Wien Med Wochenschr (2010) 160/13–14: 349–355
DOI 10.1007/s10354-009-0737-x

Printed in Austria

wmw
Wiener Medizinische Wochenschrift

Sleep apnea is common in patients with coronary artery disease

Christian Prinz, Thomas Bitter, Cornelia Piper, Dieter Horstkotte, Lothar Faber and **Olaf Oldenburg**

Department of Cardiology, Heart and Diabetes Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

Received July 8, 2009, accepted (after revision) November 18, 2009

Patienten mit koronarer Herzerkrankung leiden häufig unter Schlafapnoe

Zusammenfassung. Schlafapnoe hat eine prognostisch ungünstige Bedeutung für Herzpatienten. Wir schlossen 257 konsekutive Patienten mit erhaltener linksventrikulärer Pumpfunktion und angiographisch gesicherter koronarer Herzerkrankung (KHK) in unsere Studie ein. Alle Patienten erhielten eine kardiorespiratorische Polygraphie. Bei 251 Patienten wurde hochsensitives C-reaktives Protein (hsCRP) und Fibrinogen bestimmt. 188 Patienten demonstrierten eine Schlafapnoe (Apnoe-Hypopnoe-Index [AHI] 16,4 ± 1,9/h): 58 Patienten präsentierten eine zentrale (CSA) und 130 Patienten eine obstruktive Schlafapnoe (OSA). Alle Schlafapnoeiker (73 %) zeigten höhere Fibrinogenspiegel als die Patienten ohne Schlafapnoe ($p = 0{,}01$). Wir fanden 197 Patienten mit CRP-Werten unter einem cut-off von 0,5 mg/dl (Gruppe 1) und 54 Patienten ohne aktive Infektion, aber mit CRP-Werten >0,5 mg/dl (Gruppe 2). Die Gruppe 2 wies eine deutlich schwerere Schlafapnoe auf ($p = 0{,}01$). Schlafapnoe hatte eine hohe Prävalenz bei unseren KHK-Patienten und scheint mit chronischer Inflammation assoziiert zu sein, die wiederum eine Progression der KHK oder akute koronare Ereignisse triggern könnte.

Schlüsselwörter: Prävalenz, Schlafbezogene Atmungsstörung, Koronare Herzerkrankung, chronische Inflammation

Summary. Sleep-disordered breathing (SDB) has a prognostic impact in patients with cardiac diseases. We included 257 patients with preserved left ventricular function and angiographically proven coronary artery disease (CAD). All patients underwent cardiorespiratory polygraphy. In 251 patients high-sensitive C-reactive protein and fibrinogen were measured. SDB was documented in 188 patients (apnea-hypopnea-index [AHI] 16.4 ± 1.9/h): 58 patients presented central sleep apnea (CSA) and 130 patients obstructive sleep apnea (OSA). All patients (73%) with SDB had higher blood fibrinogen levels than those without SDB ($p = 0.01$). We found 197 patients with CRP-values below the cut-off of 0.5 mg/dl (group 1) and 54 patients with no active infection but CRP > 0.5 mg/dl (group 2). Severity of SDB was significantly higher in group 2 ($p = 0.01$). SDB has a high prevalence in CAD patients and seems to be associated with chronic inflammation, which may be linked to CAD progression and/or acute coronary events.

Key words: Prevalence, sleep-disordered breathing, coronary artery disease, chronic inflammation

Introduction

The reported prevalence of sleep apnea syndrome (including symptoms) in the general population is 1–4% [1, 2]. Sleep apnea (with apnea-hypopnea-index [AHI] ≥5/h regardless of symptoms) in particular has been recognized as an important public health problem affecting 9–24% of the middle-aged population [2]. About 50% of patients with obstructive sleep apnea have a significant obesity [3]. In patients with cardiac diseases, especially chronic heart failure, the prevalence of sleep-disordered breathing is remarkably high [4]. Central sleep apnea (CSA) in particular Cheyne-Stokes-respiration has been found in up to 40% of patients with symptomatic heart failure (NYHA class ≥II) and impaired left ventricular pump function (left ventricular ejection fraction, LV-EF ≤40%) [5]. Sleep-disordered breathing has also a high prevalence in hypertensive patients [4] and has an important prognostic impact in cardiac patients [7–9].

Epidemiological data suggest that obstructive sleep apnea is overrepresented in coronary artery disease [10–12], and that long-term outcome in these patients is poor [13, 14]. Patients with obstructive sleep apnea have the highest rate of sudden cardiac death

Correspondence: *Christian Prinz, M.D.*, Heart and Diabetes Center North-Rhine Westphalia, Ruhr University Bochum, Georgstrasse 11, 32545 Bad Oeynhausen, Germany.
Fax: ++49-5731-97 2194, E-mail: akleemeyer@hdz-nrw.de

during sleeping hours while otherwise sudden cardiac death is rare at that time [15]. Obstructive sleep apnea leads to recurrent episodes of partial or complete upper airway obstruction during sleep with consequent oxygen desaturation, arousals [16] and activation of the sympathetic system [17]. This phenomenon may be an independent risk factor for major cardiac events and cardiac death [18].

Despite growing epidemiological support for the association of obstructive sleep apnea and coronary artery disease [19], clinical studies focusing on patients with sleep apnea and angiographically verified coronary artery disease are rare. Clinical data suggest that obstructive sleep apnea results in a dysfunction of the vascular micromilieu. Nocturnal hypoxemia seems to aggravate endothelial dysfunction, a known promoter of arterial hypertension and arteriosclerosis [20] by the synthesis of acute phase proteins like fibrinogen and high-sensitive C-reactive protein (hs-CRP) [21]. In patients with acute ischemic stroke sleep apnea was independently associated with raised levels of CRP and fibrinogen [22]. A significant reduction of vascular reactivity has been documented in patients with severe obstructive sleep apnea [23]. Intima-media diameter of the carotid arteries was found to be thicker in patients with obstructive sleep apnea [24]. This study aims to examine the prevalence of sleep apnea and nocturnal hypoxemia in patients with stable symptomatic coronary artery disease, in whom lung disease had been excluded and preserved left ventricular function was documented. In addition we explored the impact of chronic inflammation and sleep apnea on the progression of coronary artery disease.

Tab. 1: Demographic and clinical data of 257 pts with CAD

Parameter	
Age, years	67.5 ± 1.0 [49–88]
Male, *n*	212 (82%)
Weight, kg	85.6 ± 1.7 [50–150]
Height, cm	174 ± 1.0 [150–192]
BMI, kg/m^2	28 ± 0.5 [19–58]
Blood pressure	
Systolic, mmHg	139 ± 2.6 [240–90]
Diastolic, mmHg	79 ± 1.3 [120–53]
Rhythm	
Sinus rhythm, *n*	217 (84%)
Atrial fibrillation, *n*	40 (16%)
CAD vessel (*n*/%)	
One	60 (23%)
Two	59 (23%)
Three	138 (54%)
CCS-class	1.4 ± 0.2 [1–4]
NYHA-class	1.4 ± 0.1 [1–4]
Medication (*n*/%)	
ACE/AT1	223 (87%)
ß-blocker	210 (82%)
Diuretics	143 (56%)
Statins	234 (91%)
Digitalis	18 (7%)
Amiodarone	9 (4%)

Material and methods

Patients

In accordance to local ethical guidelines screening for sleep-disordered breathing in cardiac patients is routine clinical practice in our institution [25]. We consecutively included 257 patients with relevant coronary artery disease (at least one stenosis ≥70%) and preserved left ventricular ejection fraction (LVEF) ≥50% (Tab. 1). Obesity (BMI > 25 kg/m^2) was present in 213 patients (83%). Patients with lung disease, acute infective disease or a history of infection in the last four weeks, acute coronary syndrome, diabetes mellitus, valve lesions and 6 patients without markers for inflammation were excluded. All patients were on coronary artery disease consensus medication. We investigated an age and sex-matched control group of 47 patients with angiographically exclusion of coronary artery disease and preserved left ventricular ejection fraction.

Cardiorespiratory polygraphy

Sleep studies were performed by in-hospital unattended cardiorespiratory polygraphy (Embletta^{TM}, Embla, The Netherlands) as previously described [21]. With Embletta^{TM} we continuously recorded nasal air flow, chest and abdominal effort, puls oximetry and body position (Fig. 1). Data were analyzed using Somnologica for Embletta^{TM} software (Medcare, Embla, The Netherlands). Three independent sleep-disordered breathing specialists not involved in patient's treatment reviewed and corrected the automated analysis. In case the apnea-hypopnea-index (AHI) was >5/h patients were identified to have sleep-disordered breathing. If

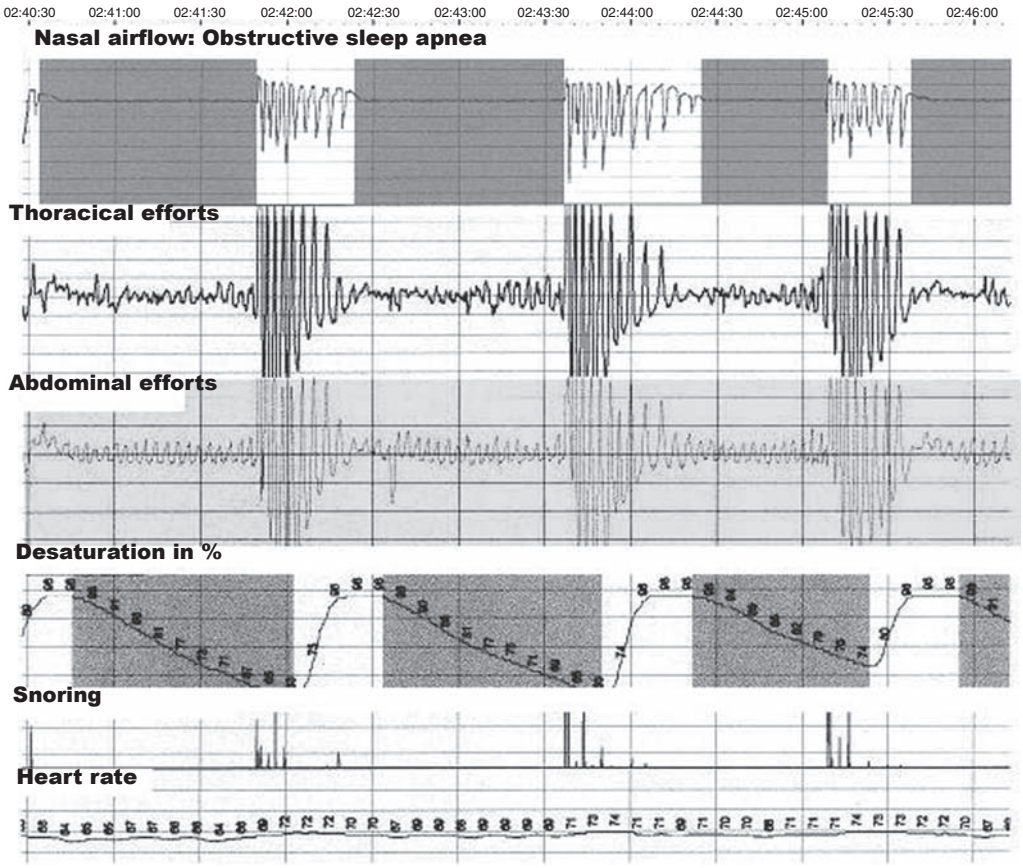

Fig. 1: Cardiorespiratory polygraphy from a patient with obstructive sleep apnea (OSA): curve for nasal air flow, thoracic and abdominal efforts and O_2-saturation measured by pulse oximetry are shown

thoracic and abdominal inspiration efforts were documented, sleep-disordered breathing was considered to be obstructive (OSA), otherwise central sleep apnea (CSA) was diagnosed. In patients that had a mixture of obstructive and central sleep apnea, majority of obstructive or central events was the decisive factor for classification as OSA or CSA. Patients with a classical mixed sleep apnea were excluded.

Laboratory measurements

High-sensitive C-reactive protein (hs-CRP; > 0.5 mg/dl) and fibrinogen (> 350 mg/dl) as acute phase proteins were used as markers for chronic inflammation, low density lipoprotein (LDL; > 130 mg/dl) and high density lipoprotein (HDL; < 50 mg/dl) were used as marker for the lipid status, glycohemoglobin (HbA1c; < 6.1%) to exclude diabetes. Blood samples were taken on admission.

Heart catheterization

All patients had cardiac catheterization, and if necessary percutanous coronary interventions (PCI). A relevant coronary artery disease (CAD) was diagnosed if there was at least one stenosis ≥70%.

Statistics

Continuous data are expressed as mean value ± SD. Statistical analyses were performed with SigmaStat™ software (SPSS Inc.). For continuous and normally distributed data, unpaired t-tests otherwise Wilcoxon rank tests were used to test differences. For pairwise multiple comparison procedures Dunn's method was used to test differences. A $p < 0.05$ was considered significant for all comparisons.

Results

Sleep-disordered breathing (AHI > 5/h) was documented in 188 patients (74% vs. 62% in control group, ns) with a mean apnea-hypopnea-index of 16.4 ± 1.9/h. In our control group sleep apnea (AHI > 5/h) was found in 29 patients with a mean AHI of 9.5 ± 2.3/h ($p < 0.05$). We observed in 41% of our patients with coronary artery disease a relevant sleep apnea with a need for treatment (AHI > 15/h). In our control group only 17% had a relevant sleep-disordered breathing ($p = 0.002$). Obstructive sleep apnea was found in 130 patients (51% vs. 59% in control group, ns) with a mean apnea-hypopnea-index of 16.9 ± 2.2/h versus a mean apnea-

Tab. 2: Severity of sleep-disordered breathing in patients with coronary artery disease (CAD) and different comorbodities: adipositas, impaired glucose tolerance (IGT) and atrial fibrillation (AF)

Patients with CAD and comorbidities	Pts, *n*	Prevalence of SDB	Mean AHI
Only CAD	35	37%	6.2 ± 2.0/h
CAD + Adipositas	113	72%	15.2 ± 2.9/h
CAD + Adipositas + IGT	56	72%	18.1 ± 4.3/h
CAD + Adipositas + IGT + AF	15	100%	35.1 ± 10.6/h

hypopnea-index of 12.9 ± 3.2/h in our control group (ns). Central sleep apnea could be observed in 58 patients (23% vs. 6% in control group) with a mean apnea-hypopnea-index of 29.7 ± 4.5/h (control group: AHI 10.7 ± 8.7/h, $p < 0.05$). Severity of sleep-disordered breathing measured by apnea-hypopnea-index was significantly higher in patients with central sleep apnea than in patients with obstructive sleep apnea (mean apnea-hypopnea-index 29.7 vs. 16.9/h; $p < 0.01$; in control group ns). In obese patients mean apnea-hypopnea-index was 17.8 ± 2.2/h and higher than in not obese patients (AHI 9.9 ± 3.4/h; $p < 0.01$). The same tendency could be observed in the control group (AHI 10.3 ± 2.9 vs. 6.6 ± 2.9; ns). Compared to patients without sleep-disordered breathing (body mass index [BMI] 26.7 ± 0.8 kg/m^2), patients with obstructive sleep apnea (body mass index [BMI] 29.0 ± 0.8 kg/m^2) as well as patients with central sleep apnea (body mass index [BMI] 28.9 ± 1.0 kg/m^2) had significantly higher mean body mass indices ($p < 0.001$). The same tendency could be observed in the control group (BMI 26.1 ± 2.4 vs. 29.7 ± 2.6 kg/m^2; ns).

Because sleep-disordered breathing is influenced by comorbidities the effect of obesity, impaired glucose tolerance and atrial fibrillation on the incidence and severity of sleep-disordered breathing was analyzed (Tab. 2). Patients with coronary artery disease, obesity, impaired glucose tolerance and atrial fibrillation ($n = 15$) demonstrated sleep-disordered breathing in 100% and had a significant higher apnea-hypopnea-index than patients with coronary artery disease, obesity and impaired glucose tolerance (apnea-hypopnea-index 35.1 vs. 18.1/h; $p < 0.05$).

We found no correlation between medication (particularly statin therapy) and sleep-disordered breathing or triglyceride/cholesterol serum level and sleep-disordered breathing (also in control group). Patients in CCS (Canadian Cardiovascular Society) class 1 and class 2 had a lower apnea-hypopnea-index than symptomatic patients with CCS class 3 and class 4 (AHI 16.0 vs. 18.4/h; $p > 0.05$). Severity of sleep-disordered breathing increased in patients with higher NYHA classes (New York Heart Association) and 3-vessel coronary artery disease.

Patients with sleep-disordered breathing had higher blood fibrinogen level (340.3 ± 10.7 mg/dl) than patients with no sleep-disordered breathing (313 ± 17.6 mg/dl; $p = 0.01$). The same demonstrated the control group. Patients in control group with no sleep apnea had lower blood fibrinogen level (274.7 ± 22.4 mg/dl) than patients with sleep-disordered breathing (317.5 ± 24.3 mg/dl; $p = 0.03$).

Patients with both obstructive sleep apnea (340.5 ± 12.6 mg/dl; $p = 0.01$) as well as patients with central sleep apnea (340 ± 20.6; $p < 0.05$) had higher fibrinogen levels (Fig. 2). The same could be demonstrated in the control group for obstructive sleep apnea in comparison with patients with no sleep-disordered breathing (mean fibrinogen 318.3 ± 27.9 vs. 282 ± 26.1 mg/dl; $p = 0.04$). For CSA we observed the same tendency (mean fibrinogen 314 ± 114 vs. 282 ± 26 mg/dl, ns).

In total, 140 of 197 patients with a CRP below the cut-off of 0.5 mg/dl (group 1) had 71.1% sleep-

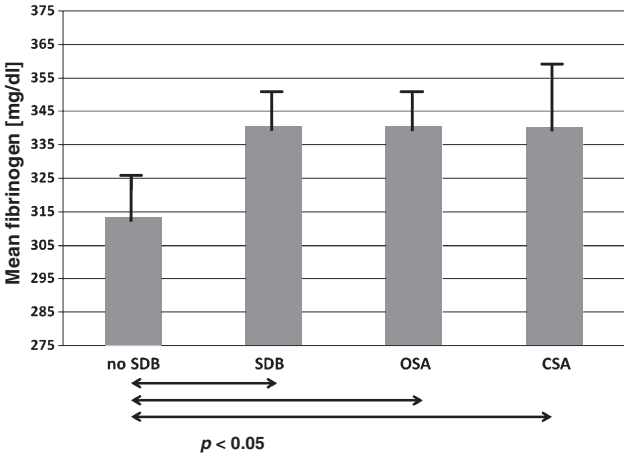

Fig. 2: Fibrinogen serum levels in patients with SDB, without SDB, with OSA and with CSA. We found only significant differences between fibrinogen serum levels in patients with vs. without SDB

disordered breathing. In total, 42 of 54 patients with no active infection in the last 4 weeks and a CRP > 0.5 mg/dl had sleep-disordered breathing in 77.8% (group 2). Severity of sleep-disordered breathing was significantly higher in group 2 (AHI 21 ± 5.4/h) than in group 1 (AHI 15.0 ± 2.0/h; $p = 0.01$). The same could be observed in our control group. Patients with CRP < 0.5 mg/dl had a mean AHI of 7.9 ± 2.4/h, patients with CRP > 0.5 mg/dl had a mean AHI of 17.4 ± 5.1/h ($p < 0.001$). In our control group patients with OSA had higher CRP level than patients with no sleep apnea (0.41 ± 0.2 vs. 0.14 ± 0.05 mg/dl; $p = 0.009$). The same could be demonstrated for patients with CSA in our control group (mean CRP 0.28 ± 0.3 vs. 0.14 ± 0.05 mg/dl; $p = 0.03$).

There were no correlations between fibrinogen or CRP serum levels and different comorbidities.

Discussion

This study demonstrates that sleep-disordered breathing is a common comorbidity in patients with coronary artery disease and is associated with elevated inflammatory markers. Three-fourths of our patients with coronary artery disease had sleep-disordered breathing, 23% central sleep apnea and 51% obstructive sleep apnea. Particularly a relevant sleep apnea was found more often in patients with coronary artery disease than in patients with angiographically exclusion of coronary artery disease (control group).

In accordance with our study results Mooe et al. reported the prevalence of sleep-disordered breathing in patients with coronary artery disease [11]. In a case-control study 142 men with angina pectoris and angiographically verified coronary artery disease were compared to 50 controls without heart disease. Screening for sleep-disordered breathing included registration of oronasal airflow using a three-way thermistor, blood oxygen saturation, heart rate by pulse oximetry with a finger transducer and body position movement. Men with coronary artery disease had a 61% prevalence of sleep-disordered breathing (apnea-hypopnea-index ≥5) as compared to the control group ($p < 0.001$). In another case-control study including 102 randomly selected women with angina pectoris and angiographically verified coronary artery disease the prevalence of sleep-disordered breathing was 54% [12]. In contrast to our study Mooe et al. could not differentiate between obstructive and central sleep apnea, because thoracical and abdominal breathing efforts were not documented. By differentiation between central and obstructive sleep apnea we demonstrated that severity of sleep-disordered breathing measured by apnea-hypopnea-index was higher in patients with central sleep apnea than in patients with obstructive sleep apnea. In our control group these results were not statistically significant, but we had only 6% of patients with central sleep apnea. It seems that the occurrence of central sleep apnea is more often in patients with coronary artery disease than in the control group ($p = 0.002$).

Patients in our study were older than in the study by Mooe (64.4 vs. 57.9 years). Further the patient population with 77% of more vessel disease may be a selected one (tertiary center, no acute angiographies included). Because of our population and because sleep-disordered breathing's prevalence and severity is increasing with age, the higher prevalence in our cohort could be explained.

Berger et al. [26] recently showed that patients with primary snoring, mild and moderate obstructive sleep apnea had an increase in apnea-hypopnea-index over time mainly dependent on weight gain and to a lesser degree on older age. Severity of sleep-disordered breathing was significantly lower in patients with body mass index ≤25 kg/m^2 than in patients with body mass index >25 kg/m^2. We also observed that patients with obstructive sleep apnea had a significant higher body mass index than patients with no sleep-disordered breathing. Interestingly patients with central sleep apnea had also a higher body mass index than patients without sleep-disordered breathing. The patients in our control group demonstrated the same tendencies. In order to reduce the influence of comorbidities we divided patients into different groups. Patients without obesity, atrial fibrillation or impaired glucose tolerance had a relative mild sleep-disordered breathing (apnea-hypopnea-index 6.2 ± 2.0/h; control group: 6.8 ± 5.4/h, ns) and demonstrated sleep apnea in only 37%. Coronary artery disease patients with obesity had a significantly higher apnea-hypopnea-index (15.2 ± 2.9/h), which demonstrates the high importance of obesity in patients with sleep-disordered breathing. Similar results demonstrated the control group (mean AHI 6.6 ± 2.9 vs. 10.3 ± 2.9/h, ns).

Recent studies indicate an emerging link between sleep-disordered breathing and atrial fibrillation. In most of these studies patients with impaired left ventricular function were included, which may cause both atrial fibrillation and sleep-disordered breathing. Stevenson et al. studied the prevalence of sleep-disordered breathing in a population of patients with atrial fibrillation and normal left ventricular function [29]. 62% of all patients with atrial fibrillation demonstrated a significant sleep-disordered breathing (apnea-hypopnea-index >15/h vs. 38% in control group). In our study all

patients despite coronary artery disease had a preserved left ventricular function. 40 patients were in persistent atrial fibrillation. A significant higher apnea-hypopnea-index was present in patients with coronary artery disease and atrial fibrillation than in patients with coronary artery disease and sinus rhythm (apnea-hypopnea-index 25.7 vs. 14.7/h; $p < 0.001$). The combination of coronary artery disease and atrial fibrillation seems to be associated with a more severe sleep-disordered breathing [30]. This was also demonstrated in patients with coronary artery disease, obesity, impaired glucose tolerance and atrial fibrillation ($n = 15$). These patients demonstrated in 100% sleep-disordered breathing and had a significant higher apnea-hypopnea-index than patients with coronary artery disease, obesity and impaired glucose tolerance (apnea-hypopnea-index 35.1 vs. 18.1/h; $p < 0.05$), indicating that atrial fibrillation is often related with sleep-disordered breathing. Despite same tendencies in our control group, these findings should be interpreted with caution, because of the small number of patients.

The relationship between severity of sleep-disordered breathing and impaired glucose tolerance is not yet fully understood. We measured glycohemoglobin (cut-off: 6.1%), an established marker for impaired glucose tolerance during previous weeks. Tamura et al. [30] found a high prevalence (60.5%) of impaired glucose tolerance in Japanese patients with obstructive sleep apnea (apnea-hypopnea-index $\geq$5/h). The prevalence of impaired glucose tolerance increased parallel with the severity of obstructive sleep apnea. In our study patients with coronary artery disease, obesity and impaired glucose tolerance ($n = 56$) had sleep-disordered breathing in 72% and no significant higher apnea-hypopnea-index than the coronary artery disease patients with obesity and no impaired glucose tolerance (apnea-hypopnea-index 18.1 vs. 15.2/h; $p > 0.05$). The results in our control group were equal. Therefore the association of coronary artery disease and impaired glucose tolerance seems not as important as the combination of coronary artery disease and obesity or coronary artery disease and atrial fibrillation.

Earlier studies have demonstrated an association of obstructive sleep apnea and increased fibrinogen levels. Guardiola et al. [27] found a correlation of obstructive sleep apnea, fibrinogen levels and blood hypercoagulability to be reversed by chronic nasal continuous positive airway pressure treatment. In our study all patients with sleep-disordered breathing had a significant higher blood fibrinogen level than those without sleep-disordered breathing. The fibrinogen level in our control group supported these results. In addition to the findings of Guardiola et al. we were able to demonstrate that both, patients with obstructive and central sleep apnea had significant higher fibrinogen levels, suggesting that sleep-disordered breathing is an indicator for cardiovascular complications in obstructive sleep apnea and in central sleep apnea patients.

Obstructive sleep apnea is associated with increased levels of high-sensitive C-reactive protein (hs-CRP), a marker for inflammation and cardiovascular risk [28]. Shamsuzzaman et al. [21] found in a small study with 22 patients that severity of obstructive sleep apnea is proportional to the CRP level. In our study patients with CRP under the cut-off of 0.5 mg/dl (group 1) had 71.1% sleep-disordered breathing. Patients with CRP > 0.5 mg/dl had sleep-disordered breathing in 77.8% (group 2). Severity of sleep-disordered breathing was significantly higher in group 2 (AHI 21 ± 5.4/h) than in group 1 (AHI 15.0 ± 2.0/h; $p = 0.01$). The results in our control group supported these findings. In conclusion, patients with more severe sleep-disordered breathing had increased CRP plasma levels regardless the type of sleep-disordered breathing and regardless the various comorbidities: there were no correlations between CRP and fibrinogen serum levels and comorbidities like obesity, atrial fibrillation or impaired glucose tolerance (also in control group). Therefore our study is confirmative of previous work. Lui et al. demonstrated in a study with 111 men that elevated CRP levels were associated with obstructive sleep apnea independent of visceral obesity [32]. Mechanisms linking sleep-disordered breathing, not only obstructive sleep apnea, to increased CRP may include repetitive hypoxemic stress and activation of the sympathetic nervous system.

Limitations

Due to some comorbidities like atrial fibrillation or impaired glucose tolerance the results should be interpreted with caution (small number of patients). Diagnosis and classification of sleep-disordered breathing is based on cardiorespiratory polygraphy, not on polysomnography as the gold-standard to diagnose sleep-disordered breathing. Using polygraphy to distinguish between obstructive and central sleep apnea may lead to some inaccuracy of the data. We included only patients with preserved systolic LV function. From our results it appears that patients with diastolic heart failure may also be included, which could have affected the results. Further studies concerning coronary artery disease and

sleep-disordered breathing, particularly focusing on diastolic heart failure, are warranted.

Conclusions

There is a high prevalence of sleep-disordered breathing in patients with stable coronary artery disease with a predominance of obstructive sleep apnea. Both types of sleep-disordered breathing, obstructive as well as central sleep apnea, are associated with elevated inflammatory markers, which may result in hypercoagulability and acute coronary syndromes and may explain the known negative prognostic impact of sleep-disordered breathing in coronary artery disease.

Acknowledgments

Conception and interpretation of data were performed by C. Prinz, T. Bitter, C. Piper and O. Oldenburg, the manuscript was drafted and critically reviewed by C. Prinz, C. Piper, L. Faber and O. Oldenburg. Final approval of the manuscript submitted was done by C. Prinz and D. Horstkotte.

Conflict of interest

The authors declare that there is no conflict of interest.

References

[1] Gislason T, Almquist M, Eriksson G, et al. Prevalence of sleep apnea syndrome among Swedish men – an epidemiological study. J Clin Epidemiol, 41: 571–576, 1988.
[2] Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med, 328: 1230–1235, 1993.
[3] Levinson PD, McGarvey ST, Carlisle CC, et al. Adipositas and cardiovascular risk factors in men with obstructive sleep apnea. Chest, 103: 1336–1342, 1993.
[4] Oldenburg O, Lamp B, Töpfer V, et al. Prevalence of sleep-related breathing disorders in ischemic and non-ischemic heart failure. Dtsch Med Wochenschr, 132: 661–666, 2007.
[5] Oldenburg O, Lamp B, Faber L, et al. Sleep disordered breathing in patients with symptomatic heart failure. Eur J Heart Failure, 9: 251–257, 2007.
[6] Kales A, Cardieux RJ, Shaw LC, et al. Sleep apnea in a hypertension population. Lancet, 2: 1005–1008, 1984.
[7] He J, Kryger MH, Zorick FJ, et al. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. Chest, 94: 9–14, 1988.
[8] Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients: mortality. Chest, 94: 1200–1204, 1988.
[9] Hung J, Whitford EG, Parsons RW, et al. Association of sleep apnea with myocardial infarction in men. Lancet, 336: 261–264, 1990.
[10] Peker Y, Kraiczi H, Hedner J, de M. An independent association between obstructive sleep apnoea and coronary artery disease. Eur Respir J, 14: 179–184, 1999.
[11] Mooe T, Rabben T, Wiklund U, et al. Sleep-disordered breathing in men with coronary artery disease. Chest, 109: 659–663, 1996.
[12] Mooe T, Rabben T, Wiklund U, et al. Sleep-disordered breathing in women: occurrence and association with coronary artery disease. Am J Med, 101: 251–256, 1996.
[13] Peker Y, Hedner J, Kraiczi H, et al. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med, 162: 81–86, 2000.
[14] Mooe T, Franklin KA, Holmström K, et al. Sleep-disordered breathing and coronary artery disease: long-term prognosis. Am J Respir Crit Care Med, 164: 1910–1913, 2001.
[15] Gami AS, Howard DE, Olson EJ, et al. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med, 352: 1206–1214, 2005.
[16] American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. Sleep, 22: 667–689, 1999.
[17] Hedner J, Ejnell H, Sellgren J, et al. Is high and fluctuating muscle nerve sympathetic activity in the sleep apnoea syndrome of pathogenetic importance for the development of hypertension? J Hypertens Suppl, 6: 529–531, 1988.
[18] Lanfranchi P, Somers V, Braghiroli A, et al. Central sleep apnea in left ventricular dysfunction. Prevalence and implications for arrhythmic risk. Circulation, 107: 727–732, 2003.
[19] Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. Eur Respir J, 28: 596–602, 2006.
[20] Ip MS, Tse HF, Lam B, et al. Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med, 169: 348–353, 2004.
[21] Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation, 105: 2462–2464, 2002.
[22] Dziewas R, Ritter M, Kruger L, et al. C-reactive protein and fibrinogen in acute stroke patients with and without sleep apnea. Cerebrovasc Dis, 24: 412–417, 2007.
[23] Nieto FJ, Herrington DM, Redline S, et al. Sleep Apnea and markers of vascular endothelial function in a large community sample of older adults. Am J Respir Care Crit Care Med, 169: 354–360, 2004.
[24] Schulz R, Seeger W, Fegbeutel C, et al. Changes in extracranial arteries in obstructive sleep apnoea. Eur Respir J, 25: 69–74, 2005.
[25] Oldenburg O, Lamp B, Horstkotte D. Cardiorespiratory screening for sleep-disordered breathing. Eur Respir J, 28: 1065–1067, 2006.
[26] Berger G, Berger R, Oksenberg A. Progression of snoring and obstructive sleep apnea: the role of increasing weight and time. Eur Respir J, 2008; doi: 10.1181/09031936.00075408.
[27] Guardiola JJ, Matheson PJ, Clavijo LC, et al. Hypercoagulability in patients with obstructive sleep apnea. Sleep Med, 6: 517–523, 2001.
[28] Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation, 103: 1813–1818, 2001.
[29] Stenvenson IH, Teichtahl H, Cunnington D, et al. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. Eur Heart J, 29: 1662–1669, 2008.
[30] Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation, 110: 364–367, 2004.
[31] Tamura A, Kawano Y, Watanabe T, et al. Relationship between the severity of obstructive sleep apnea and impaired glucose metabolism in patients with obstructive sleep apnea. Respir Med, 102: 1412–1416, 2008.
[32] Lui MM, Lam JC, Mak HK, et al. C-reactive protein is associated with obstructive sleep apnea independent of visceral obesity. Chest, 135: 950–956, 2009.