Sleep-Disordered Breathing in Patients Referred for Angina Evaluation—Association with Left Ventricular Dysfunction

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Summary

Background: Clinical observations have linked sleep-disordered breathing to cardiovascular morbidity and mortality, and especially to coronary artery disease.

Hypothesis: The study was undertaken to determine the prevalence of sleep-disordered breathing in consecutive patients referred for angina evaluation, and analyzed the parameters influencing the severity of sleep-disordered breathing.

Methods: In all, 68 consecutive patients (53 men, 15 women, aged 63.4 ± 10.0 years) referred for angina evaluation were studied. Coronary angiography, selective left ventriculography, and a polygraphic study with a validated six-channel monitoring device were performed. Full-night polysomnography was used to reevaluate patients with an apnea/hypopnea index $\geq 10/h$.

Results: Sleep-disordered breathing as defined by an apnea/hypopnea index $\geq 10/h$ was found in 30.9% of patients; its prevalence was not increased in patients with and without coronary artery disease (26.5 vs. 42.1%). Multiple stepwise linear regression analysis revealed that the severity of sleep-disordered breathing was significantly and independently associated with left ventricular ejection fraction ($r = -0.38$; $p = 0.002$), but not with age, body mass index, gender, diabetes mellitus, hypertension, hyperuricemia, hypercholesterolemia, smoking habits, or coronary artery disease. In this group of patients, multiple logistic regression analysis could not demonstrate sleep-disordered breathing to be an independent predictor of coronary artery disease.

Conclusions: Sleep-disordered breathing is common in patients referred for angina evaluation. The degree of sleep-disordered breathing is mainly determined by the extent of left ventricular dysfunction.

Key words: obstructive sleep apnea, coronary artery disease, cardiovascular morbidity, coronary angiography, left ventricular dysfunction

Introduction

Sleep-disordered breathing is a common health problem that mainly affects middle-aged persons. The prevalence of untreated sleep-disordered breathing, ranging from mild to severe, is high in both women and men (9 and 24%, respectively).¹ Patients with severe sleep-disordered breathing seem to have a reduced cumulative survival rate,² probably due to an increased cardiovascular morbidity and mortality.³ Therefore, special attention should be paid to accompanying cardiovascular diseases, which may even be induced by sleep-disordered breathing, such as, for instance, hypertension and pulmonary hypertension.^{4–8}

In this respect, the correlation between coronary artery disease and sleep-disordered breathing is of prime concern since patients with a combination of both diseases are probably at particularly high risk of cardiovascular complications. Repetitive obstructions of the upper airways induce not only hypoxemia but also intrathoracic pressure swings, and, as a result, a volume strain of the right ventricle and impaired left ventricular function. Hypoxemia and this increased ventricular wall stress may lead to an imbalance between myocardial oxygen supply and demand. It could be shown, accordingly, that apneic events can cause myocardial ischemias and bradyarrhythmias in patients with preexistent coronary artery disease.⁹

Several studies indicate an increased prevalence of sleep-disordered breathing in patients with coronary artery disease,^{10–14} but it is still under discussion whether there is an independent association between these two conditions not only in patients requiring intensive care for angina pectoris or myocardial infarction but also in the chronic coronary syndrome.^{15, 16} We therefore determined the prevalence of

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sleep-disordered breathing in consecutive patients referred for angina evaluation to test the hypothesis that sleep-related breathing disorders are more prevalent in patients with than in those without coronary heart disease. Furthermore, we analyzed the parameters influencing the severity of sleep-disordered breathing.

Methods

Seventy consecutive patients referred for angina evaluation were selected for the study. All patients gave their written informed consent prior to examination. In all patients coronary angiography was performed using standard techniques and analyses.¹⁷ Left ventricular ejection fraction was determined at the time of catheterization by selective left ventriculography. The angiographic study was documented on video tape and on cine film.

The second night after cardiac catheterization, a sleep study with a portable monitoring device was performed. Two patients refused to participate in the study, all other 68 patients gave their informed consent. The mean age of the 68 patients (53 men, 15 women) was 63.4 ± 10.0 years; the mean body mass index (BMI) was 28.8 ± 4.1 kg/m². Twenty-seven patients (39.7%) had known or newly diagnosed arterial hypertension and 17 patients (25.0%) had diabetes mellitus. Of the patients with arterial hypertension, 14 were receiving regular antihypertensive treatment, and 10 of the patients with diabetes mellitus were treated with sulphonylureas or insulin. No alcohol consumption or use of sedatives was allowed during the night or the day before the recording.

The sleep study was performed with a validated portable six-channel monitoring device (Eden Trace, Edentec Monitoring System, Eden Prairie, Minn., USA).¹⁸ The sleep study consisted of continuous polygraphic recording from a three-way thermistor that measured nasal/oral airflow, and from noninvasive leads measuring chest wall impedance, oxygen saturation (finger-pulse oximetry), heart rate, tracheal sounds (microphone), and body position. All signals were recorded and analyzed with the help of computer software.

Sleep time was estimated by use of a patient diary in conjunction with visual assessment of the overnight tracing for evidence of an awake state as suspected by movement, upright position or artifact, and acceleration of the heart rate. Respiratory events were independently scored manually during the estimated sleep time by two of the authors. An abnormal breathing event was defined as apnea if a complete cessation of airflow lasting ≥ 10 s took place, or as hypopnea if a reduction in respiratory airflow accompanied by a decrease of $\geq 4\%$ in oxyhemoglobin saturation could be discerned. The average number of episodes of apnea and hypopnea per hour of sleep (apnea/hypopnea index [AHI]) was calculated. The events were classified as obstructive if they were associated with chest wall effort, and as central if no chest wall movements could be detected. Cheyne-Stokes respiration was defined as a sinusoidal pattern of rhythmic waxing and waning of airflow, interspersed with periods of central apnea. The evaluators of

the polygraphic study were blinded with regard to the results of cardiac catheterization.

To determine cardiovascular risk factors for coronary artery disease, a careful history, including a family history for cardiovascular events, and physical examination were obtained in all patients. The documented risk factors included obesity, hypertension, diabetes mellitus, hyperuricemia, and cigarette smoking. In addition, cholesterol levels were determined. Hypercholesterolemia was defined as cholesterol concentration > 5.1 mmol/l (200 mg/dl), high-density lipoprotein (HDL) cholesterol < 0.9 mmol/l (35 mg/dl), or low-density lipoprotein (LDL) cholesterol > 4.65 mmol/l (180 mg/dl).

Patients with an AHI ≥ 10 /h, as determined by the six-channel monitoring device, were additionally examined by polysomnography (Somnostar 4100, SensorMedics Co., Yorba Linda, Calif., USA), which was performed according to widely accepted methods.¹⁹ It consisted of continuous polygraphic recording from surface leads for electroencephalography, electrooculography, electromyography, and electrocardiography, and from noninvasive sensors for nasal and oral airflow, tracheal sounds (microphone), thoracic and abdominal respiratory effort (inductance plethysmography), and oxyhemoglobin level (Sat-Trak™, finger-pulse oximeter, SensorMedics Co.). The transducers and lead wires permitted normal positional changes during sleep. Bedtime and awakening time were at each subject's discretion. Polysomnography was terminated after final waking. Polysomnography records were scored manually in 30-s periods for sleep, breathing, and oxygenation. Sleep was staged using the methods of Rechtschaffen and Kales.²⁰

Statistical Analyses

Results are presented as mean with one standard deviation. All reported *p* values are two-tailed. A *p* value of < 0.05 was considered to indicate statistical significance. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) for Windows software (SPSS, Chicago, Ill., USA).

Intergroup differences were analyzed with 2×2 contingency tables using the Fisher exact test. Correlations were assessed by linear regression analysis. To determine the independent association of left ventricular ejection fraction with the severity of obstructive sleep apnea in the presence of other significant risk factors, stepwise multiple logistic regression analysis was performed. The multivariate statistical model was built in steps and was designed to select only factors that correlated with the apnea/hypopnea index at a level of significance of ≤ 0.05 for the final multiple regression model. Possible risk factors including age, BMI, gender, diabetes mellitus, arterial hypertension, hyperuricemia, hypercholesterolemia, smoking habits, and coronary artery disease were allowed to compete. In addition, multiple logistic regression analysis was performed with coronary artery disease as dependent variable, and with age, body mass index, parameters of the severity of sleep-disordered breathing, diabetes mellitus, gender, hypertension, hyperuricemia, hypercholesterolemia, and smoking habits as independent variables.

TABLE I Results of the polygraphic study of the patients with and without coronary artery disease

	Coronary artery disease	
	Yes (n = 49)	No (n = 19)
Apnea/hypopnea index, n/h	9.0 ± 10.6	11.8 ± 13.4
t < 90%, % ^a	7.4 ± 15.6	9.1 ± 24.0
SaO ₂ mean, % ^b	94.5 ± 2.1	93.3 ± 4.3
SaO ₂ minimum, %	86.3 ± 4.7	82.3 ± 8.6

^a Percentage of time during the night with an oxygen saturation < 90%.
^b Arterial oxyhemoglobin saturation.
Mean values and standard deviation.

Results

In all, 49 patients (43 men, 6 women) had coronary artery disease as determined by cardiac catheterization, while 19 patients (10 men, 9 women) had no evidence of atherosclerosis of the coronary arteries. Of these 19 patients, 2 had no signs of organic heart disease and 17 had nonischemic heart disease such as cardiomyopathies or valvular heart disease. Patients with and without coronary artery disease did not differ with respect to age (62.9 ± 10.8 vs. 64.8 ± 7.5 years), left ventricular ejection fraction (67.5 ± 13.1 vs. 64.8 ± 22.2 %), or the prevalences of diabetes mellitus (28.6 vs. 15.8%), a positive family history for cardiovascular events (14.3 vs. 5.3%), hypertension (69.4 vs. 63.2%), or hyperuricemia (8.2 vs. 10.5%), but patients without coronary artery disease were significantly more obese (BMI 30.7 ± 3.9 vs. 28.0 ± 4.0 kg/m²; p < 0.05), had significantly less often associated hypercholesterolemia (42.1 vs. 79.6 %; p < 0.01), and a significantly higher percentage of these patients was female (47.4 vs. 12.2%; p < 0.01).

Sleep-disordered breathing as defined by an apnea/hypopnea index ≥ 10/h, determined by the six-channel monitoring device, was found in 30.9% of all patients, and its prevalence was not higher in patients with than in those without coronary artery disease (26.5 vs. 42.1%). The additional results of the sleep study are given in Table I; there was no significant difference between the results in patients with and without coronary artery disease.

Polysomnography could be performed in 16 of the 21 patients with an AHI ≥ 10/h. The results of polysomnography are given in Table II, and there was no significant difference in the results obtained by polysomnography and the monitoring device with respect to the AHI or the parameters of oximetry.

To clarify the question which factors underlie sleep-disordered breathing in patients with and without coronary artery disease, correlation analyses were performed. Univariate correlation analysis revealed a significant association between AHI and left ventricular ejection fraction (r = -0.38; n = 68; p = 0.002) (Fig. 1) and between BMI and minimum oxygen saturation at night (r = -0.27; n = 68; p = 0.03). The association between AHI and left ventricular ejection fraction persisted even after controlling for age, BMI, gender, or the prevalences of diabetes mellitus, hypertension, hyperuricemia,

TABLE II Results of the polysomnographic study of the patients with an apnea/hypopnea index > 10/h, compared with the polygraphic study

	Polysomnographic study	Polygraphic study
Apnea/hypopnea index, n/h	24.9 ± 12.6	23.6 ± 11.6
t < 90%, % ^a	16.1 ± 26.7	14.3 ± 20.7
SaO ₂ mean, % ^b	93.2 ± 3.1	93.6 ± 3.2
SaO ₂ minimum, %	83.3 ± 5.8	81.0 ± 7.3

^a Percentage of time during the night with an oxygen saturation < 90%.
^b Arterial oxyhemoglobin saturation.
Mean values and standard deviation.

hypercholesterolemia, smoking habits, or coronary artery disease (r = -0.39; p = 0.004).

In addition, multiple stepwise linear regression analysis was performed with the AHI as the dependent variable and age, BMI, left ventricular ejection fraction, diabetes mellitus, gender, hypertension, hyperuricemia, hypercholesterolemia, smoking habits, and coronary artery disease as independent variables. The regression analysis disclosed an independent and significant association between AHI and left ventricular ejection fraction (r = -0.38; p = 0.002). None of the other variables could be included in the multivariate linear regression model.

Correlation analyses in the subgroups of patients with and without coronary artery disease revealed that the association between AHI and left ventricular ejection fraction was present in patients without coronary artery disease (r = -0.52; n = 19; p = 0.03), and that there was also an association between left ventricular ejection fraction and the percentage of time during night with an oxygen saturation below 90% (r = -0.56; n = 19; p = 0.02), but this relationship was not seen in patients with coronary artery disease.

Further analysis of the polygraphic study demonstrated that out of the 21 patients with an AHI ≥ 10/h, 6 had a breathing pattern resembling Cheyne-Stokes respiration. This could be confirmed by full night polysomnography in all of these pa-

FIG. 1 Apnea/hypopnea index plotted against left ventricular ejection fraction.

tients. Of the 15 patients who demonstrated obstructive sleep apnea on their initial portable study, 10 had a subsequent full night polysomnogram performed. In all 10 patients, obstructive events were again noted to be present and the absence of Cheyne-Stokes respiration was confirmed. Of the six patients with Cheyne-Stokes respiration, three had coronary artery disease while the other three did not.

Left ventricular ejection fraction was significantly worse in patients with than in those without Cheyne-Stokes respiration (46 ± 21 vs. 69 ± 13 %; $p < 0.05$).

To find out whether sleep-disordered breathing is a predictor of coronary artery disease, multiple logistic regression analysis was performed with coronary artery disease as dependent variable and age, BMI, sleep-disordered breathing, diabetes mellitus, gender, hypertension, hyperuricemia, hypercholesterolemia, and smoking habits as independent variables. The regression analysis revealed that male gender ($r = 0.18$; $p = 0.03$), a history of smoking ($r = 0.21$; $p = 0.02$), and the presence of diabetes mellitus ($r = 0.18$; $p = 0.03$) and hypercholesterolemia ($r = 0.17$; $p = 0.04$), but not sleep-disordered breathing, were significantly associated with coronary artery disease.

Discussion

The results of our study clearly indicate that patients who are referred for angina evaluation have a high prevalence of sleep-disordered breathing. In our study group, 30.9% of all patients and 26.5% of those with coronary artery disease had an AHI ≥ 10 /h. Given the high prevalence of sleep-disordered breathing in patients referred for angina evaluation, the question arises whether this association is just coincidental or causal.

One important finding of the study is that there was a significant correlation between the AHI and left ventricular ejection fraction, even after controlling for age, BMI, gender, or the prevalences of diabetes mellitus, hypertension, hyperuricemia, hypercholesterolemia, smoking habits, or coronary artery disease.

Further analysis revealed that this correlation was essentially due to Cheyne-Stokes breathing in patients with impaired left ventricular function. It thus has to be concluded that sleep-disordered breathing is more likely a result of impaired left ventricular function than the cause of myocardial damage.

It was shown recently that sleep apnea, chiefly of the central type, not only characterizes acute myocardial infarction but also unstable angina studied after recent stabilization.¹⁵ In these patients requiring intensive care for angina pectoris or myocardial infarction, an independent association between obstructive sleep apnea and coronary artery disease was found.¹⁶ On the other hand, it was shown that coronary disease-related apnea was absent in the chronic coronary syndrome.¹⁵

In our study, in which patients with impaired left ventricular function in the chronic state of disease were included, multiple logistic regression analysis showed that male gender, a history of smoking, and the presence of diabetes mellitus and hypercholesterolemia were significantly associated with coronary

artery disease, but sleep-disordered breathing was not. Our results may therefore suggest that there is more than one cause for disordered breathing in sleep in patients with heart disease.

There are several mechanisms that might be responsible for Cheyne-Stokes respiration in patients with left ventricular dysfunction: they seem to have (1) an increased central nervous system sensitivity to changes in arterial oxygen tensions, (2) a decrease in total body stores of oxygen and carbon dioxide with resulting instability of arterial blood gas tensions in response to changes in ventilation, and (3) an increased circulatory time.^{21, 22} Furthermore, patients with heart failure and Cheyne-Stokes respiration have an enhanced sensitivity to carbon dioxide. In addition, the degree of sensitivity correlates with the severity of central sleep apnea, a finding that supports the possibility that increased sensitivity has a destabilizing effect on breathing during sleep.²³

In view of these pathomechanisms, continuous recording of carbon dioxide tensions would have been interesting. However, this aspect was not the aim of our study and was therefore not pursued. A further limitation of our study is that most of our patients had normal left ventricular ejection fraction.

It is noteworthy that even minor degrees of left ventricular dysfunction can be associated with Cheyne-Stokes breathing, and that there is a close correlation between the severity of both left ventricular dysfunction and Cheyne-Stokes breathing. In most studies analyzing the occurrence of Cheyne-Stokes breathing in myocardial insufficiency, it is mainly severe cardiac failure that is accompanied by Cheyne-Stokes breathing. However, it is obvious that Cheyne-Stokes breathing may also occur early in the course of myocardial failure. Our study suggests that Cheyne-Stokes breathing detected in evaluation of sleep disorders should prompt a thorough evaluation of cardiac function.

It is speculated that patients with left ventricular dysfunction and associated Cheyne-Stokes respiration not only have an impaired daytime performance—as a result of frequent central nervous arousals—but also increased mortality.^{24, 25} Cheyne-Stokes respiration can be effectively treated. Oxygen and theophylline reduce central sleep apnea in eucapnic patients.^{26, 27} Recent studies also demonstrated a beneficial influence of continuous positive airway pressure not only on sleep-disordered breathing but also on left ventricular ejection fraction.^{28, 29} This might be due to a reduction of the sympathetic drive and a decrease of left ventricular afterload.³⁰

Conclusion

Patients referred for angina evaluation have a high prevalence of sleep-disordered breathing, with left ventricular ejection fraction being the most important parameter influencing the severity of these nocturnal breathing disorders.

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