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Research Article

Temporal Relation of Myocardial Ischemia to Nocturnal Desaturation of Oxygen in Patients with Coronary Artery Disease

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Abstract

Purpose: Obstructive sleep apnea (OSA) is frequently associated with coronary artery disease. Causal relation of nocturnal respiratory disorders to the onset of myocardial ischemia has been discussed controversially. **Methods:** Patients with coronary artery disease (CAD) were enrolled in the present pilot study. Overnight polygraphy and 12-lead ECG were performed in all patients. Patients with nocturnal myocardial ischemia in the study night were eligible for analysis of breathing parameters preceding myocardial ischemia. Backwards from the first second of myocardial ischemia, a preceding period of 900 seconds was analysed for OSA and subsequent reduction of oxygen saturation. The frequency of respiratory events within this period was compared to frequency within the total time of sleep assessment. **Results:** We present data of 19 patients (4 women; 15 men) aged 45 to 79 years (mean 64.1 years; ± 9.4 (standard deviation)) with a mean body mass index (BMI) of 29.5 $kg(m^2)^{-1}$ ± 4.4. No patient had been diagnosed with OSA before study participation. In all patients an Apnea-Hypopnea-Index (AHI) ≥5/h (median 11/h; IQR: 8/25), in 9 patients (47%) an AHI of ≥15/h (median 25; IQR: 20/47.5) was calculated. Nocturnal myocardial ischemia was found in 8 patients and furthermore, one patient reported nocturnal chest pain. Preceding myocardial ischemia OSA was more frequent compared to the time without ischemia 100% (95%/100%) versus 66.8% (58%/75.9%); p= 0.012. **Conclusion:** The present study concludes that nocturnal myocardial ischemic events frequently occur with a temporal related accumulation of preceding OSA.

Keywords: Myocardial ischemia; nocturnal hypoxemia, OSA, temporal relation

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Introduction

Strong association between sleep disordered breathing (SDB) and, in particular, between obstructive sleep apnea (OSA) and cardiovascular disease has been highlighted in previous studies by Shahar et al. (2001) and Franklin and co-workers (1995). Besides others, OSA has been associated with ischemic heart disease and hypertension as shown by Peker and colleagues (2002). OSA has shown to be a risk factor for coronary events and a predictor for cardiovascular death found by Shah et al. (2010) and Martinez et al. (2012). Causal relation of OSA with regard to the onset of nocturnal myocardial ischemia has been controversially discussed by Keyl et al. (1994), Smith et al. (1996) and Gögenur et al. (2004). OSA is characterized by recurrent occlusion of the upper airway with subsequent total or partial flow limitation, as well as intermittent hypoxemia. Normally, this situation is terminated by an arousal reaction with a sympathetic burst. Blood pressure and heart frequency increase within a hypoxemic condition. We hypothesized intermittent hypoxemia to be a trigger for nocturnal myocardial ischemia prior to elective surgery.

This study was designed to analyse the temporal association of myocardial ischemia detected with nocturnal 12-lead-Holter-electrocardiogram (ECG) and related parameters indicative for OSA.

Methods

The study protocol was approved by the ethics committee of the Philipps-University of Marburg (AZ 76/04). Informed written consent was obtained from all patients.

Coronary artery disease (CAD) was pre-known in all patients who came routinely for check-up after previous coronary intervention (coronary stenting) to the hospital. Stress ECG was performed in all patients, and those with pathological result were scheduled for coronary angiography. These patients were eligible for study enrolment, and overnight polygraphy with time-synchronized 12-lead Holter-ECG was performed the night before. Patient`s coronary status was documented according to results of coronary angiography. Re-stenosis ≥ 70% of minimum one coronary vessel was found in all assessed patients.

Patients who had a history of drug or alcohol abuse and patients with a long term sleep medication were excluded. Furthermore, patients were excluded if they had abnormalities in the ECG such as left and right bundle block. Nocturnal breathing assessment was made by overnight polygraphy (SOMNOcheck®, Weinmann, Germany) including assessment of peripheral arterial oxygen saturation, breathing flow, snoring and movement of thorax and abdomen. This assessment was performed from 10 p.m. to 6 a.m. on the cardiology ward in rooms with two beds. Periods with reduction of breathing flow of more than 30% of baseline with an accompanying decrease of oxygen saturation of ≥4% of baseline were scored as hypopneas; periods with a total flow-suppression of more than 10 seconds were counted as apneas. Apneas and hypopneas were manually assessed. Patients received no sedative agents the evening before measurement. ECG monitoring was performed using a 12-lead-recorder (WelchAllyn CardioPerfect Holter-ECG). The ST-segment was measured 0.08 s after the J-point. Ischemia was defined by ST changes in two contiguous leads. First, it was planned to assess data of ECG with a related commercial computer algorithm. Unfortunately the frequency of false results and artefacts via automated assessment was high. Therefore, data were manually analyzed by an experienced physician blinded with respect to medical records and the individual patient. These results were taken for final analysis. Over 24 hours, time on Holter-ECG differed from time on SOMNOcheck device a minimum of 2 seconds to a maximum of 8 seconds. Both devices were synchronized before each recording and equipped with a new battery before starting.

Previous data of other authors (Mooe et al. (2000) and Reeder et al. (1991)) show temporal relationship between ST-depression and decrease of oxygen saturation within a period of 2 minutes and 30 minutes, respectively. In the present study a period for time assessment of 15 minutes was chosen. For the final assessment, data were analysed in segments of seconds. Backwards from the first second of myocardial ischemia on ECG a preceding time of 900 seconds (15 minutes) was analysed for apneas, hypopneas and oxygen desaturations in the same individual. Results were set in relation to the frequency of apneas and hypopneas within the total time of sleep assessment (10 p.m. to 6 a.m.).

Statistical Analysis

Statistical analysis was performed by a statistician blinded to the individual cases using SPSS (version 15.0; SPSS Inc., Chicago, Illinois). Data were checked for deviations from the normal distribution by means of the Kolmogorov-Smirnov one sample test. Apnoea-Hypopnoea-Index (AHI) and arterial oxygen saturation were not normally distributed. Thus, a non-parametric test (Wilcoxon signed rank test) was applied. Results are given as median, first and third quartile. Results of normally distributed data are presented as mean and standard deviation (SD). Differences of normally distributed data were assessed by Student`s t-test. A p-value < 0.05 was considered statistically significant.

Results

Within the present study 22 patients were prospectively recruited. Agreement was revoked prior to polygraphy by two patients, and data quality was poor in one case. These data sets were therefore discarded. Thus, we are presenting data of 19 patients (4 women and 15 men) aged 45

to 79 years (mean 64.1 ± 9.4 years) with a mean body mass index (BMI) of 29.5 ± 4.4 kg $(m^2)^{-1}$. Patient´s characteristics are shown in **Table1**. No patient had a previous diagnosis of OSA.

In all patients, an AHI ≥ 5/h was observed (median 11/h; IQR: 8/25) and in 9 of 19 patients (47%) an AHI of ≥15/h (median 25/h; IQR: 20/47.5).

Nocturnal reduction of oxygen saturation was frequently found in all patients, whereas overall 13 episodes of nocturnal myocardial ischemia were detected only in 8 of 19 patients (42%). Both, ST depression and ST elevation were considered to be ST abnormalities. However, only ST depression occurred in the study population. One of these patients reported nocturnal chest pain the morning after measurement. A cutout of the nocturnal ECG of a study patient is shown in **Figure1**. Patients with myocardial ischemia and patients without did not differ with regard to the characteristics shown in **Table1**

Table1: Characteristics of the study population. (BMI = body mass index [kg $(m^2)^{-1}$]; SpO_2 (n) = nadir arterial oxygen saturation; SpO_2 (oa) = arterial oxygen saturation on average; AHI = Apnoea-Hypopnoea-Index; MI = number of detected myocardial ischemic events)

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Patient	Gender	Age	BMI	SpO_2 (n)	SpO_2 (oa)	AHI	MI
1	M	51	27,6	83 %	95 %	27	0
2	F	75	31,2	81 %	93 %	21	1
3	F	74	22,7	84 %	96 %	9	2
4	M	79	30,3	86 %	92 %	50	0
5	M	73	25,7	85 %	93 %	7	2
6	M	45	36,6	85 %	91 %	7	0
7	M	65	33,8	66 %	83 %	45	0
8	F	79	24,8	84 %	94 %	8	0
9	M	58	26,7	88 %	95 %	7	2
10	F	63	26,6	86 %	94 %	8	0
11	M	55	36,8	81 %	95 %	7	0
12	M	62	29,8	78 %	92 %	23	0
13	M	65	27,7	87 %	95 %	19	0
14	M	65	23,3	88 %	96 %	11	3
15	M	51	32,2	71 %	93 %	58	1
16	M	63	25,5	84 %	92 %	9	1
17	M	67	30,4	87 %	96 %	8	0
18	M	64	36,1	79 %	92 %	25	1
19	M	64	32	81 %	92 %	16	0

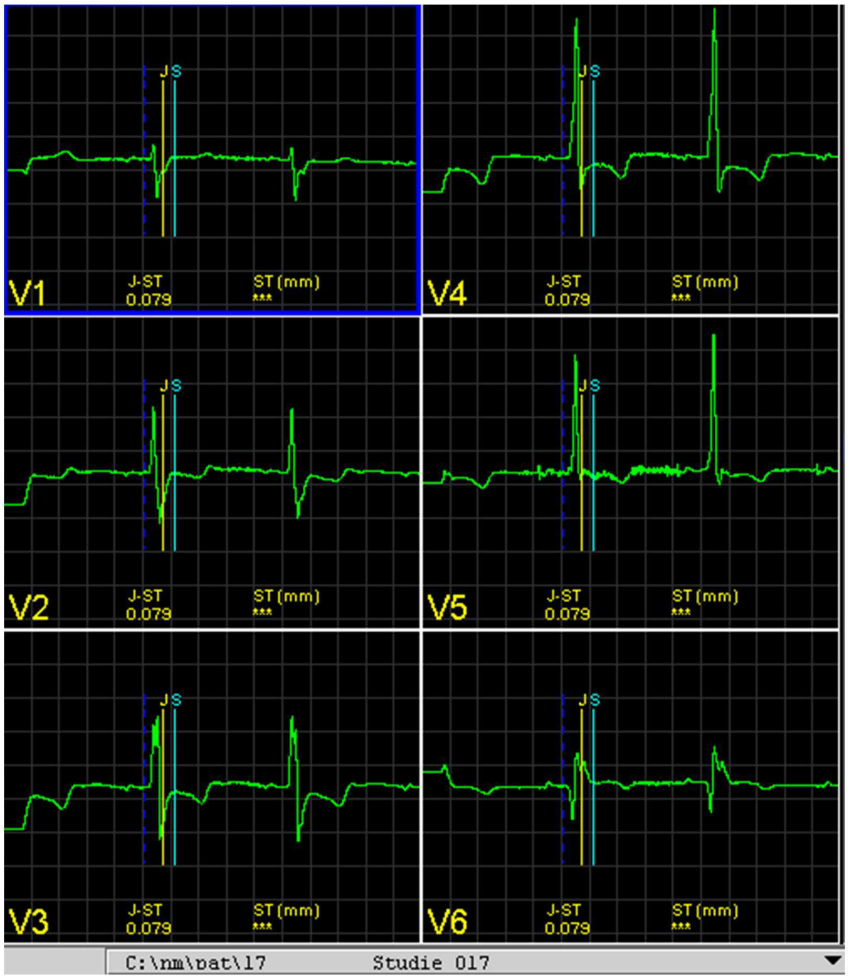

Figure1:Shown is a cutout of the nocturnal 12-lead ECG of a study patient who reported chest pain the morning after within a period of myocardial ischemia.

(age: p=0.59; BMI: p=0.46; nadir SpO_2: p=0.9; SpO_2 on average: p=0.53; AHI: p=0.45; number of stenosed coronary vessels: p=0.44). Co-morbidity profile and patients' medication is shown in **Table2.** Episodes of nocturnal hypoxemia were also frequently detected without temporal related ischemic events in ECG. To quantify these results, data of patients with nocturnal ischemic events in ECG (8 of 19) were finally analyzed in segments of seconds. Moreover, the distribution of breathing events and ischemic events in ECG were analyzed over the time of the study night. This analysis yielded to the following results:

Over a median of 167 seconds (IQR: 76/279 seconds) myocardial ischemia was detected. Within the preceding 900 seconds, OSA was found with a frequency of 100% (95%/100%). Within the time without ischemic events, OSA occurred only in 66.8% (58%/75.9%); p= 0.012 (**Figure2**).

Table2: Co-morbid profiles and medication of the study participants (ACE-I = angiotensin-converting enzyme inhibitors; CG= cardiac glycosides; AT1-RA= AT1-receptor antagonists; HLP= hyperlipoproteinemia; Smoker= smoker and former smoker).

Patient	ß-blockers	ACE-I	CG	Nitrates	Diuretics	AT1-RA	Hypertension	HLP	Smoker	Diabetes
1	X	X	X	X	X		X	X	X	X
2	X							X		X
3	X	X					X			
4	X	X					X	X	X	X
5	X	X					X			
6	X	X		X			X	X	X	
7	X	X					X	X		
8	X	X	X	X			X	X		X
9	X	X			X		X	X	X	
10	X		X						X	
11	X	X					X	X	X	
13	X	X			X		X	X	X	X
14	X	X	X	X	X		X			
15	X	X	X		X			X		
16	X	X					X	X	X	
17	X						X	X	X	
18	X	X					X	X		
19	X					X	X	X	X	X

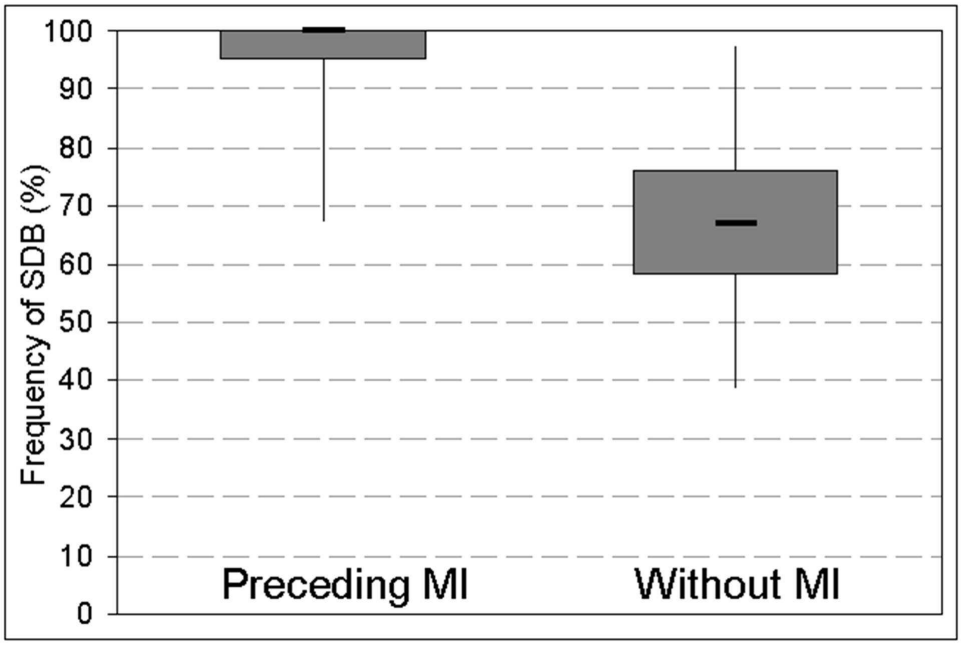

Figure2: Frequency of sleep disordered breathing the time before myocardial ischemia (left) and the time without (right)

Discussion

The present results indicate a high frequency of previously unrecognized and therefore untreated OSA in a group of patients with CAD. An AHI of ≥5/h with consecutive reduction of arterial oxygen saturation was observed in all recruited patients. Of note, all patients with myocardial ischemia during the observation period experienced OSA in the preceding period of 900 seconds.

A high prevalence of OSA in patients with CAD has been previously demonstrated by Shahar et al. (2001) and Peker et al. (2002). Marin and co-workers (2005) showed higher incidence of cardiovascular events in patients with OSA in comparison to patients without. Furthermore, SDB was associated with re-stenosis, remodeling (Steiner et al. 2008) and cardiac mortality after percutaneous intervention as shown by Yumino et al. (2007). Treatment of SDB with continuous positive airway pressure (CPAP) was presumed by Drager et al. (2007) to impede progression of atherosclerosis to clinically important cardiovascular diseases. Milleron and colleagues (2004) showed a reduction of new cardiovascular events in patients with CAD when sleep disordered breathing had been treated by CPAP-therapy. On the other hand, Shah and colleagues (2013) found OSA to have a protective role in acute myocardial infarction by chronic but mild intermittent hypoxic preconditioning.

In the present study, a temporal association of nocturnal respiratory disorders on myocardial ischemia was hypothesized. As described by other authors, nocturnal impairment of oxygen saturation occurred frequently, whereas myocardial ischemia was only detected in less than 50% of the study population during the study night. The presumed temporal association was controversial discussed in the literature. Keyl and colleagues (1994) as well as Smith and co-workers (1996) found no association between oxygen saturation and myocardial ischemia, whereas Reeder et al. (1991) described myocardial ischemia as temporally associated with hypoxemia. These results are in agreement with our findings, as accumulation of OSA events preceding episodes of myocardial ischemia was found.

Arbab-Zadeh and co-workers (2009) demonstrated the inability of diseased coronary artery segments to react to hypoxemia. However, all patients of the study population had diseased coronary arteries. Thus, other factors i.e. rapid-eye-movement (REM) and non-REM sleep should be considered. Kim and colleagues (2008) found severe myocardial ischemia in an animal model with stenosed coronary arteries during non-REM sleep. Nocturnal myocardial ischemia potentially occurs if oxygen partial pressure in blood has fallen below a critical level. This threshold probably differs between subjects. Temporal and accumulating SDB as shown in the present study would lead to reduced level of oxygen partial pressure.

Limitations and Strength

The present study was not performed with polysomnography (PSG). Therefore, an allocation of myocardial ischemia to sleep stages was not possible. It should be mentioned that nocturnal ischemic events frequently occur in REM sleep as shown by Schäfer et al. (1997). Furthermore, heart rate as an important determinant of myocardial oxygen consumption was not assessed and analyzed.

Due to its small sample size, the power of the study is limited. However, to the best of our knowledge this is the first study that employed long-term 12-lead-ECG for the detection of nocturnal myocardial ischemia associated with cardio-respiratory polygraphy. Body position while measuring ST abnormalities was not addressed within the analysis.

The present study concludes that nocturnal myocardial ischemic events frequently occur with a temporal related accumulation of preceding SDB.

Conflict of Interest

The authors declare that they have no conflict of interest

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