



Clinical Characteristics and Prevalence of Sleep Disordered Breathing in Patients with Coronary Artery Disease

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Abstract

Introduction: Obstructive sleep apnea syndrome (OSAS) and coronary artery disease (CAD) are highly prevalent diseases in the population and both appear to be associated.

Objectives: This study aimed to identify the clinical characteristics and prevalence of sleep disordered breathing (SDB) and OSAS among CAD patients.

Methods: A hundred and thirty-two consecutive patients (111 males and 21 females with mean age of 67.1 ± 11.5 years, BMI of 27.7 ± 4.5 kg/m²) referred to the Cardiology Division for evaluation of CAD by coronary angiography (CA) were studied. As a first step, the subjects underwent a standard medical interview and general physical examination. Secondly, a sleep questionnaire including questions regarding the history of snoring, breathing pauses during sleep, and excessive daytime sleepiness was applied. The third step was a cardiorespiratory polygraphy that was conducted one or two days before finally carrying out a cardiac catheterization and a CA.

Results: 114 patients (86%) presented a positive CA; 18.4% one-vessel disease, 27.2% two-vessel disease and 64.4% three-vessel disease. With respect the SDB levels; 59.1% showed an AHI ≥ 5 , 38.6% an AHI ≥ 10 ; and 21.2% an AHI ≥ 20 . In addition, 6.8% reported OSAS (AHI ≥ 5 , disrupted breathing during sleep together with excessive daytime sleepiness).

The group of patients with AHI ≥ 10 had higher age, BMI and snoring than those patients with AHI < 10 . OSAS patients had a higher prevalence of diabetes and hypertension than non-OSAS patients. In addition, OSAS patients had lower left ventricular ejection fraction. No significant differences among groups were observed in the number of coronary vessels affected.

Conclusion: SDB and OSAS are very common among coronary disease patients and may be associated to left ventricle performance. This finding suggests the need for physicians to perform routine screening and individual evaluation of coronary patients for sleep-disordered breathing.

Keywords: Coronary artery disease; Sleep disordered breathing; Obstructive sleep apnea syndrome; Coronary angiography

Introduction

Obstructive sleep apnea syndrome (OSAS) is a respiratory disorder characterized by recurrent airflow obstruction caused by the total or partial collapse of the upper airway [1]. In adult populations, the prevalence is estimated to be 4% among males and 2% among females [2]. Epidemiological studies in our community have shown an OSAS prevalence of 7% among people 50 to 70 years of age [3].

OSAS may be an important independent risk factor for cardiovascular disease [4-7]. The mechanisms involved in the association between OSAS and vascular diseases are complex and diverse. Patients with OSAS experience repetitive episodes of hypoxia and reoxygenation during temporary cessation of breathing that may provoke systemic effects. These patients also present increased levels of biomarkers linked to endocrine-metabolic and cardiovascular alterations [8]. Data from cohort-based studies suggest that OSAS is an independent risk factor for myocardial infarction and other coronary events [9-13]. Furthermore, subjects with OSAS are at increased risk for sudden death from cardiac causes [14,15]. It has been shown that active continuous positive airway pressure (CPAP) treatment reduces the incidence of hypertension and cardiovascular events [16,17].

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Table 1: Demographic data, clinical characteristics, comorbidities, CA results, level of sleep disordered breathing and OSAS of the study population (n=132).

Variable	Values
Age (years)	67.1 ± 11.5
BMI (Kg/m²)	27.7 ± 4.5
Males (%)	101 (76.5)
History of snoring (%)	66 (50.0)
Daytime sleepiness (%)	15 (13.2)
Smoking (%)	22 (16.7)
Alcohol (%)	26 (19.7)
Diabetes mellitus (%)	11 (8.3)
COPD (%)	5 (3.8)
Hypertension (%)	64 (48.5)
Positive CA (%)	114 (86.4)
One-vessel disease	21 (18.4)
Two-vessels disease	31 (27.2)
Three-vessels disease	62 (64.4)
AH ≥ 5 (%)	78 (59.1)
AHI ≥ 10 (%)	51 (38.6)
AHI ≥ 20 (%)	28 (21.2)
OSAS (%)	9 (6.8)

BMI: Body Mass Index; Smoking: Smoking History (current or former); COPD: Chronic Obstructive Pulmonary Disease; AHI: Apnea–Hypopnea Index; OSAS: Obstructive Sleep Apnea Syndrome; Positive CA: Positive Coronary Angiography. * Values are mean ± SD; percentage.

While the risk factors involved in the association between OSAS and coronary artery disease (CAD) have been identified, few studies have focused on the levels of sleep disordered breathing (SDB) and OSAS in CAD patients. The hemodynamic stress induced by OSAS may be of importance in CAD patients. In addition, the severity of CAD may also influence the level of sleep disordered breathing.

The aim of this study was to identify the clinical characteristics and prevalence of sleep disordered breathing and OSAS among CAD patients verified by CA.

Patients and Methods

Study design and patient population

Over a period two years, 132 consecutive patients were referred to the Cardiology Division for CAD evaluation by CA (111 males and 21 females with a mean age of 67.1 years, ranging from 33 to 85, BMI of 27.7 ± 4.5 kg/m₂). This study was approved by the Ethics Committee in Research. Informed consent was obtained from each patient before participation in the study.

All patients referred to the cardiac catheterization lab for elective coronary angiography were eligible to participate and those who refused were excluded.

Study protocol

At the time the patients checked into the hospital to undergo CA, they were also asked to participate in our study. If they agreed, subjects completed a sleep questionnaire, underwent a complete general physical examination and a respiratory polygraphy in a hospital setting.

As a first step, subjects underwent a standard medical interview and general physical examination. Traditional cardiovascular risk

Table 2: Comparison of demographic data, clinical features, comorbidities, level of sleep disordered breathing and OSAS in relation to gender.

	Males n = 101	Females n = 31	P value
Age (years)	66.3 ± 11.0	70.2 ± 12.8	0.08
BMI (Kg/m²)	27.4 ± 4.0	28.4 ± 5.8	0.30
Snoring (%)	55 (54.5)	11 (35.5)	0.05
Daytime sleepiness (%)	15 (14.9)	4 (12.9)	0.52
Smoking (%)	22 (21.8)	0 (0)	0.01
Alcohol (%)	25 (24.8)	1 (3.2)	0.005
Diabetes mellitus (%)	9 (8.9)	2 (6.5)	0.49
COPD (%)	4 (4.0)	1 (3.2)	0.66
Hypertension (%)	51 (50.5)	13 (41.9)	0.26
AHI	11.4 ± 10.8	12.0 ± 12.5	0.79
AHI ≥ 5 (%)	63 (62.4)	15 (48.4)	0.12
AHI ≥ 10 (%)	39 (38.6)	12 (38.7)	0.57
AHI ≥ 20 (%)	23 (22.8)	5 (16.1)	0.30
OSAS (%)	6 (5.9)	3 (9.7)	0.36

factors were assessed according to several criteria. “Hypertension” was defined as ongoing pharmacologic antihypertensive treatment and/or a recorded systolic blood pressure of (BP) ≥ 160 mm Hg and/or diastolic BP ≥ 95 mm Hg, measured on at least three different days or during the hemodynamic study. Patients were classified as having diabetes mellitus if they received treatment with insulin or oral hypoglycemic agents or if their fasting blood sugar concentration was > 140 mg/dl on three separate occasions. Subjects were classified as current smokers, former smokers (those who had stopped smoking at least six months before the study inclusion), and those with no history of smoking [18].

Secondly, a questionnaire was administered to each patient in the presence of a bed partner when available. The sleep questionnaire included items such as history of snoring, breathing pauses during sleep, and excessive daytime sleepiness. Patients who reported a snoring frequency of at least three days per week were classified as “snorers”. The degree of self-reported sleepiness/drowsiness was analyzed by the Spanish version of the Epworth sleepiness scale test. If the score was 10 or more, subjects were classified as having excessive daytime sleepiness [19].

The third step in our analysis was a respiratory polygraphy that was conducted one or two days before CA. The diagnosis was based on the guidelines of the Spanish national consensus [20].

As for the classification of SDB, we used respiratory disturbance index cut-off points (AHI ≥ 5; AHI ≥ 10 and AHI ≥ 20). A diagnosis of OSAS was reached when AHI ≥ 5, disrupted breathing during sleep together with daytime sleepiness unexplained by other factors [2].

The final step of our analysis consisted of cardiac catheterization. This procedure included a CA and ventriculography. CAD was defined as diameter lumen stenosis of more than 50% in at least one major coronary artery. The extent of coronary artery disease was scored as a single-vessel disease, two-vessel disease, or three-vessel disease, according to the number of main vessels with stenosis [21]. In 103 patients, we obtained the aortic systolic pressure (AOSP) and the aortic diastolic pressure (AODP). In addition, we measured the left ventricle ejection fraction (LVEF) and left ventricle end diastolic pressure (LVEDP) using ventriculography.

The LVEF was scored as either normal (≥ 0.50) or abnormal (< 0.50). The LVEDP was scored as normal (<12 mmHg) or abnormal (≥ 12 mmHg).

Statistical analysis

Data were analyzed using the SPSS software program (IBM SPSS Statistics Version 20). Variables were expressed as the mean \pm standard deviation or percentage. Subgroups of CAD patients were compared using Student's t-test for continuous variables; non-normally distributed variables were compared using Mann-Whitney test. The Chi-square test was utilized to test for the association and difference between the categorical variables. A p value of less than 0.05 was statistically significant.

Results

The baseline characteristics of the study population are given in (Table 1), which presents the distribution of anthropometric measurements, clinical features, comorbidities and SDB levels. The high prevalence of hypertension and SDB in this population is worth highlighting; 48.5% of participants suffered from high blood pressure. 114 patients (86.4%) presented a positive CA; 18.4% one-vessel disease, 27.2% two-vessel disease and 64.4% three-vessel disease. With respect to SDB levels; 59.1% showed an AHI ≥ 5 , 38.6% an AHI ≥ 10 ; and 21.2% presented an AHI ≥ 20 . In addition, 6.8% reported OSAS.

Table 2 shows that males presented a lower age and higher prevalence of snoring, smoking history and alcohol consumption than females. There were no significant differences between the two groups in BMI, the prevalence of COPD and hypertension, AHI, the level of sleep disordered breathing and OSAS.

Table 3 compares patients who presented positive CA and those who presented negative CA. Of patients with a positive CA, 4.4% had COPD; of the patients with a negative CA, 0% had COPD. There were no significant differences between the two groups in the remaining variables.

Table 4 shows that patients with an AHI ≥ 10 had higher age, BMI and snoring than those with AHI < 10 . No differences among groups were observed in the remaining variables.

The OSAS group (n = 9) had a higher prevalence of diabetes (55.5% vs. 4.9%) and hypertension (66.7% vs. 47%) than the non-OSAS group. No differences were observed in the remaining variables.

Table 5 shows that in the positive CA group, patients with AHI ≥ 10 had higher age, BMI and snoring than patients with AHI < 10 . No differences were observed in gender, excessive daytime sleepiness, alcohol, smoking habit, diabetes, hypertension or severity of coronary vessels affected. These results are similar to those in (Table 4) regarding the total population.

Finally, (Table 6) shows the comparison of ventriculographic measurements among groups; the AHI ≥ 10 group had lower AODP and higher LVEDP than the AHI < 10 group. No differences were found in AOSP or LVEF. With respect to the OSAS group, OSAS patients had higher LVEDP (21.5 ± 9.4 vs. 17.7 ± 8.4) and lower AODP (81.6 ± 12.5 vs. 87.0 ± 15.3) and LVEF (0.38 ± 0.14 vs. 0.61 ± 0.16) than non-OSAS patients.

All patients in the OSAS group and 89% of patients with AHI ≥ 10 had an LVEDP ≥ 12 (abnormal) as compared to 39% of patients with AHI < 10 . 83% of patients in the OSAS group had a LVEF < 0.50

Table 3: Comparison of demographic data, clinical features, comorbidities, the level of sleep disordered breathing and OSAS in patients with positive CA and negative CA.

	Positive CA n=114	Negative CA n = 18	P value
Age (years)	67.0 \pm 11.6	67.8 \pm 10.9	0.82
BMI (Kg/m ²)	27.5 \pm 4.5	28.5 \pm 3.4	0.59
Males (%)	88 (77.2)	13 (72.2)	0.42
Snoring (%)	57 (50.0)	9 (50.0)	0.60
Daytime sleepiness (%)	15 (13.2)	4 (22.2)	0.24
Smoking (%)	20 (17.5)	2 (11.1)	0.38
Alcohol (%)	23 (20.2)	3 (16.7)	0.50
Diabetes mellitus (%)	9 (7.9)	2 (11.1)	0.46
COPD (%)	5 (4.4)	0 (0)	0.00
Hypertension (%)	58 (50.9)	6 (33.3)	0.24
AHI	12.2 \pm 14.2	11.4 \pm 10.5	0.79
AHI ≥ 5 (%)	69 (60.5)	9 (50.0)	0.27
AHI ≥ 10 (%)	45 (39.5)	6 (33.0)	0.41
AHI ≥ 20 (%)	24 (21.2)	4 (22.2)	0.56
OSAS (%)	8 (7.0)	1 (5.6)	0.64

Table 4: Comparison of demographic data, clinical characteristics and comorbidities between patients in the overall sample with AHI < 10 and patients with AHI ≥ 10 .

	AHI < 10 n=81	AHI ≥ 10 n= 51	P value
Age (years)	64.9 \pm 11.6	70.4 \pm 10.5	0.018
BMI (Kg/m ²)	26.9 \pm 4.2	28.5 \pm 4.8	0.025
Males (%)	62 (76.5)	39 (76.5)	0.57
Snoring (%)	22 (27.2)	44 (86.3)	0.000
Daytime sleepiness (%)	10 (12.3)	9 (17.6)	0.27
Alcohol (%)	16 (19.8)	10 (19.6)	0.58
Smoking habit (%)	15 (18.5)	7 (13.7)	0.32
Diabetes mellitus (%)	7 (8.6)	4 (7.8)	0.57
Hypertension (%)	41 (50.6)	23 (45.1)	0.33
COPD (%) ^b	2 (2.5)	3 (5.9)	0.29

(abnormal) as compared to 39% of patients with AHI ≥ 10 and 29% of patients with AHI < 10 . 83% of patients in the OSAS group had a LVEDP ≥ 12 and a LVEF < 0.50 as compared to 36% of patients with AHI ≥ 10 and 22% of patients with AHI < 10 .

Discussion

The results of our study clearly indicate that patients who undergo CAD evaluation also present a high prevalence of SDB and OSAS. Among these patients, we found that 59.1% presented some degree of SDB (AHI ≥ 5), and 21.2% showed high levels of SDB (AHI ≥ 20). In addition, 6.8% presented OSAS. Thus, our findings strongly reinforce the belief that SDB and OSAS are common among patients with CAD.

A number of studies have shown a higher prevalence of SDB and OSAS in patients with CAD compared to the general population. Moee et al. [9], studied 142 patients with CAD and positive CA, and found that 37% had an AHI ≥ 10 . Using a similar SDB cut-off point, Sanner et al. [22], found a prevalence of 30.9% and Peker et al. [18], a prevalence of 30.7%. However, Yumino et al. [11], reported a prevalence of 57% using a sample of patients with acute coronary

Table 5: Comparison of demographic data, clinical characteristics, comorbidities and CA results among groups AHI < 10 and AHI ≥ 10 in patients with positive CA.

	AHI < 10 n = 69	AHI ≥ 10 N = 45	P value
Age (years)	64.8 ± 11.7	70.3 ± 10.6	0.018
BMI (Kg/m ²)	26.8 ± 2.4	28.8 ± 4.9	0.025
AHI	4.4 ± 14.2	20.3 ± 10.3	0.000
Males (%)	53 (76.8)	35 (77.8)	0.54
Snoring (%)	17 (24.6)	40 (88.9)	0.000
Daytime sleepiness (%)	8 (11.6)	7 (15.6)	0.57
Alcohol (%)	15 (18.5)	9 (13.7)	0.58
Smoking habit (%)	14 (20.3)	6 (13.3)	0.24
Diabetes mellitus (%)	6 (8.7)	3 (6.7)	0.49
Hypertension (%)	37 (53.6)	21 (46.7)	0.05
COPD (%)	2 (2.9)	3 (6.7)	0.30
Three-vessels disease (%)	24 (34.3)	27 (43.5)	0.18

Table 6: Comparison of ventriculographic measurements between patients with AHI < 10 and patients with AHI ≥ 10.

	AHI<10 n=62	AHI ≥ 10 n= 41	P value
AOSP (mmHg)	129.2 ± 21.8	125.4 ± 20.0	0.39
AODP (mmHg)	89.0 ± 15.3	83.1 ± 14.5	0.053
LVEF (%)	0.61 ± 0.16	0.59 ± 0.18	0.68
LVEDP (mmHg)	16.8 ± 7.8	20.0 ± 9.2	0.60

AOSP: Aortic Systolic Pressure; AODP: Aortic Diastolic Pressure; LVEF: Left Ventricle Ejection Fraction; LVEDP: Left Ventricle End Diastolic Pressure

syndrome who underwent percutaneous coronary intervention. Despite these high levels of SDB, Konecny et al. [23], highlighted the under-recognition of OSAS among patients admitted for diagnosis of acute myocardial infarction. These authors reported that 41% of patients presented an AHI ≥ 15.

In a large study involving 3017 patients with CAD and heart failure, Varoneckas et al. [24], found a 23.5% prevalence of mild SDB (AHI > 5 and ≤ 15), a 10.6% prevalence of moderate SDB (AHI > 15 and ≤ 30), and a 6.4% prevalence of severe SDB (AHI > 30). In a study of 93 patients with CAD, Tan et al. [13], observed that 34.4% had OSAS (AHI ≥ 15). Recently, in a cross-sectional study of 156 patients who exhibited evidence of CAD, Wali et al. [25], performed a complete sleep study in 48 patients at high-risk for OSAS and confirmed that 68.8% did, in fact, suffer from OSAS.

Our findings are in line with these authors, although Yumino and Wali reported somewhat higher values. This variation in SDB and OSAS prevalence data among patients with CAD can be attributed to factors including differences in CAD stage, differences in study methodology, different AHI cut-off points, and differences in sample characteristics.

Among patients known to have OSAS, a high prevalence of CAD has also been reported. Several studies have shown that OSAS patients have a higher incidence of fatal and nonfatal cardiovascular events compared to non-OSAS patients [5,26-30]. An observational study by Marin et al. [26], involving simple snorers, patients with untreated OSAS, patients treated with CPAP, and healthy men recruited from the general population found that the risk of fatal and non-fatal cardiovascular events was significantly higher among severe untreated OSAS patients.

Barbé et al. [30], performed an observational study to evaluate the impact of OSAS on the severity and short-term prognosis of patients with acute coronary syndrome. Patients underwent respiratory polygraphy during the first 48–72 h after admission. Out of 213 patients with OSAS, 77.5% presented the first episode of acute coronary syndrome. CA showed that 43.7% presented one- vessel disease, 25.6 % two-vessel disease and 30.7% three-vessel disease. The present study found a prevalence of 18.4% for one-vessel disease, 27.2% for two-vessel disease, and 64.4% for three-vessel disease. This suggests a greater CAD severity, though no significant relationship with SDB levels was found.

Furthermore, in our study, men presented a higher prevalence of snoring, smoking history, and alcohol than females. However, the small number of women in our sample may account for the lack of a significant gender difference in some variables such as SDB and OSAS. Nevertheless, the existence of confounding factors makes it difficult to draw a conclusion regarding the relation between OSAS and CAD. Although OSAS and CAD share certain common risk factors such as obesity, male sex, smoking, and advanced age (2-4), the question of a causal relationship is still unclear.

We must keep in mind that OSAS has also been closely associated with other adverse clinical outcomes, including hypertension and diabetes mellitus. In fact, we found both hypertension and diabetes to be more common in the OSAS group.

In our study, patients an AHI ≥ 10 had higher age, BMI, and snoring than patients with an AHI < 10. Moee et al. [9], studied CAD in subjects with and without OSAS and found that history of snoring and reported apneas did not differ significantly between groups, while excessive daytime sleepiness was more common in the OSAS group.

Regarding patients with positive and negative CA, Sanner et al. [22] found no significant difference in age, diabetes mellitus and hypertension. We have similar results.

In the our study, 86% of patients presented positive CA and these patients had a higher prevalence of COPD than patients with negative CA. 4.4% of patients with positive CA had COPD, while there were none in the negative CA group. Previous studies have shown an association between COPD and reduced lung functions with subclinical atherosclerosis. Iwamoto et al. [31] reported that smokers with obstructive lung disease also had subclinical atherosclerosis. In the ARIC Study and MESA Lung Study, low FEV1 was found to be associated with increased atherosclerosis [32,33]. Lahousse et al. [34], showed that patients with COPD had twice the risk of carotid wall thickening compared to healthy subjects. Along these same lines, we found that subjects with COPD also were more likely to present CAD.

In the present study, 100% of patients with OSAS and 89% of patients with an AHI ≥ 10 had an LVEDP ≥ 12. 83% of OSAS patients had an LVEF < 0.50. OSAS patients had higher LVEDP and lower LVEF than patients without OSAS.

Patients with OSAS often have coexisting disorders such as obesity, hypertension, and diabetes mellitus which have been associated with increased diastolic dysfunction. The existence of these confounding factors makes it difficult to determine the influence of OSAS itself. After adjusting for confounding factors, Glantz et al. [35], investigated whether OSAS severity predicts blood pressure or cardiac left ventricular thickness in a clinical population of OSAS patients. These authors concluded that AHI is an independent

predictor of several measures of blood pressure and that OSAS severity and LV muscle thickness appear to be primarily linked via increased blood pressure. However, Sanner et al. [22], found that there was a significant correlation between AHI and LVEF even after adjusting for confounding factors.

In a prospective study of 15 OSAS patients with no co-morbidities, Alchanatis et al. [36], concluded that repetitive apnoeas/hypopnoeas influence the development of left ventricle diastolic dysfunction in patients with untreated OSAS. Treatment with CPAP was found to lead to significant improvement [36]. Liu et al. [37], investigated the effects of CPAP on cardiac structure and function in patients with CAD combined with OSAS. CPAP therapy was found to significantly reduce left ventricular and systolic and diastolic diameters, improve heart function and reduce the occurrence of cardiovascular complications.

The present study has several limitations: first of all, instead of overnight polysomnography, we measured AHI by respiratory polygraphy, and this method is known to underestimate AHI. Secondly, our study group was relatively small, since this was a single-center study. As is typically for OSAS, most of our patients were male, aged over 40, and in many cases had coexisting diseases such as diabetes, arterial hypertension, CAD, and obesity. Therefore, our results cannot be readily extrapolated to general population. Thirdly, all the patients in the study were recruited for a hemodynamic study in a referral center and a referral bias is possible.

In conclusion OSAS is very common among coronary disease patients and may be associated to left ventricle performance. This finding suggests the need for physicians to perform routine screening and individual evaluation of coronary patients for sleep-disordered breathing.

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