General Cardiology

CARDIOLOGY

Cardiology 1999;92:79–84

Received: April 29, 1999
Accepted after revision: July 20, 1999

Obstructive Sleep Apnea as a Risk Marker in Coronary Artery Disease

Harald Schäfer[a] Ulrich Koehler[b] Santiago Ewig[a] Ekkhard Hasper[a]
Selcuk Tasci[a] Berndt Lüderitz[a]

[a]Department of Cardiology and Pulmonary Medicine, University of Bonn, Bonn, and
[b]Department of Internal Medicine, University of Marburg, Marburg, Germany

Key Words
Coronary artery disease · Sleep apnea · Risk factors

Abstract

Study Objectives: Obstructive sleep apnea (OSA) is associated with a range of cardiovascular sequelae and increased cardiovascular mortality. The aim of our study was to assess the prevalence of OSA in patients with symptomatic angina and angiographically verified coronary artery disease (CAD). In addition, we analyzed the association of OSA and other coronary risk factors with CAD and myocardial infarction. ***Methods:*** Overnight non-laboratory-monitoring-system recordings for detection of OSA was performed in 223 male patients with angiographically verified CAD and in 66 male patients with exclusion of CAD. A logistic regression analysis was performed to assess associations between risk factors and CAD and myocardial infarction. ***Results:*** CAD patients were found to have OSA in 30.5%, whereas OSA was found in control subjects in 19.7%. The mean apnea/hypopnea index (AHI) was significantly higher ($p < 0.01$) in CAD patients (9.9 ± 11.8) than in control subjects (6.7 ± 7.3). Body-mass-index (BMI) was significantly higher in patients with CAD and OSA than in patients with CAD without OSA (28.1 vs. 26.7 kg/m^2; $p < 0.001$). No significant difference was found with regard to other risk factors and left ventricular ejection fraction (LVEF) between both groups. Hyperlipidemia (OR 2.3; CI 1.3–3.9; $p < 0.005$) and OSA defined as AHI ≥20 (OR 2.0; CI 1.0–3.8, $p < 0.05$) were independently associated with myocardial infarction. ***Conclusions:*** There is a high prevalence of OSA among patients with angiographically proven CAD. OSA of moderate severity (AHI ≥20) is independently associated with myocardial infarction. Thus, in the care of patients with CAD, particular vigilance for OSA is important.

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive apneas during sleep owing to complete or partial pharyngeal obstruction, which lead to oxygen desaturation, fragmentation of sleep and daytime sleepiness [1]. Epidemiologic studies estimate a high prevalence of the condition affecting 2 to 4 percent of middleaged adults

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0008–6312/99/0922–0079$17.50/0

Accessible online at:
www.karger.com/journals/crd

Dr. Harald Schäfer
Department of Cardiology and Pulmonary Medicine
University of Bonn, Sigmund-Freud-Strasse 25
D–53105 Bonn (Germany)
Fax +49 228 287 4707, E-Mail haschaef@mailer.meb.uni-bonn.de

[2]. Although the pathophysiology of OSA is complex, obesity and age were found to be strong risk factors for OSA [3]. Patients with OSA have an increased risk of diurnal hypertension independent of obesity and age [4]. The prevalence has been reported to exceed 50% and the repetitive increase in sympathetic tone may be responsible for the development of diurnal hypertension [5, 6]. Retrospective studies indicate that there is an association of OSA with morbidity and mortality due to cardiovascular and cerebrovascular causes [7, 8]. Up to now it is unclear in which extent the risk of vascular disease is a result of the hemodynamic changes and sympathetic activation that may occur during apnea or the concomitant vascular risk factors that are frequent in OSA. The aim of our study was to assess the prevalence of OSA in male patients with symptomatic angina and angiographically verified coronary artery disease (CAD) and in patients without angiographically verified CAD. In addition, we analyzed the association of OSA and other coronary risk factors with CAD and history of myocardial infarction prior to coronary angiography.

Patients and Methods

Patients

Two hundred and eighty-nine men with a mean age of 59 ± 8 years (35–80 years) were consecutively included in the study. The patients were referred for evaluation of CAD by coronary angiography because of angina pectoris. Patients with additional valvular heart disease or cardiomyopathy were excluded. The risk factors and concomitant diseases were recorded from all patients according to the following criteria: *obesity:* body-mass-index (BMI) >27 kg/m^2; *hypertension:* systolic blood pressure ≥160 mm Hg and/or diastolic ≥95 mmHg or mean blood pressure ≥140/90 mm Hg during a 24-h blood-pressure recording or antihypertensive medication; *hyperlipidemia:* cholesterol ≥220 mg/dl or cholesterol <220 mg/dl and lipid lowering medication; *diabetes mellitus:* blood glucose >120 mg/dl or >200 mg/dl after 2 h following 75 mg glucose given orally or treatment with oral antidiabetic drugs or with insuline; *cigarette smoking:* current smokers with at least 1 pack-year. All patients underwent ventriculography and coronary angiography using the standard Judkins approach. CAD was diagnosed by a stenotic lesion of at least 50% in one or more coronary arteries. Patients with stenotic lesions less than 50% or diffuse wall defects were classified as control subjects. An overnight recording for sleep-related breathing disorders was performed in all patients using a non-laboratory monitoring system (NLMS) the night following coronary angiography.

Sleep Studies

Overnight sleep studies were performed with the MESAM IV system (MAP Medizintechnik, Martinsried, Germany) in 209 patients and with the Nellcor Eden-Trace system (Nellcor, Idstein, Germany) in 80 patients. These ambulatory devices are validated for diagnosis of sleep related breathing disorders [9–11]. The MESAM IV system measured continuously heart rate, oxygen saturation, snoring sound and body-position. The following variables were recorded continuously by the Nellcor Eden-Trace system: oro-nasal air-flow by thermistry, heart-rate, oxygen-saturation and chest-wall impedance. Data were recorded from 10.00 p.m. to 6.00 a.m. The lights-out and lights-on times were determined by the patients' sleep logs. Movement periods and artifacts (appearing on any of the channels) were excluded and the remaining time was defined as total sleep time. The data were evaluated by visual analysis from two experienced technicians, with differences resolved by consensus. Both observers were unaware of the results of the coronary angiography. Respiratory events appearing on the MESAM IV recordings were classified as follows: oxygen desaturation ≥4% accompanied by variation of the heart rate or cessation of snoring of a least 10 seconds. The total account of these events divided by sleeping time was reported as the respiratory disturbance index = apnea/hypopnea index (AHI). Respiratory events appearing on the Nellcor Eden-Trace recordings were classified as follows: cessation of airflow for at lesat 10 seconds associated with chest wall effort was classified as obstructive apnea. Reduced airflow of at least 50% associated with a fall in oxygen saturation ≥4% was classified as hypopnea. The total account of these events divided by sleeping time was reported as the apnea/hypopnea index (AHI). Patients were classified as having OSA with an AHI of ≥10/hour sleep. The study was approved by the local ethics committee and all patients gave written informed consent.

Statistical Analysis

Descriptive statistics for continuous variables were expressed as the mean ± standard deviation (SD). Differences in continuous variables were assessed using the Mann-Whitney U test. The χ^2 test was used for categorical variables, and Fisher's exact test in the case of small expected frequencies. A logistic regression analysis was performed to assess associations between risk factors and CAD and myocardial infarction. In all cases, p values < 0.05 were considered to be significant. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for Windows™.

Results

CAD was found by definition in 223 patients and was excluded in 66 patients. The mean BMI and the mean left ventricular ejection fraction (LVEF) were not significantly different in both groups. Hyperlipidemia was found far more frequently in CAD patients than in control subjects (71.0 vs. 36.4%; $p < 0.0001$). OSA was diagnosed more often (30.5%) in CAD patients than in control subjects (19.7%), but this difference did not reach statistical significance. However, the mean AHI was significantly higher ($p < 0.01$) in CAD patients (9.9 ± 11.8) than in control subjects (6.7 ± 7.3). The characteristics of the patients in detail are given in table 1. A correlation ($p = 0.001$; $r = 0.2$) between AHI and BMI of the 289 patients was found. Only a weak correlation ($r = 0.19$; $p = 0.01$) was found between age and AHI. No correlation was found between AHI and LVEF. Moreover, the factors age (OR 1.3;

Table 1. Data on demographic factors and risk factors of the group with coronary artery disease (CAD) and without

Parameter	Patients with CAD (n = 223)	p value	Patients without CAD (n = 66)
Age, years	59.6±7.6	<0.005	55.2±9.6
BMI, kg/m²	27.2±3.3	n.s.	27.2±2.7
LVEF, %	64.7±14.7	n.s.	66.6±13.8
AHI	9.9±11.8	<0.01	6.7±7.3
OSA	30.5%	n.s.	19.7%
Obesity	46.6%	n.s.	44.6%
Hypertension	58.3%	n.s.	53.0%
Hyperlipidemia	71.0%	<0.0001	36.4%
Diabetes mellitus	18.9%	n.s.	12.3%
Smoking	56.5%	n.s.	60.6%

AHI = Apnea/hypopnea-index; BMI = body-mass-index; LVEF = left ventricular ejection fraction; OSA = obstructive sleep apnea.

Table 2. Data on demographic factors and risk factors of the groups with coronary artery disease (CAD) with and without obstructive sleep apnea (OSA)

Parameter	Patients with CAD and OSA (n = 68)	p value	Patients with CAD without OSA (n = 155)
Age, years	61.4±6.7	<0.05	58.8±7.8
BMI, kg/m²	28.1±3.3	<0.01	26.7±3.2
LVEF, %	63.3±17.1	n.s.	65.3±13.6
AHI	23.5±13.3	<0.0001	4.0±2.6
Myocard infarction	50.0%	n.s.	43.2%
Obesity	57.4%	<0.05	41.8%
Hypertension	57.4%	n.s.	58.7%
Hyperlipidemia	77.9%	n.s.	68.0%
Diabetes mellitus	16.2%	n.s.	20.1%
Smoking	54.4%	n.s.	57.4%

AHI = Apnea/hypopnea-index; BMI = body-mass-index; LVEF = left ventricular ejection fraction.

CI 1.1–1.5; $p < 0.001$) and BMI (OR 2.1; CI 1.4–3.1; $p < 0.0001$) were both independently associated with AHI in a linear regression analysis. LVEF was not associated with AHI.

BMI was significantly higher in patients with CAD and OSA than in patients with CAD without OSA (28.1 vs. 26.7 kg/m²; $p < 0.001$). Consequently, the diagnosis obesity was more often in the former group (57.4 vs. 41.8%; $p < 0.05$). No significant difference was found with regard to other risk factors and LVEF between both groups. These data in detail are given in table 2. No difference was found in the frequency of OSA in patients with one-vessel-CAD, two-vessel-CAD or three-vessel-CAD (31 vs. 34 vs. 28%). In addition, the mean AHI was not significantly different in these patients and the frequency of affected coronary arteries was not different between patients with and without OSA.

Multiple logistic regression analysis revealed hyperlipidemia as the only risk factor, which was independently associated with CAD (OR 4.4; CI 2.4–7.9; $p < 0.0001$) and with myocardial infarction (OR 2.3; CI 1.4–4.0; $p < 0.005$). However, hyperlipidemia (OR 2.3; CI 1.3–3.9; $p < 0.005$) and OSA defined as AHI ≥20 (OR 2.0; CI 1.0–3.8; $p < 0.05$) were both independently associated with myocardial infarction.

Table 3. Studies for association of OSA and CAD

Reference	Study group	OSA prevalence	Comments
De Olazabal [26]	n = 17 (m) CAD	65%	polysomnography small study group no control group
Hung [15]	n = 101 (m) CAD n = 53 (m) controls	14%	polysomnography after acute MI AHI >5.3 independent predictor for MI
Andreas [27]	n = 50 (47 m, 3 f) CAD	50%	NLMS no control group
Mooe [14]	n = 142 (m) CAD n = 50 (m) controls	37%	NLMS AHI, BMI and hypertension independent predictors for CAD
Mooe [28]	n = 102 (w) CAD n = 50 (w) controls	30%	NLMS AHI, hypertension and smoking independent predictors for CAD
Present study	n = 223 (m) CAD n = 66 (m) controls	30%	NLMS AHI ≥20 and HLP independent predictors for MI

AHI = Apnea/hypopnea-index; BMI = body-mass-index; CAD = coronary artery disease; HLP = hyperlipidemia; MI = myocardial infarction; NLMS = non-laboratory-monitoring system; OSA = obstructive sleep apnea.

Discussion

We found a high prevalence of OSA in patients with angiographically documented CAD. In addition, the mean AHI was higher in patients with CAD than in control subjects. Hyperlipidemia and OSA with AHI ≥20 were found to be independently associated with myocardial infarction.

Earlier epidemiologic population-based studies demonstrated an association between habitual snoring and the prevalence of angina pectoris and myocardial infarction [12, 13]. In these studies only a minority of subjects underwent sleep studies, and underlying sleep apnea is possible. The high occurrence of OSA in ischemic heart disease in the present study is in accordance with other studies (table 3). Mooe et al. [14] found a prevalence of 37% in 142 men with CAD. The prevalence in control subjects was significantly smaller. In contrast to our study angiography was not performed in control subjects, exclusion of CAD was based on history. The authours found apnea- and hypopnea index, BMI and hypertension as significant predictors for CAD. In our study, we did not find the sleep-related breathing disorder being a predictor for CAD, but found it by definition of AHI ≥20 to be an independent predictor for myocardial infarction. This is in accordance with the study of Hung et al. [15], who found an apnea-index >5.3 to be an independent predictor of myocardial infarction in unselected male survivors of acute myocardial infarction.

The present study, which represents the largest study group to date, and those given in table 3 suggest a relationship between OSA and CAD. What remains unclear is if this relationship is a causal one. Both diseases are frequent in middleaged men and share a similar spectrum of risk factors, e.g. obesity, hypertension and hyperlipidemia. Acute obstructive apneas are associated with hypoxemic events and autonomic responses including tachycardia/bradycardia, elevations in pulmonary and systemic artery pressure and an increase in sympathetic activity [16]. These repetitive hypoxemic events and an

increase in sympathetic activity, which exceeds during wakefulness [17], may contribute to the development of atherosclerosis or to a progression in the case of pre-existing atherosclerotic lesions due to oxyradical formation, intimal proliferation and tissue damage [18–20].

Patients with the combination of CAD and OSA are considered as a particular group at risk, because apnea-associated oxygen desaturation can trigger nocturnal myocardial ischemia. In a previous study we found apnea and oxygen desaturation-related nocturnal myocardial ischemia only in those patients with CAD, and in one patient with diffuse coronary artery defects [21]. Franklin et al. [22] found sleep apnea in 9 of 10 patients with nocturnal angina pectoris. During treatment of sleep apnea by continuous positive airway pressure, nocturnal angina diminished and the number of nocturnal myocardial ischemic events was reduced [22]. Besides the effects of oxygen desaturation on myocardial ischemia, OSA may reduce myocardial blood flow supply and/or increase demand by acute changes in heart rate and elevations of blood pressure-induced left ventricular afterload at the resumption of breathing at each apnea termination [16]. In addition, interventricular septum shift leads to impediment of the diastolic function of the left ventricle [23]. The observed independent association of higher degree OSA (AHI ≥ 20) with myocardial infarction in the present study may reflect the endpoint of the interaction of obstructive apnea and myocardial ischemia.

Age and BMI were both independently associated with AHI. This is in accordance with epidemiologic data indicating that age and obesity are strong, well-documented risk factors for OSA [3]. Moreover, in our study BMI was significantly higher in patients with CAD and OSA than in patients with CAD without OSA.

Several possible limitations of the present study have to be addressed. The diagnosis of OSA was not confirmed by polysomnography but based on in-hospital non-laboratory-monitoring-system recordings using systems which are well-established for screening procedures [9–11]. In addition, we found a high sensitivity in diagnosis of obstructive sleep apnea in our laboratory with the MESAM system [24]. However, an underestimation of OSA by excluding breathing events without a desaturation is possible with the MESAM system. Although both systems used in our study are well-established, a problem remains by combining data from different devices. The recording was standardized for all patients monitoring always the night after cardiac catheterization. Sedativa were not given and alcohol intake was not allowed. Although all recordings were analyzed visually by two experienced technicians, separation of obstructive apnea from central apnea is not always possible when using the MESAM system. Central sleep apnea is uncommon in the general population but is commonly seen in association with Cheyne-Stokes respiration in patients with congestive heart failure with severely impaired left ventricular function [25]. The occurrence of central sleep apnea in our study is unlikely, since no patients had congestive heart failure. Moreover, LVEF was not associated with AHI in a linear regression analysis and no correlation between LVEF and AHI was found. CAD was excluded in patients of the control group by angiography. However, atherosclerosis may be present in these patients, because minimal lesions were no exclusion criteria.

In conclusion, there is a high prevalence of OSA among patients with angiographically proven CAD. OSA of moderate severity (AHI >20) is independently associated with myocardial infarction. Thus, in the care of patients with CAD, particular vigilance for OSA is important.

References

1 Guilleminault C: Clinical features and evaluation of obstructive sleep apnea; in Kryger MH, Roth T, Dement WC (eds): Principles and Practice of Sleep Medicine. Philadelphia, Saunders, 1994, pp 667–677.

2 Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S: The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–1235.

3 Strohl KP, Redline S: Recognition of obstructive sleep apnea. Am J Respir Crit Care Med 1996;154:279–289.

4 Carlson JT, Hedner JA, Ejnell H, Peterson LE: High prevalence of hypertension in sleep apnea patients independent of obesity. Am J Respir Crit Care Med 1994;150:72–77.

5 Working Group on OSA and Hypertension: Obstructive sleep apnea and blood pressure – What is the relationship? Blood Press 1993;2:166–182.

6 Fletcher EC: The relationship between systemic hypertension and obstructive sleep apnea: Facts and theory. Am J Med 1995;98:118–128.

7 He J, Kryger MH, Zorick FJ, Conway W, Roth T: Mortality and apnea index in obstructive sleep apnea. Chest 1988;94:9–14.

8 Partinen M, Jamieson A, Guilleminault C: Long-term outcome for obstructive sleep apnea syndrome patients. Chest 1988;94:1200–1204.

9 Penzel T, Amend G, Meinzer K, Peter JH, von Wichert P: MESAM: A heart rate and snoring recorder for detection of obstructive sleep apnea. Sleep 1990;13:175–182.

10 Stoohs R, Guilleminault C: MESAM 4: An ambulatory device for the detection of patients at risk for obstructive sleep apnea syndrome (OSAS). Chest 1992;101:1221–1227.
11 Redline S, Tosteson T, Boucher MA, Millman RP: Measurement of sleep-related breathing disturbances in epidemiologic studies. Assessment of the validity and reproducibility of a portable monitoring device. Chest 1991;100: 1281–1286.
12 Koskenvuo M, Kapiro J, Partinen M, Langinvaino H, Sarna S, Heikkila K: Snoring as a risk factor for hypertension and angina pectoris. Lancet 1985;i:893–896.
13 Koskenvuo M, Kapiro J, Telakivi T, Partinen M, Heikkila K, Sarna S: Snoring as a risk factor for ischaemic heart disease and stroke in men. Br Med J 1987;294:16–19.
14 Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P: Sleep-disordered breathing in men with coronary artery disease. Chest 1996;109: 659–663.
15 Hung J, Whitford EG, Parsons RW, Hillman DR: Association of sleep apnoea with myocardial infarction in men. Lancet 1990;336:261–264.
16 Weiss JW, Remsburg S, Garpestad E, Ringler J, Sparrow D, Parker JA: Hemodynamic consequences of obstructive sleep apnea. Sleep 1996; 19:388–397.
17 Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG: Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993;103:1763–1768.
18 Gainer JL: Hypoxia and atherosclerosis: Reevaluation of an old hypothesis. Atherosclerosis 1987;68:263–266.
19 Crawford DW, Blankenhorn DH: Arterial wall oxygenation, oxyradicals and atherosclerosis. Atherosclerosis 1991;89:97–108.
20 Dean RT, Wilcox I: Possible atherogenic effects of hypoxia during obstructive sleep apnea. Sleep 1993;16(suppl 8):S15–S21.
21 Schäfer H, Koehler U, Ploch T, Peter JH: Sleep-related myocardial ischemia and sleep structure in patients with obstructive sleep apnea and coronary heart disease. Chest 1997; 111:387–393.
22 Franklin KA, Nilsson JB, Sahlin C, Näslund U: Sleep apnoea and nocturnal angina. Lancet 1995;345:1085–1087.
23 Shiomi T, Guilleminault C, Stoohs R, Schnittger I: Leftward shift of the interventricular septum and pulsus paradoxus in obstructive sleep apnea syndrome. Chest 1991;100:894–902.
24 Schäfer H, Ewig S, Hasper E, Lüderitz B: Predictive diagnostic values of clinical assessment and non-laboratory-monitoring-system-recordings in patients with symptoms suggestive of obstructive sleep apnea syndrome. Respiration 1997;64:194–199.
25 Javaheri S, Parker TJ, Wexler L, Michales SE, Stanberry E, Nishyama H, Roselle GA: Occult sleep-disordered breathing in stable congestive heart failure. Ann Intern Med 1995;122:487–492.
26 De Olazabal JR, Miller MJ, Cook WR, Mithoefer JC: Disordered breathing and hypoxia during sleep in coronary artery disease. Chest 1982;82:548–552.
27 Andreas S, Schulz R, Haro W, Werner S, Kreuzer H: Schlafbezogene Atmungsstörungen bei Patienten mit koronarer Herzkrankheit. Dtsch med Wschr 1995;120:1533–1537.
28 Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P: Sleep-disordered breathing in women: Occurrence and association with coronary artery disease. Am J Med 1996;101:251–256.