confounding. Prev Med 2009;49:468–472. doi: 10.1016/j.ypmed.2009.09.019. [PubMed: 19804795]
24. Randby A, Namtvedt SK, Hrubos-Strøm H, Einvik G, Somers VK, Omland T. Sex-dependent impact of OSA on digital vascular function. Chest 2013;144(3):915–922. doi: 10.1378/chest.12-2283. [PubMed: 23471187]
25. Faulx MD, Larkin EK, Hoit BD, Aylor JE, Wright AT, Redline S. Sex influences endothelial function in sleep-disordered breathing. Sleep 2004;27(6):1113–20. [PubMed: 15532205]
26. Lin CM, Davidson TM, Ancoli-Israel S. Gender differences in obstructive sleep apnea and treatment implications. Sleep Med Rev 2008;12(6):481–96. [PubMed: 18951050]
27. Ye L, Pien GW, Weaver TE. Gender differences in the clinical manifestation of obstructive sleep apnea. Sleep Med 2009;10(10):1075–84. [PubMed: 19403333]
28. Matsuzawa Y, Guddeti RR, Kwon TG, Lerman LO, Lerman A. Treating coronary disease and the impact of endothelial dysfunction. Prog Cardiovasc Dis 2015;57(5):431–42. doi: 10.1016/j.pcad.2014.10.004. [PubMed: 25459974]

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29. Verdecchia P, Reboldi G, Angeli F, et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. Hypertension 2005;46(2):386–92. [PubMed: 16009786]
30. Chen GJ, Yang MS. The effects of calcium channel blockers in the prevention of stroke in adults with hypertension: Meta-analysis of data from 273,543 participants in 31 randomized controlled trials. PLoS One 2013;8(3):e57854. doi: 10.1371/journal.pone.0057854. [PubMed: 23483932]
31. Seeland U, Regitz-Zagrosek V. Sex and gender differences in cardiovascular drug therapy. Handb Exp Pharmacol 2012;(214):211–36. doi: 10.1007/978-30726-3_11.
32. Al Suwaidi J, Higano ST, Holmes DR, Jr, Lennon R, Lerman A. Obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. J Am Coll Cardiol 2001;37:1523–8. [PubMed: 11345360]
33. Jelic S, Lederer DJ, Adams T, et al. Vascular inflammation in obesity and sleep apnea. Circulation 2010;121:1014–1021. doi: 10.1161/CIRCULATIONAHA.109.900357. [PubMed: 20159829]
34. Olafiranye O, Kip KE, Rhinehart Z, et al. Impact of race and obesity on arterial endothelial dysfunction associated with sleep apnea: Results from the Heart SCORE study. Int J Cardiol 2015;15;201:476–478. doi:10.1016/j.ijcard.2015.08.098.
35. Araújo J, Teixeira J, Gaio AR. Dietary patterns among 13-y-old Portuguese adolescents. Nutrition. 2015;31:148–154. doi:10.1016/j.nut.2014.06.007. [PubMed: 25466659]
36. Blomster H, Laitinen T, Lyyra-Laitinen T, et al. Endothelial function is well preserved in obese patients with mild obstructive sleep apnea. Sleep Breath 2014;18:177–186. doi: 10.1007/s11325-013-0867-7. [PubMed: 23733256]
37. Hermida N, Balligand JL. Low-density lipoprotein-cholesterol-induced endothelial dysfunction and oxidative stress: The role of statins. Antioxid Redox Signal 2014;20(8):1216–37. doi: 10.1089/ars.2013.5537. [PubMed: 23924077]
38. Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990;323(1):22–7. [PubMed: 2355955]
39. Shimbo D, Grahame-Clarke C, Miyake Y, et al. The association between endothelial dysfunction and cardiovascular outcomes in a population-based multi-ethnic cohort. Atherosclerosis 2007;192(1):197–203. [PubMed: 16762358]
40. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001;103(13):1813–8. [PubMed: 11282915]
41. Borsini E, Nogueira F, Nigro C. Apnea-hypopnea index in sleep studies and the risk of over-simplification. Sleep Sci 2018;11(1):45–48. doi: 10.5935/1984-0063.20180010. [PubMed: 29796201]
42. Randerath W, Bassetti CL, Bonsignore MR, et al. Challenges and perspectives in Obstructive Sleep Apnoea [published online ahead of print May 31, 2018]. Eur Respir J 10.1183/13993003.02616-2017.
43. Garbarino S, Scoditti E, Lanteri P, et al. Obstructive Sleep Apnea with or without excessive daytime sleepiness: Clinical and experimental data-driven phenotyping. Front Neurol 2018;9:505. doi: 10.3389/fneur.2018.00505. [PubMed: 29997573]

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Table 1

Baseline Data (N = 126)

Variable	Total Sample
Sex, male	94 (74.60%)
Age, years	70.2 ± 2.9
Race	
Caucasian	105 (83.3%)
African-American	16 (12.7%)
Other	5 (4.00%)
Income	
Under $29,999	39 (35.8%)
$30,000 to $74,999	42 (38.5%)
$75,000 or more	28 (25.7%)
Employment status	
Working (full- or part-time)	40 (31.8%)
Not employed/retired	86 (68.3%)
Body mass index, kg/m^2	32.7 ± 5.5
Waist-to-hip ratio	0.99 ± 0.07
Neck circumference, cm	41.7 ± 3.9
Framingham RHI	0.51 ± 0.40
Systolic blood pressure, mmHg	128.2 ± 16.3
Diastolic blood pressure, mmHg	70.9 ± 8.9
Total cholesterol, mg/dL	157.8 ± 32.2
Low-density lipoprotein cholesterol, mg/dL	86.4 ± 24.5
High-density lipoprotein cholesterol (HDL-C), mg/dL	46.2 ± 13.1
Total cholesterol to HDL-C ratio	3.6 ± 0.8
Blood glucose, mg/dL	113.4 ± 32.0
Smoking status, yes	10 (11.6%)
Apnea hypopnea index, events/hr	26.4 ± 8.9
High sensitivity C-reactive protein, ug/mL	3.5 ± 5.7
Plasminogen activator inhibitor-1, ng/mL	42.8 ± 36.5
Hypertension diagnosis, yes	114 (90.5%)
Hyperlipidemia diagnosis, yes	113 (89.7%)
Diabetes, yes	52 (41.6%)
Percent of time with O2 sats < 90%	9.5 ± 13.2
Nitrate usage, yes	24 (19.5%)
Calcium channel blocker usage, yes	43 (34.1%)
Beta-blocker usage, yes	82 (65.1%)
Ace inhibitor usage, yes	90 (71.4%)
Statin usage, yes	117 (92.9%)
Diuretic usage, yes	50 (40.5%)
Peripheral dilator usage, yes	12 (9.5%)

Abbreviations: RHI, reactive hyperemia index

Data expressed as mean ± standard deviation or frequency (n) and percentage (%)

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Table 2

Univariate association between variables of interest and Framingham RHI

Variable	Coefficient	p-value
Sex, male	−.345	<.001
Employment, Employed full-time	.190	.042
BMI	−.176	.060
Waist circumference	−.283	.002
Hip-to-waist ratio	−.316	<.001
Neck circumference	−.334	<.001
Diastolic blood pressure	.155	.099
Total cholesterol	.157	.095
HDL-C	−.266	.004
Total cholesterol to HDL-C ratio	−.196	.037
Plasminogen activator inhibitor-1	−.223	.018
Calcium channel blocker usage, yes	−.225	.016
Beta-blocker usage, yes	−.166	.077

Abbreviations: BMI, body mass index; HDL-C, High-density lipoprotein cholesterol; RHI, reactive hyperemia index

Note: Age, race, income, systolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, glucose, smoking status, apnea hypoxia index, history of diabetes, history of hypertension, history of hypercholesterolemia, angiotensin converting enzyme inhibitor usage, statin usage, diuretic usage, and peripheral dilators usage were not associated with Framingham RHI ($p > .10$)

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Table 3

General linear model results for factors associated with Framingham RHI with plasminogen activator inhibitor-1

Predictor	b	SE	95% CI	p-value
Sex, male	−.306	.083	−.471, −.141	<.001
Employment, full-time	.124	.070	−.015, .262	.080
Calcium channel blocker usage, yes	−.169	.071	−.309, −.029	.019
Beta-blocker usage, yes	−.001	.076	−.150, .151	.993
Body mass index	−.011	.007	−.025, .002	.088
Diastolic blood pressure	.006	.004	−.002, .014	.115
Total cholesterol to high-density lipoprotein cholesterol ratio	−.017	.044	−.105, .070	.681
Plasminogen activator inhibitor-1	−.002	.001	−.004, .000	.053
Apnea hypoxia index	−.003	.004	−.010, .005	.508

Abbreviations: SE, standard error; CI, confidence interval; RHI, reactive hyperemia index

R squared = .287

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Table 4

General linear model results for factors associated with Framingham RHI without plasminogen activator inhibitor-1

Predictor	b	SE	95% CI	p-value
Sex, male	−.305	.083	−.471, −.139	<.001
Employment, full-time	.126	.071	−.014, .26	.077
Calcium channel blocker usage, yes	−.148	.070	−.287, −.010	.036
Beta-blocker usage, yes	−.007	.076	−.144, .159	.925
Body mass index	−.014	.006	−.026, −.001	.037
Diastolic blood pressure	.006	.004	−.002, .014	.098
Total cholesterol to high-density lipoprotein cholesterol ratio	−.048	.042	−.131, .035	.256
Apnea hypoxia index	−.002	.004	−.010, .005	.562

Abbreviations: SE, standard error; CI, confidence interval; RHI, reactive hyperemia index

R squared = .263