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Severity of obstructive sleep apnea and extension of coronary artery disease

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Abstract

Purpose Obstructive sleep apnea (OSA) is highly prevalent among patients with coronary artery disease (CAD). The relationship between the severity of OSA and the severity of CAD has not been entirely established. The objective was to explore the type of correlation existent between the apnea-hypopnea index and the Gensini score, which provides granularity in terms of CAD extension and severity, in search of a dose-response relationship.

Methods A cross-sectional study was conducted among patients that underwent cardiac catheterization due to the suspicion of CAD. Coronary lesions were classified according to one's Gensini score. The severity of OSA was determined by the apnea-hypopnea index (AHI), obtainable through a respiratory polysomnography.

Results Eighty patients were eligible for the study. The mean age was 55 years, and 37% had AHI ≥ 15. Forty-four subjects (55%) had a Gensini score of 0, and five had a score < 2, indicating a 25% obstruction in a non-proximal artery; these individuals were considered non-CAD controls; and clinical characteristics were similar between them and CAD cases. Attempts to correlate the AHI with the Gensini score either converting both variables to square root ($r = 0.08$) or using Spearman's rho (rho = 0.13) obtained small, non-significant coefficients. AHI ≥ 15 was a predictor of a Gensini score ≥ 2 with a large effect size (OR 4.46) when adjusted for age ≥ 55 years, BMI ≥ 25 kg/m^2, uric acid, and hypertension.

Conclusions In patients undergoing coronary angiography due to suspected CAD, moderate-severe OSA was associated with the presence of CAD but no significant correlation was found between the lesion severity and the AHI. Our results suggest that OSA influences CAD pathogenesis but a dose-response relationship is unlikely.

Keywords Sleep apnea · Atherosclerosis · Cardiovascular disease · Coronary disease · Gensini score

Introduction

Up to 65% of patients who seek medical evaluation due to coronary artery disease (CAD) have some degree of obstructive sleep apnea (OSA) [1]. Applying simple questionnaires in either in- or outpatient settings can assess the probability of OSA in patients [2–4]. OSA has also been considered a stronger risk factor than some classic factors, such as dyslipidemia [5]. There has been even an association between OSA and CAD when important factors such as age, diabetes, and tobacco use are excluded from the analysis [6].

The association of OSA with early atherosclerosis has been proposed and is plausible since OSA promotes cellular changes at the endothelial level, which may trigger atherosclerosis [7]. Among the mechanisms that are thought to explain the link between OSA and cardiovascular morbidity, elevated blood pressure and oxidative stress are potential influences. Treating OSA with CPAP reduces blood pressure, which can potentially reduce cardiovascular outcomes [8]. CPAP reverts early atherosclerotic changes like the intima-media thickness only in severe OSA cases [9, 10]. Turmel et al. [11] have demonstrated that the OSA severity is associated with a larger plaque volume.

Jorge P. Ribeiro is deceased. This paper is dedicated to his memory.

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The relationship between severity of OSA and cardiovascular mortality is described in the literature [12], and this may be due to a larger extension of CAD in patients with higher apnea-hypopnea index (AHI). Hayashi et al. [13] have found that OSA was associated with a larger CAD extension determined by the Gensini score, while sleep apnea was determined by pulse oximetry. Our aim was to evaluate the association between the severity and the extent of CAD with the severity of OSA through a polysomnography measurement.

Methods

This was a cross-sectional study, designed according to the guidelines and regulatory standards for research involving humans, Resolution 196/96 of the National Council of Health. It was conducted in a tertiary university hospital in southern Brazil between May 2009 and October 2010.

Patients

The study comprised 80 patients aged between 35 and 70 years with a medical indication for a coronary angiography due to chest pain of suspected ischemic heart disease (myocardial ischemia, stable angina, acute coronary syndrome without ST elevation). Exclusion criteria included refusing to participate and sign the consent form; living in another city, making it difficult to follow and perform home portable polysomnography; and experiencing technical failure in polysomnography or cardiac catheterization. Patients with acute myocardial infarction with ST segment elevation, clinical instability, heart failure, ejection fraction < 50%, valvar disease, or body mass index (BMI) greater than 40 kg/m^2 were also excluded from the study.

The Gensini score [14] adds 1, 2, 4, 8, 16, and 32 points for reductions in luminal diameter of 25%, 50%, 75%, 90%, 99%, and 100%, respectively. The left main coronary artery multiplies the points by 5; proximal branches of the left anterior descending (LAD) and circumflex artery by 2.5; the middle segment LAD by 1.5; the right coronary artery, distal segment of the LAD, posterolateral artery, and obtuse marginal by 1; and other artery segments by 0.5.

The left heart catheterization technique followed the standard protocol of the Hemodynamics Unit [15]. After cannulation of the left and right coronary arteries, intracoronary 200 mcg of nitroglycerin was administered. Digital images were stored and submitted to a quantitative coronary angiography offline. After at least 8 h of fasting and right before the angiography, arterial blood was collected and analyzed for total cholesterol, HDL cholesterol, triglycerides, high sensitivity C-reactive protein (Hs-CRP), and glucose.

Portable respiratory polygraphy with level III monitor (SomnoCheck effort, Weinmann, Hamburg, Germany) was performed within 10 days of the angiographic procedure, which included airflow, snoring, inspiratory effort, pulse oximetry, heart rate, and position as previously validated in our laboratory [16]. The apnea-hypopnea index (AHI) was calculated by dividing the total number of apneas and hypopneas per hour of recording time without artifacts. AHI < 5 events/h was considered normal. The tracings were analyzed by a sleep specialist blinded to the angiography results.

Through a standardized questionnaire, traditional risk factors and demographic factors as well as one's complete medical history were evaluated using the chi-square test. Independent samples test was performed to compare means between groups. The AHI was converted to square root to obtain a distribution non-different from normal in the Kolmogorov-Smirnov test. The correlations between AHI and Gensini score, both non-normally distributed variables, were tested using Spearman's coefficient. Multivariate logistic analysis was used to determine the adjusted odds ratio to predict abnormal Gensini, adjusting for usual confounders and variables significantly associated with the Gensini outcome. The regressors were included either as binary or continuous variables, whichever provided the highest Nagelkerke r square for the model. AHI was used as the binary variable, split at 15 events per hour and as square root of AHI in the model. Variables associated with the dependent variable were selected by the stepwise method, entering with $p < 0.10$. Results were expressed as odds ratio (OR) and adjusted odds ratio, with 95% confidence interval. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL).

Results

Eighty patients were eligible among the routine patients undergoing coronary catheterization. The mean age was 54 years, 50% of the patients were female, and the mean BMI was 28 kg/m^2. Considering AHI > 5 events/h, mild OSA was present in 81% of patients with a Gensini score > 0 and 86% of patients with a Gensini score = 0. Moderate-severe OSA defined by apnea-hypopnea index ≥ 15 events/h was present in 59% of patients with a Gensini score > 0 and in 37% of patients with a Gensini score = 0 ($p = 0.06$). Median apnea-hypopnea index was 16 [9–26] in patients with a Gensini score > 0 and 10 [3–22] in patients with a Gensini score = 0 ($p = 0.06$). None of the baseline characteristics were statistically different between groups. Table 1 shows anthropometric, polysomnographic, and biochemical variables in patients with Gensini 0, ≥ 2, and overall patients.

Attempts to correlate the AHI with the Gensini score either converting both variables to square root ($r = 0.08$) or using Spearman's rho (rho = 0.13) obtained small, non-significant coefficients. Even excluding the non-CAD cases and utilizing only the 32 CAD cases in search for AHI-Gensini score

Table 1 Characteristics of study population

	Gensini 0 $n = 48$	Gensini ≥ 2 $n = 32$	Total $n = 80$	P
Anthropometric				
Gender male—*n* (%)	21 (44)	19 (59)	40 (50)	0.25
Age (years)	54 ± 7	55 ± 5	54 ± 7	0.09
Skin color (white)—*n* (%)	36 (75)	25 (79)	61 (76)	0.97
Weight (kg)	77 ± 15	74 ± 11	76 ± 14	0.32
Waist circumference (cm)	101 ± 24	99 ± 5	101 ± 20	0.14
BMI (kg/m^2)	28 ± 5	27 ± 4	28 ± 5	0.17
BMI > 25 kg/m^2—*n* (%)	36 (75)	20 (64)	56 (70)	0.23
Portable polysomnography				
Apnea-hypopnea index—events/h [Q1–Q3]	10 [3–21]	16 [9–25]	11 [5–24]	< 0.01*
Apnea-hypopnea index ≥ 15 events/h—*n* (%)	18 (37)	19 (59)	37 (46)	0.06
Average saturation (%)	94.7 ± 2	95 ± 2	95 ± 2	0.22
Minimum saturation (%)	85 ± 5	84 ± 4	82 ± 7	0.66
Biochemistry				
Glucose (mg/dL)	105 ± 12	106 ± 10	105 ± 11	0.26
LDL cholesterol (mg/dL)	107 ± 35	88 ± 36	99 ± 36	0.46
HDL cholesterol (mg/dL)	49 ± 13	40 ± 11	46 ± 13	0.70
Triglycerides (mg/dL)	123 ± 110	137 ± 56	128 ± 92	0.12
Uric acid (mg/dL)	5.3 ± 1.45	6.15 ± 1.45	5.64 ± 1.5	0.04
Iron (g/dL)	84 ± 27	81 ± 25	83 ± 26	0.56
Glucose (mg/dL)	105 ± 12	106 ± 10	105 ± 11	0.59
Medications				
Statin—*n* (%)	34 (72)	24 (75)	58 (72)	0.66
Antihypertensive drugs—*n* (%)	41 (86)	29 (90)	70 (87)	0.45
Aspirin—*n* (%)	41 (86)	29 (90)	70 (87)	0.45
Prior disease				
Dyslipidemia—*n* (%)	33 (69)	25 (79)	58 (72)	0.54
Hypertension—*n* (%)	39 (81)	28 (87)	67 (83)	0.32
Diabetes mellitus—*n* (%)	23 (48)	16 (50)	39 (49)	1.00
Smoking—*n* (%)	25 (52)	17 (53)	42 (52)	0.72

Values are mean ± SD, *n* (%), or median [Q1–Q3]. *BMI*, body mass index; *Ev/h*, events per hour; *CAD*, coronary artery disease; *Hs*, high sensitivity; *IQR*, interquartile range; *HDL*, high-density lipoprotein cholesterol; *P*, probability of differences by *t* test or chi^2

**P* obtained from difference between square roots of AHI

correlations, no significant results were obtained. The non-parametric correlation coefficient between minimum oxygen saturation and the Gensini score was 0.27 ($P = 0.052$). Controlling for sex, age, and BMI, the resulting adjusted r square was 0.03. Testing the Gensini as a binary variable, split at < 2 and ≥ 2, the univariate odds ratios were significant for uric acid and square root of AHI (OR 1.76), meaning that for an increase of 1 in AHI square root, e.g., when AHI increases from 16 (square root 4) to 25 (square root 5), increases 76% the odds of having a Gensini score ≥ 2. Only square root of AHI remained a significant predictor of a Gensini score ≥ 2 in a parsimonious multivariate model, adjusting for hypertension, age, uric acid, and BMI (Table 2).

Categorizing age ≥ 55 years, BMI ≥ 25 kg/m^2, and AHI ≥ 15/h, the latter was a predictor of a Gensini score ≥ 2 with a large effect size (OR greater than 4). None of the other regressors were statistically significant (Fig. 1).

Discussion

The present study indicates that, in patients referred for coronary angiography, the extension and severity of CAD are not directly associated with the severity of OSA, assessed by AHI in the respiratory polygraphy. This preliminary study is, to our knowledge, the first to evaluate the association of CAD

Table 2 Predictors of coronary artery disease (CAD) in univariate and multivariate analysis. Values are expressed in odds ratio (OR) and confidence interval (CI) of 95%. *AHI*, apnea-hypopnea index; *BMI*, body mass index

Characteristic	OR	95% CI	*P*	Adjusted OR	95% CI	*P*
Hypertension	2.15	0.53–8.68	0.381	1.16	0.21–6.28	0.866
Uric acid	1.51	1.02–2.29	0.049	1.32	0.84–2.08	0.222
AHI square root	1.76	1.18–2.65	0.006	1.56	1.03–2.38	0.037
Age	1.03	0.96–1.09	0.505	1.03	0.93–1.14	0.589
BMI	0.98	0.88–1.08	0.633	0.98	0.83–1.16	0.860

severity and OSA severity using coronary angiography and a reliable method for apnea quantification.

We found only one previous study by Hayashi et al. [l3] that reported significant correlation between the Gensini score and nocturnal oxygen desaturation index (ODI) for desaturation events > 3%, an indirect marker of OSA obtained by pulse oximetry. The correlation between AHI and Gensini score in our study was non-significant, but the minimum oxygen saturation was near-significantly correlated with the Gensini score. Several studies have shown that oxygen-related indices are better predictors of cardiac outcomes in OSA [17]. Different from our study, the severity of coronary lesions was greater, with a higher mean Gensini score in their study compared to that of ours. This may be due to our population, even having risk factors that led to cardiac catheterization, being mostly of elective cases, resulting in a high percentage of non-significant lesions. Also, ODI is insensitive to detect mild cases of OSA compared to the AHI. These differences make the findings difficult to compare between studies. Our analysis is, therefore, the first to suggest the lack of correlation between CAD severity and OSA severity using diagnostic approaches for both diseases which provide a reliable indication disease severity.

The prevalence of AHI > 5 in 81% and 86% in CAD and no CAD groups indicates that the recommendation by cardiology textbooks and societies to consider OSA a frequent cardiovascular risk factor is correct [18, 19]. Similar percentages of OSA are observed in patients with resistant hypertension [20]. Our finding of an odds ratio of 4.46 for a Gensini score ≥ 2 in a multivariate model is consistent with the previous reports that OSA is a stronger risk factor than classical ones such as dyslipidemia, glycemia, uric acid, and overweight [5]. However, the lack of a dose-response gradient would reduce the probability of a cause-effect association despite some evidence that OSA is a causal factor of CAD [7]. Although a study showed no benefit of OSA treatment with CPAP in reducing cardiovascular outcomes [21], the adherence to treatment and follow-up time may have not been sufficient to result in a difference between groups. Observational studies have found that patients using CPAP had lower rates of adverse outcomes [22–24]. Two meta-analyses suggest that the benefit may be restricted to adherent patients, especially those who use CPAP during 4+ hours per night [25, 26].

One of the main limitations of the present study is the relatively small sample size. The fact that known risk factors for coronary disease are non-significant in the study represents

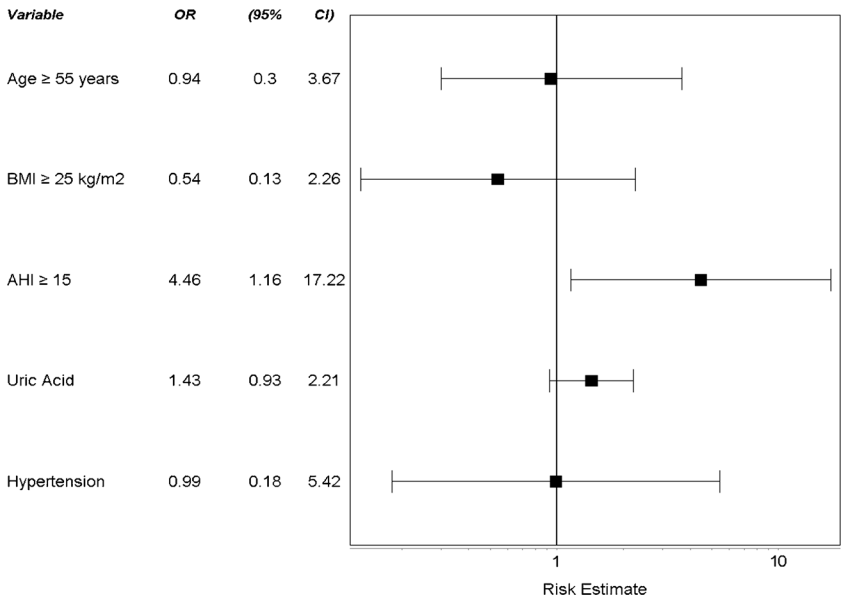

Fig. 1 Forrest plot with predictors of coronary artery disease (CAD) in univariate and multivariate analysis. Values are expressed in odds ratio (OR) and confidence interval (CI) of 95%. AHI, apnea-hypopnea index; BMI, body mass index

further indication of it being underpowered. Therefore, the possibility of type II error is elevated when dismissing the existence of correlation between OSA severity and the Gensini score. However, previous observational studies found significant binary associations between OSA and CAD with similar sample sizes [4, 13]. Another limitation is including only individuals referred for coronary angiography with suspected myocardial ischemia, an obvious selection bias. To solve this obstacle to find a granularity in the OSA-CAD relationship, the association between OSA and CAD would need to be explored in population-based studies. This would demand using noninvasive diagnostic methods such as the calcium score of coronary arteries, inflammatory markers, and endothelial function, a task difficult to achieve.

In conclusion, in patients undergoing coronary angiography due to suspected CAD, moderate- severe OSA was associated with the presence of CAD but no significant correlation was found between the lesion severity and the AHI. Our results suggest that OSA influences CAD pathogenesis but a dose-response relationship is unlikely.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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Comment

In this relatively small study which used PSG to assess SDB in patients having coronary angiography and in which CAD severity was measured using the Gensini score showed that AHI was a powerful predictor of the presence of CAD when conventional risk factors were not. This implies AHI may indeed be an important risk factor for developing coronary artery disease. The relationship between OSA and coronary artery disease in both its chronic and acute forms is a critical one given the prevalence of OSA in patients with CAD. The authors show there is a relationship between OSA and CAD which seems not to reflect OSA severity defined using conventional agreed severity criteria. Larger studies are needed to determine whether AHI or ODI are indeed equivalent and whether PSG is really needed to stratify OSA severity. A coronary calcium score would be of interest but is obtained from CT not angiography. The study should encourage more investigation discourse on this topic

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