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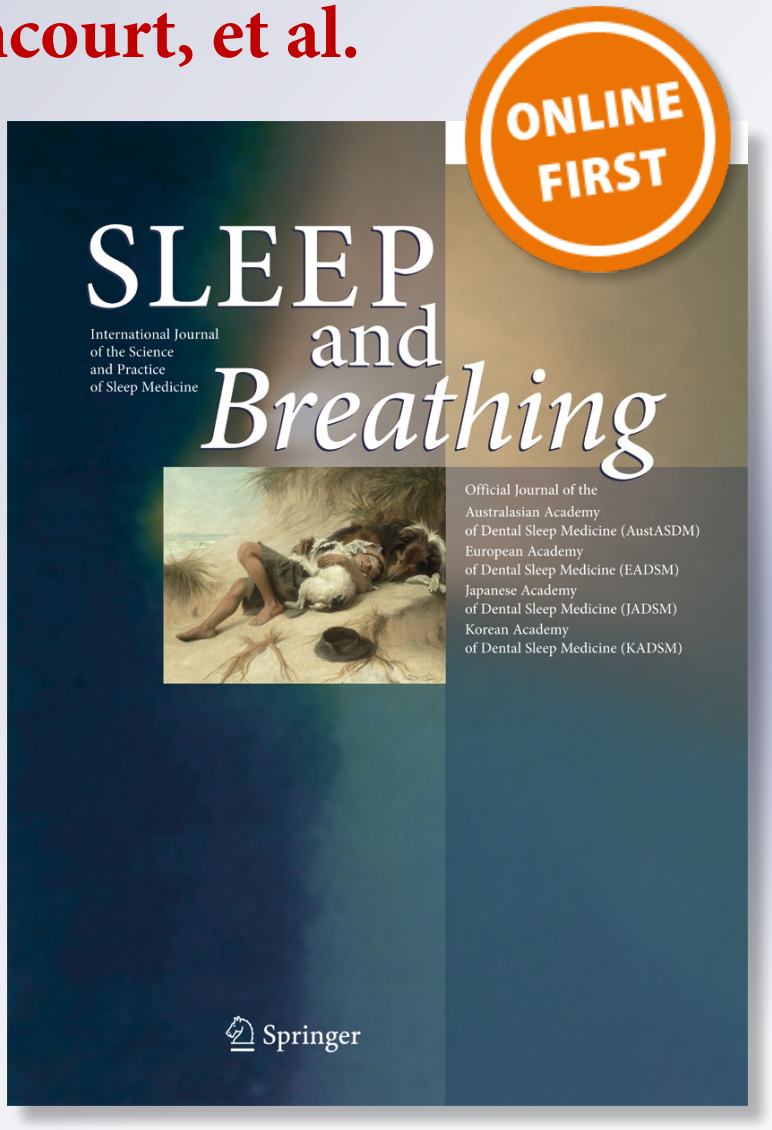

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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Obstructive sleep apnea is independently associated with subclinical coronary atherosclerosis among middle-aged women

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Abstract
Purpose Obstructive sleep apnea (OSA) is associated with coronary disease among men. However, this association is not clear for women. In this study, we evaluate the association between OSA and presence of subclinical atherosclerosis assessed by tomographic coronary calcium score in middle-aged women.
Methods We evaluated consecutive women aged between 45 and 65 years in perimenopause or postmenopause period (with menstrual irregularity—amenorrhea > 60 days), without manifest cardiovascular disease (heart failure, coronary disease, and stroke), from two gynecologic clinics. All patients underwent clinical evaluation, computed tomographic examination for coronary artery calcium (CAC > 100 Agatston units), and portable sleep study. Multiple logistic regression models were used to evaluate the association between OSA and CAC, controlling for traditional risk factors including Framingham Risk Score (FRS), body mass index (BMI), and diabetes.
Results We studied 214 women (age 56 years (52–61); BMI 28 kg/m^2 (25–31), 25 % diabetes, 62 % hypertension). OSA (apnea-hypopnea index (AHI) ≥5 events/h) was diagnosed in 82 women (38.3 %). CAC was more prevalent in patients with moderate/severe OSA (AHI ≥15 events/h) than in patients without or with mild OSA, 19 % vs 4.5 and 1.6 %, respectively ($p < 0.01$). Moderate to severe OSA was associated with CAC in unadjusted (odds ratio = 6.25, 95 % CI 1.66–23.52; $p < 0.01$) and adjusted (odds ratio = 8.19, 95 % CI 1.66–40.32; $p = 0.01$) logistic regression analysis.
Conclusion Moderate to severe OSA is independently associated with the presence of CAC in middle-aged women. These results reinforce the concept that women are also susceptible to the cardiovascular consequences of OSA.

Keywords Obstructive sleep apnea · Women · Atherosclerosis · Coronary heart disease

Abbreviations

AHI	Apnea-hypopnea index
BMI	Body mass index
BP	Blood pressure
CAC	Coronary artery calcium
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram

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ODI Oxygen desaturation index
OSA Obstructive sleep apnea

Introduction

Despite improvements in the treatment and prevention of cardiovascular diseases, cardiovascular morbidity and mortality are still highly prevalent among women [1]. This is particularly true for women in the menopausal transition, a physiological process characterized by age-related changes in female organism associated with reduced estrogen production and increase in cardiovascular risk [2]. Therefore, there is a need to search for residual risk factors to decrease cardiovascular deaths among women.

One potential candidate is obstructive sleep apnea (OSA), a condition characterized by repetitive episodes of upper airway obstruction, intermittent hypoxia, and disrupted sleep [3]. OSA is common in the general population [4, 5], with higher prevalence with increasing age. Despite the higher prevalence in men [5], OSA is also common in women [4]. There is growing evidence that OSA independently contributes to poor cardiovascular outcome [6]. Additionally, OSA is independently associated with several cardiovascular risk factors or diseases, such as arterial stiffness, hypertension, and atherosclerosis [7–9]. However, the vast majority of studies evaluating those associations were restricted to middle-aged men. Thus, the association of OSA and cardiovascular disease in women remains controversial. While one study demonstrated that OSA was associated with increased risk of myocardial infarction in males but not in females [10], recent observational data demonstrated that severe and untreated OSA is associated with increased mortality among women [11, 12], with incident heart failure and with left ventricular hypertrophy [12].

In this study, we explored the potential impact of OSA in middle-aged women measuring coronary artery calcium (CAC) score, a well-established surrogate marker of future acute coronary events [13]. Higher CAC scores are directly associated with future risk of cardiovascular events and provide risk information that is incremental to traditional risk factors [14]. We hypothesized that OSA is independently associated with coronary atherosclerosis in middle-aged women.

Methods

The local Ethics Committee approved the protocol (Complexo Hospitalar-Hospital Universitário Oswaldo Cruz-Universidade de Pernambuco/UPE/Procape, Approval Number CAAE-0135.0.106.000-10), and all participants gave written informed consent.

Subjects

We recruited 235 consecutive women, aged between 45 and 65 years, in the perimenopause or postmenopause (with menstrual irregularity—amenorrhea > 60 days) [15], from two primary care gynecological clinics from May 2011 to June 2012. This is part of a cohort that is evaluating the cardiovascular risk factors of middle-aged women [7]. We excluded from the study women with history of smoking in the last 5 years, use of hormone replacement therapy, heart failure symptoms, prior coronary disease, atrial fibrillation or stroke, and previous OSA diagnosis. All participants underwent specific evaluations as described below in the morning after the sleep study. Physical activity was evaluated by the IPAQ questionnaire, which has been proposed by the Consensus Group for the Development of an International Physical Activity Questionnaire, formed under the seal of the World Health Organization and with representatives in 25 countries, including Brazil [16].

Blood samples

All samples were collected from venous blood in the early morning (7 to 9 AM) after 12 h of fasting for measurement of serum creatinine, total cholesterol, low-density lipoprotein, high-density lipoprotein, and glucose, following standard protocols. Framingham Risk Score (FRS) [17] that comprises several variables, including gender, age, blood pressure, total cholesterol, LDL and HDL cholesterol, and smoking, was calculated for all participants.

Office blood pressure

The blood pressure (BP) was measured after 5-min resting. The mean of two readings obtained at 5-min intervals with an automatic digital sphygmomanometer (OMRON-742, Japan) was used in the analysis [18]. Participants were considered to have hypertension if they were on antihypertensive therapy or had systolic or diastolic BP over 140 or 90 mm Hg, respectively.

Coronary calcification score measurement

All subjects underwent nonenhanced multislice computed tomography with ECG-gating, using standard protocol [19]. Exams were performed with a 10-MDCT scanner (Philips, Amsterdam, Netherlands) and scored by a radiologist blinded to the OSA status. Patients with CAC scores greater than 100 Agatston units were considered with coronary atherosclerosis, a strong predictor of incident coronary heart disease [14].

Sleep evaluation

All patients underwent a portable overnight sleep recording in the sleep laboratory using a validated device [20] (Embletta, PDS; Medcare, Reykjavik, Iceland), to evaluate oxygen saturation, body position, measurements of nasal flow (pressure canula), and measurements of respiratory effort using impedance belts. Apnea was defined as a total absence (>90 %) and hypopneas as a decrease (>30 %) in nasal flow for ≥10 s, followed by a 4 % desaturation (in hypnoeas), respectively [21]. The apnea-hypopnea index (AHI) was calculated dividing the total number of apneas and hypopneas by total time in bed. OSA was defined by an AHI ≥5 events/h (mild OSA 5 to 14.9 events/h; moderate to severe OSA ≥15 events/h). The oxygen desaturation index (ODI) was calculated dividing the total number of desaturations by total time in bed. In addition, subjective daytime sleepiness was evaluated using the Epworth Sleepiness Scale. A total score >10 was considered excessive somnolence [22].

Statistical analysis

Normality distribution was evaluated with the Kolmogorov-Smirnov test, and the results were expressed as mean ± SD, median (interquartile range), or percentage. Chi-squared, one-way analysis of variance, or Kruskal-Wallis tests were used to compare variables between groups. Univariate and multivariable logistic regression models were used to estimate the association between CAC and severity of OSA. We used a cut-off of 15 for the AHI in the logistic regressions. The multivariable models were adjusted for known confounders, including FRS (which comprises several variables, including blood pressure), body mass index (BMI), and diabetes. Due to the nonnormality of the FRS, we used a log-transformed version of this variable in the multivariable models. Data were analyzed with SPSS 21. A two-sided p value below <0.05 was considered significant.

Results

From the initially screened population of 235 women, 20 refused to participate or did not fulfill inclusion criteria, while one woman was excluded due to inadequate sleep study (oxymeter malfunction). CAC was obtained from 214 participants, which was our final sample.

The population consisted of predominantly middle-aged and overweight women (Table 1). OSA (AHI ≥5 events/h) and moderate/severe OSA (AHI ≥15 events/h) was diagnosed in 82 (38.3 %) and 21 (9.8 %) of women, respectively. Of note, none of the participants had a previous OSA diagnosis. The anthropometrics and clinical characteristics of patients with no OSA, with mild OSA, and with moderate/severe OSA are summarized in Table 1. When compared to participants without OSA, those with OSA were more likely to be obese, had a higher prevalence of hypertension, and use more antihypertensive drugs. Interestingly, excessive daytime sleepiness, evaluated by Epworth Sleepiness Scale, was not different between groups, neither physical activity. The lipid

Table 1 Baseline anthropometrics and clinical characteristics

	No OSA $N=132$	Mild OSA $N=61$	Mod/severe OSA $N=21$	p value
Age (years)	55 (51–59)	59 (54–62)	58 (53–63)	<0.01
BMI (kg/m^2)	27 (24–29)	29 (25–34)	32 (29–35)	<0.01
Neck circumference (cm)	34.2 ± 2.5	35.9 ± 2.4	36.4 ± 3.0	<0.001
Waist (cm)	92.5 ± 9.4	99.1 ± 9.6	104.2 ± 9.2	<0.001
White (%)	22 (17 %)	9 (15 %)	3 (14 %)	0.95
Diabetes mellitus (%)	32 (24 %)	15 (25 %)	6 (29 %)	0.91
Dyslipidemia (%)	94 (77 %)	45 (75 %)	14 (70 %)	0.78
Metabolic syndrome[a] (%)	52 (43 %)	30 (50 %)	10 (50 %)	0.65
Hypertension (%)	92 (70 %)	50 (82 %)	20 (95 %)	0.02
Physical inactivity (%)	96 (73 %)	44 (72 %)	16 (76 %)	0.93
Use of antihypertensive drugs. n	66 (50 %)	34 (56 %)	18 (88 %)	0.01
Epworth Sleepiness Scale score	9 (5–13)	9 (6–13)	9 (7–15)	0.36
Heart rate (bpm)	69 (65–76)	70 (63–77)	73 (66–80)	0.42
Systolic BP (mm Hg)	133 (122–146)	139 (126–153)	149 (134–160)	<0.01
Diastolic BP (mm Hg)	83 (74–89)	85 (77–90)	86 (73–96)	0.39

Data are presented as median (interquartile range), mean ± SD, or no. (%)

BMI body mass index, *BP* blood pressure, *Mod/severe* moderate to severe, *OSA* obstructive sleep apnea

[a] Based on National Cholesterol Education Program, Adult Treatment Panel III

profile, glucose, and creatinine levels of women with and without OSA were similar (Table 2).

CAC was present in 5.1 % of the entire population (4.5, 1.6, and 19 % of controls, mild OSA and moderate/severe OSA, respectively ($p < 0.01$)) (Fig. 1). Moderate to severe OSA was associated with CAC in univariate logistic regression (odds ratio = 6.25, 95 % CI 1.66–23.52; $p < 0.01$). On a multivariable analysis, moderate to severe OSA remained independently associated with CAC after adjusting for BMI, FRS, and diabetes (odds ratio = 8.19, 95 % CI 1.66–40.32; $p = 0.01$) (Fig. 2).

Discussion

This study specifically evaluated coronary atherosclerosis in consecutive middle-aged women according to the presence of OSA. Our study demonstrated that mild OSA is not associated with CAC in this population. In contrast, moderate to severe OSA was present in nearly 10 % of the study population and was independently associated with CAC, even after adjustment for well-known risk factors for atherosclerosis, including BMI, FRS, and diabetes. These findings suggest that moderate to severe OSA is a potential residual factor that may contribute to poor cardiovascular outcome among middle-aged women.

There are many mechanisms by which OSA may increase the atherosclerotic appearance [23]. Intermittent hypoxia, increased sympathetic activation, and elevated intrathoracic negative pressure during respiratory events are the three main mechanisms involved in this process. Repetitive drops in oxygenation during the night lead to inflammation [24], oxidative stress [25], and endothelial dysfunction [26]. Moreover, respiratory-related arousals and elevated intrathoracic negative pressure during apneas trigger sympathetic activation and surges in blood pressure [27], which are able to increase not only nocturnal, but also daytime blood pressure. Hypertension is tightly linked to OSA, including resistant hypertension [28], which increases cardiovascular risk. This cause-effect relationship is proven in studies that demonstrate decrease in blood pressure after OSA treatment with CPAP [29]. All these mechanisms may increase metabolic imbalance, leading to insulin resistance and dyslipidemia, increasing atherosclerotic risk [30].

The association between OSA and CAC in populations without prior coronary disease has been addressed by few investigators. One retrospective study with patients (70 % men) that had undergone both polysomnography and CAC determination demonstrated high CAC scores in high OSA quartiles, even controlling for cardiovascular risk factors [31]. Other community-based study (50.4 % males) found no association between OSA and CAC after adjustment for BMI [32]. This lack of association between OSA and CAC was confirmed by another cohort of 252 middle-aged adults (61 % males) [29]. However, a subanalysis from this study stratified by BMI found a positive association between OSA and CAC only in nonobese participants [33]. Finally, other study with 1604 subjects (49.3 % males) [34] demonstrated association between CAC and OSA in men aged <65 years and in women of any age. Therefore, the present study provides significant advances in this important research area by focusing on consecutive middle-aged women, without prior cardiovascular diseases. Our study reinforces the concept that mild OSA may not have an impact on cardiovascular diseases [35]. However, moderate to severe OSA was independently

Table 2 Baseline laboratory and sleep study characteristics

Variable	No OSA $N = 132$	Mild OSA $N = 61$	Mod/severe OSA $N = 21$	p value
Laboratory				
Creatinine (mg/dL)	0.7 (0.6–0.8)	0.6 (0.6–0.8)	0.7 (0.6–0.8)	0.18
Fasting glucose (mg/dL)	95 (84–105)	92 (84–98)	92 (88–100)	0.09
Cholesterol (mg/dL)	206 (189–239)	218 (186–251)	191 (174–226)	0.17
LDL cholesterol (mg/dL)	136 (114–163)	146 (110–175)	123 (105–152)	0.15
HDL cholesterol (mg/dL)	51 (46–60)	49 (44–57)	50 (45–58)	0.39
Triglycerides (mg/dL)	111 (87–160)	127 (89–158)	105 (89–139)	0.40
Sleep variables				
AHI (events/h)	1.9 (0.5–3.3)	8.3 (6.0–11.1)	16.9 (15.4–24.5)	<0.001
Mean SaO_2 (%)	96 (96–98)	96 (95–96)	95 (94–96)	<0.001
Lowest SaO_2 (%)	91 (89–93)	85 (82–88)	80 (75–84)	<0.001
Desaturation index (number/h)	1.2 (0.2–2.7)	7.1 (5.2–9.6)	14.7 (12.2–19.1)	<0.001
$SaO_2 < 90$ % (% of nighttime)	0 (0)	0.5 (0.1–1.2)	2.3 (0.7–3.9)	<0.001

Data are presented as median (interquartile range)

AHI apnea-hypopnea index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *OSA* obstructive sleep apnea, *SaO_2* arterial oxygen saturation

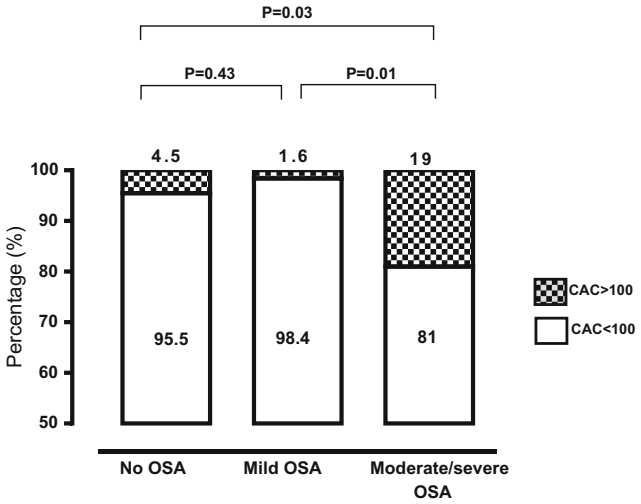

Fig. 1 Presence of abnormal coronary artery calcification in participants according to the presence or absence of obstructive sleep apnea (OSA)

associated with CAC in women, suggesting that women are not spared from the cardiovascular consequences of significant OSA [11]. Furthermore, one recent study that evaluated a cohort of 967 women studied for suspicion of OSA and followed for 6.8 years reported an association between untreated OSA with incident stroke and coronary heart disease [36].

Our study has some potential limitations. First, we used a portable sleep device that does not measure sleep. However, this device was validated against full polysomnography and may help to simplify OSA diagnosis [20]. Second, we cannot infer any causality but an association between OSA and CAC, as we performed a cross-sectional study. Lastly, this study enrolled only perimenopause and postmenopause women and we cannot apply our findings to premenopausal women. Strengths of our study include the recruitment of consecutive women from nonsleep clinic population. Most of previous studies that addressed CAC [31] have recruited from sleep clinic populations which biases toward a larger number of OSA diagnoses. The selection of middle-aged women in the menopausal transition addresses a specific population at high risk for cardiovascular diseases that has not been studied.

In conclusion, our study suggests that moderate to severe OSA may contribute to the cardiovascular risk in the middle-aged women. Therefore, efforts to increase recognition of OSA in middle-aged women may help to reduce the cardiovascular risk in this population, though more evidence is necessary to support a systematic evaluation of OSA in this population.

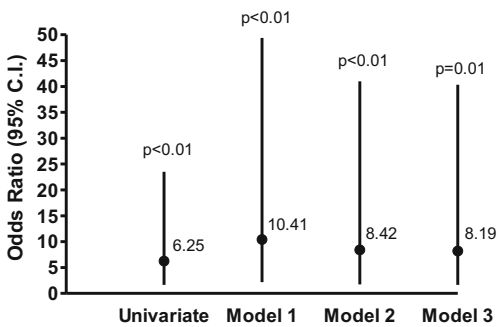

Fig. 2 Logistic regression models relating coronary artery calcification and obstructive sleep apnea. *CI* confidence interval, *Model 1* controlling for body mass index, *Model 2* controlling for body mass index and Framingham Risk Score, *Model 3* controlling for body mass index, Framingham Risk Score, and diabetes

Authors' contributions Ana Kelley L. Medeiros: data collection and analysis and manuscript draft
Ricardo Q. Coutinho: data collection and analysis
Isly M. L. Barros: data collection and analysis
Laura O. B. F. Costa: study design.
Ana Paula D. L. Leite: CAC evaluations
Marcio S. Bittencourt: data analysis and manuscript draft
Thais C. Lustosa: data collection
Martinha M. B. Carvalho: data collection
Maria Priscila Figueiredo Lira: data collection
Moacir N. L. Ferreira: study design
Geraldo Lorenzi-Filho: data analysis and manuscript draft
Luciano F. Drager: data analysis and manuscript draft
Rodrigo P. Pedrosa: study design, data collection and analysis, and manuscript draft

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institute (Complexo Hospitalar-Hospital Universitário Oswaldo Cruz-Universidade de Pernambuco/UPE/Procape, Approval Number CAAE-0135.0.106.000-10) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Informed consent Informed consent was obtained from all individual participants included in the study.

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