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Markers of Myocardial Ischemia in Patients with Diabetes Mellitus and Severe Obstructive Sleep Apnea – Impact of Continuous Positive Airway Pressure Therapy

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Abstract

Introduction: Diabetes Mellitus (T2DM) and obstructive sleep apnea (OSA) are common disorders that often coexist. Both disorders are associated with an increased risk of cardiovascular complications. Repeated nocturnal hypoxia in diabetic patients suffering also from OSA may result in myocardial ischemia. We evaluated whether myocardial ischemia is detectable by ST-segment depression and elevation of high sensitive Troponin T (hs-cTnT) and N-terminal pro B-type natriuretic peptide (NT-proBNP). We also examined the effect of continuous positive airway pressure treatment (CPAP) on these markers.

Methods: Fifteen patients with OSA and concomitant T2DM and 26 patients with OSA alone underwent polysomnography at baseline and under CPAP. Blood samples for hs-cTnT and NT-proBNP measurements were drawn prior and immediately after sleep. ST-segment depression was measured at the time of maximum oxygen desaturation during sleep.

Results: The apnea-hypopnea-index and oxygen saturation nadir were similar in both groups. Levels of hs-cTnT and NT-proBNP did not differ significantly before and after baseline polysomnography and CPAP respectively within the same group. But hs-cTnT levels were significantly higher before and after PSG and CPAP respectively in patients suffering from T2DM and OSA compared to patients with OSA alone. In both groups, we found no significant ST-segment depression at the time of oxygen saturation nadir.

Conclusions: Despite the fact that patients with T2DM and coexisting OSA experienced severe nocturnal hypoxemia we were unable to detect myocardial ischemia or myocyte necrosis evidenced by significant ST-segment depression or elevation of hs-cTnT and NT-proBNP respectively. CPAP had no influence on hs-cTnT and NT-proBNP levels.

Keywords: Obstructive sleep apnea; Diabetes mellitus; High sensitive Troponin T; NT-proBNP; Ischemia; Continuous positive airway pressure

Introduction

Diabetes Mellitus (T2DM) and Obstructive Sleep Apnea (OSA) are common disorders that often coexist [1]. Both, T2DM and OSA are associated with increased cardiovascular morbidity and mortality [2,3]. T2DM is associated with a 2 to 4-fold increased risk of coronary heart disease [4]. In cross-sectional and case-control studies an increased risk for coronary artery disease and myocardial ischemia in patients with OSA has also been suggested [5,6]. It is possible that the presence of both conditions may result in additive or even synergistic health risks.

OSA is characterized by intermittent hypoxia during sleep, which is associated with elevated sympathetic activity, cardiovascular variability, and intrathoracic pressure changes [7]. Stress imposed on the myocardium by repeated severe hypoxemia during sleep and an increased oxygen demand by sympathetic overstimulation in OSA may result in subclinical myocardial injury [8]. Cardiac troponin T is an important biomarker in myocardial injury and a predictor of clinical outcome [9]. The cardiac amino-terminal pro-B-type natriuretic peptide (NT-proBNP) is a functional biomarker, that is secreted from the myocytes of the atria and ventricles after myocardial hypoxemia and ventricular volume overload [10]. NT-proBNP production is strongly upregulated in cardiac failure and locally in the area surrounding a myocardial infarction [11].

The standard treatment for moderate and severe OSA is nasal continuous positive airway pressure (CPAP) [12].

We tested the hypothesis that severe OSA may precipitate myocardial ischemia and necrosis in patients with T2DM reflected by ST-segment depression and increased levels of the cardiac markers NT-proBNP and hs-cTnT. As well as testing this hypothesis, we aimed to evaluate whether CPAP therapy can possibly prevent myocardial injury caused by repetitive nocturnal hypoxia.

Materials and Methods

The prospective study was conducted between February 2012 and September 2013, and was approved by the ethics committee of the State

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Medical Council of Hessen, Germany (approval number FF 6/2912). Informed consent was obtained from each patient.

Study population

Patients were screened by polygraphy for the presence of severe OSA with an oxygen desaturation ≤80% during apnea. The study enrolled a group of 15 patients with T2DM and OSA concomitant (group 1) who were referred for Polysomnography (PSG) to the Center of Sleep Medicine at Krankenhaus Sachsenhausen. A group of 26 patients with OSA but without a history of diabetes served as a control (group 2).

Inclusion criteria were as follows: age >18 years, severe OSA with an apnea-hypopnea-index (AHI) ≥15/h and oxygen desaturation ≤ 80% at polysomnography, proven history of T2DM (group 1). Exclusion criteria were systolic heart failure (left ventricular ejection fraction <40% measured by echocardiography), glomerular filtration rate <50 ml/min estimated using the Cockcroft-Gault formula.

Polysomnography

The presence and severity of OSA was determined by overnight complete polysomnography using a computerized system (Alice 5, Philips Respironics, Herrsching, Germany). Standard techniques such as EEG, electrooculography, electromyography, electrocardiogram, thermistor measurements of air flow, thoracoabdominal motion, pulse oximetry of arterial oxyhemoglobin saturation (SPO_2) and body position were used to monitor sleep disordered breathing. Bedtime was 10 pm to 6 am. Sleep stages were scored according to the standard criteria of the American Academy of Sleep Medicine [13]. Apnea was defined as an absence of airflow for >10 s. Hypopnea was defined as a more than 30% reduction in airflow accompanied by a decrease in SPO_2 >4%. AHI was calculated as the average number of apneas and hypopneas per hour of sleep. An AHI ≥15/h was defined as severe OSA.

Measurement of hs-cTnT and NT-proBNP

Quantitative measurement of hs-cTnT was achieved via an immunoassay for the in vitro quantitative determination of cardiac troponin T in human serum and plasma (Cobas e 411 Roche Troponin T hs STAT; Roche Diagnostics Inc.) with a lower limit of normal <14 pg/ml representing the 99th percentile in a normal reference population and a coefficient of variation <10%. Hs-cTnT values below the Limit of Blank are reported as <3 ng/L.

NT-proBNP levels were measured with an immunoassay for the in vitro quantitative determination of NT-proBNP in heparinized venous blood (Cobas Roche Cardiac proBNP+; Roche Diagnostics Inc.). Values below the Limit of Blank are reported as <60 ng/L.

Venous blood samples (5 ml) were collected at different time points: before (9 pm) and after (7 am) polysomnography and CPAP respectively. The measurements were performed immediately after the second set of blood samples were drawn.

ST-segment analysis in the electrocardiogram

A continuous ECG recording was performed simultaneously during sleep in all patients to screen for ST-segment depression episodes as an indicator of myocardial ischemia. Lead II was used to analyze the ST-segment for myocardial ischemia. Additional leads I, III, aVL, aVR, and aVF were used as backup for further evaluation of features suggestive of cardiac ischemia observed in the main ECG lead. An ischemic episode was defined as a horizontal or downsloping ST-segment depression ≥1 mm (100 µV) from baseline, measured 80 ms after the J point. The time point of maximum oxygen desaturation during sleep was determined by continuous oximetry. Ten cardiac cycles after the minimum oxygen saturation the ST-segment changes observed in 10 consecutive cardiac cycles were analyzed and averaged.

Continuous positive air pressure treatment

Optimal CPAP pressure was titrated in the sleep laboratory on a second night after one diagnostic night at baseline. All patients were monitored under CPAP treatment conducted after pressure titration.

Statistics

The results are expressed as mean ± standard deviation (SD) for continuous variables. For the descriptive statistics, the arithmetic mean, standard deviation, median, minimum and maximum, and 1st and 3rd quartiles were calculated. For comparison of the two groups the Fisher exact test and the Wilcoxon-Mann-Whitney U test (U-test) were used. The Wilcoxon Matched Pairs Test was applied for paired samples. Statistical analyses were performed using a statistical software package (BiAS. for Windows, Version 10.05). P-values <0.05 were considered statistically significant.

Results

The study population included a group of 15 patients with T2DM and concomitant OSA (group 1). A group of 26 patients with OSA but without T2DM (group 2) served as a control. Anthropometric characteristics, clinical data, and sleep parameters of both groups are presented in Table 1. There were no statistically significant differences between the two groups other than the presence of hypercholesterolemia, body mass index and medication with ACE-inhibitors.

In patients who suffered from OSA and T2DM, the mean value for AHI was 57 ± 18 n/h, the oxygen saturation nadir was 70 ± 14%, and the maximal duration of sleep-related breathing disorders (SRBD) was 96 ± 61 seconds. In the control group, the corresponding values were 48 ± 21 n/h, 72 ± 13%, and 85 ± 39 seconds. The differences between the two groups were not significant.

ST-segment analysis revealed no significant ST depression (≥100 µV) suspicious of myocardial ischemia at the time of the deepest oxygen desaturation, neither in patients who suffered from T2DM and OSA, nor in the control group. ST segment depression was not different in patients with T2DM and OSA compared to patients with OSA alone (Figure 1).

The levels and distribution of the cardiac markers hs-cTnT and NT-proBNP did not differ significantly before and after sleep within the same group. However, hs-cTnT levels were significantly higher before sleep as well as after sleep in patients with T2DM and OSA compared to patients with OSA alone (Figure 2). Hs-cTnT was detectable (≥ 3 ng/L) in 14 (93%) patients before and in 13 (87%) patients after polysomnography in group 1. In patients with OSA alone hs-cTnT was detectable in 20 (77%) patients before and in 21 (81%) after polysomnography.

AHI was significantly reduced by CPAP in both patient groups (group 1: AHI 5 ± 4, group 2: AHI 5 ± 5), but showed no effect on hs-cTnT and NT-proBNP levels (Figure 3).

Discussion

Despite the fact that patients with T2DM and coexisting OSA experienced severe nocturnal hypoxemia we were unable to detect myocardial ischemia or myocyte necrosis evidenced by significant

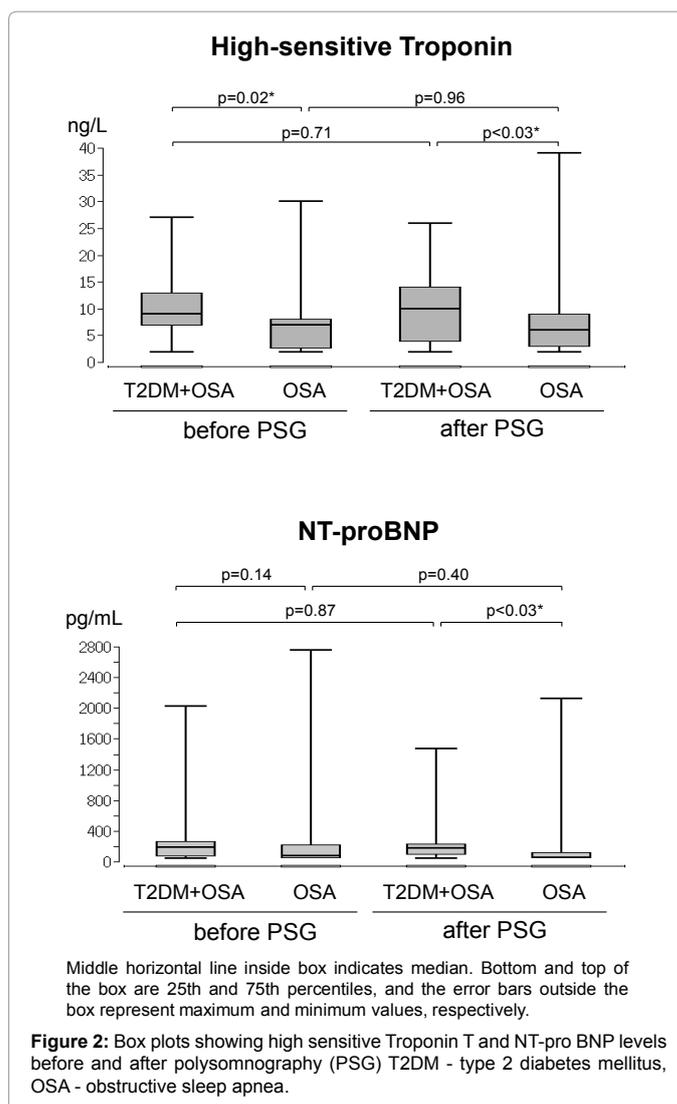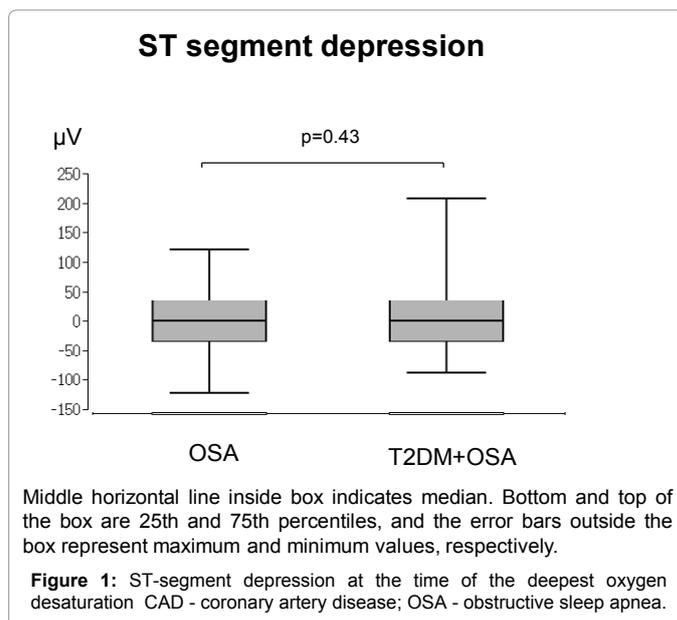|	T2DM and OSAS (n=15)	OSAS alone (n=26)	p value
Demographics			
Gender (female/male)	4/11	4/22	
Age (yr)	58 ± 9	58 ± 13	n.s
Body mass index (kg/m²)	39 ± 7	32 ± 5	<0.01
Medical history			
Hypertension	14 (93%)	18 (69%)	n.s.
Hypercholesterolemia	12 (80%)	10 (38%)	<0.05
Coronary artery disease	10 (67%)	11 (42%)	n.s.
Arrhythmia	3 (20%)	4 (15%)	n.s.
Stroke	2 (13%)	0 (0%)	n.s.
Myocardial infarction	5 (33%)	7 (27%)	n.s.
COPD	4 (19%)	2 (10%)	n.s.
Medication			
Insulin	8 (53%)	-	
Oral antidiabetic drugs	11 (73%)	-	
Nitrates	2 (13%)	1 (4%)	n.s.
β-blockers	12 (80%)	13 (50%)	n.s.
Renin inhibitor	0 (0%)	1 (4%)	n.s.
ACE inhibitors	10 (67%)	7 (27%)	<0.05
Angiotensin II receptor blockers	2 (13%)	6 (23%)	n.s.
Diuretics	8 (53%)	8 (31%)	n.s.
Calcium channel blockers	6 (40%)	8 (31%)	n.s.
α-blockers	1 (7%)	2 (8%)	n.s.
Cardiac and renal function			
LVEF (%)	60 ± 8	63 ± 6	n.s.
GFR (ml/min)	144 ± 48	120 ± 48	n.s.
Polysomnography (baseline)			
AHI (n/h)	57 ± 18	48 ± 21	n.s.
Oxygen saturation nadir (%)	70 ± 14	72 ± 13	n.s.

Data are presented as mean ± SD or No (%). ACE = angiotensin-converting enzyme; AHI = apnea-hypopnea-index; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction
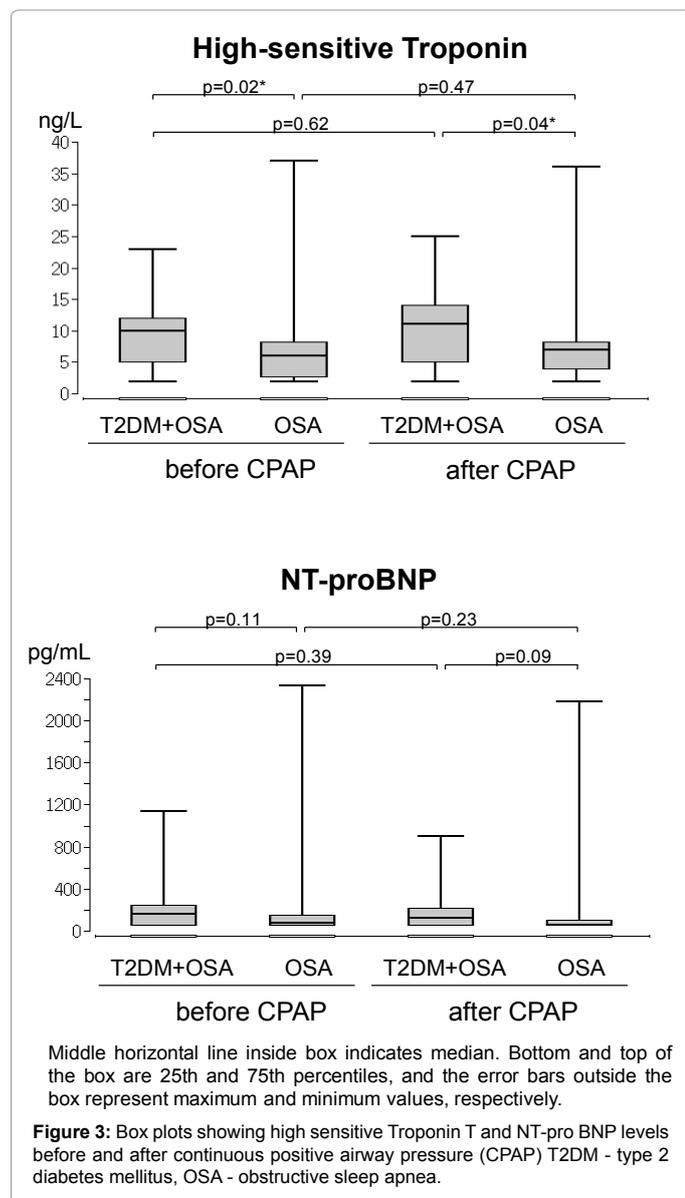
Table 1: Clinical Characteristics and Sleep Parameters.

ST-segment depression or elevation of hs-cTnT and NT-proBNP respectively. CPAP had no influence on hs-cTnT and NT-proBNP levels.

It is well known that OSA is associated with adverse effects on cardiac structure and function. There is a linear relationship between the severity of OSA and patient morbidity and mortality [14]. Cardiac damage in OSA may be caused by activation of the sympathetic nervous system due to hypoxia and changes in negative intrathoracic pressure and increased oxidative stress [15].

We found no abnormal ST-segment depression defined as >100 µV according to standard criteria in both groups and no significant difference of ST-segment depression between the two groups measured 10 cardiac cycles after the maximum oxygen desaturation. The mechanism of ST-segment depression during sleep in patients with OSA is not fully understood. Inspiration against occluded upper airways causing periodic negative changes in intrathoracic pressure and alterations in cardiac preload and afterload may result in myocardial ischemia in even the absence of hypoxemia. OSA is often accompanied by hypoxemia and thereby enhances the risk of myocardial ischemia. A previous study by Mooe examined 226 patients with angina pectoris and sleep-disordered breathing [16]. They found a temporal relationship between ST-segment depression and oxygen desaturations only in a minority of 12% of these symptomatic patients. Other studies

ST segment depression

Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles, and the error bars outside the box represent maximum and minimum values, respectively.

Figure 1: ST-segment depression at the time of the deepest oxygen desaturation CAD - coronary artery disease; OSA - obstructive sleep apnea.

High-sensitive Troponin

NT-proBNP

Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles, and the error bars outside the box represent maximum and minimum values, respectively.

Figure 2: Box plots showing high sensitive Troponin T and NT-pro BNP levels before and after polysomnography (PSG) T2DM - type 2 diabetes mellitus, OSA - obstructive sleep apnea.

High-sensitive Troponin

NT-proBNP

Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles, and the error bars outside the box represent maximum and minimum values, respectively.

Figure 3: Box plots showing high sensitive Troponin T and NT-pro BNP levels before and after continuous positive airway pressure (CPAP) T2DM - type 2 diabetes mellitus, OSA - obstructive sleep apnea.

have noted ST-segment depression in about one third of patients with OSA and coexisting coronary artery disease mainly during apneas and reduced oxygen saturation [17,18]. Nocturnal ischemia predominantly occurred during the rebreathing phase of the obstructive apneas. In a study with 23 patients, Hanley found asymptomatic ST depression during sleep in 30% of patients with OSA who did not have a history of coronary artery disease [19]. Interestingly, in this study the duration of sleep, distribution of sleep stages and mean oxygen saturation were not significantly different when ST depression was present or absent.

To our knowledge no other study examined the effect of OSA on hs-cTnT and NT-proBNP levels in T2DM patients. In the current study, we found no evidence of myocardial ischemia with myocyte necrosis in patients with T2DM and coexisting severe OSA based on a significant increase of hs-cTnT and NT-proBNP levels despite nocturnal hypoxia. Similar to our findings Gami reported no myocardial injury detectable by troponin T assay in a patient group with coronary artery disease and concomitant OSA [20]. In this study the AHI was comparable to our study but the mean nocturnal oxygen saturation nadir was less

distinct (83 ± 6%). In a study including 505 subjects drawn from the general population the proportion of subjects with detectable hs-cTnT increased with increasing severity of OSA. But after adjustment for significant univariate predictors of detectable hs-cTnT, the association between AHI and hs-cTnT was no longer statistically significant [21]. In contrast, Roca found higher hs-cTnT levels independently correlated with OSA severity in middle-aged and older individuals free of coronary heart disease and heart failure [22].

However, hs-cTnT levels were significantly higher before and after sleep in patients who suffered from T2DM and OSA in comparison to patients with OSA alone. Other studies also reported higher troponin levels in diabetic patients but no known coronary artery disease or heart failure. Baseline levels of glycated hemoglobin (HbA1c) were linearly associated with results of hs-cTnT tests [23]. Compared with normoglycemic persons, the adjusted relative risk for incident elevated hs-cTnT is higher in diabetic patients and is associated with a higher risk for future adverse cardiovascular outcome [24-26].

We found no difference in NT-proBNP levels between both groups and no significant change after nocturnal hypoxia. CPAP treatment had no effect on hs-cTnT and NT-proBNP levels in patients without heart failure in both groups despite significant reduction in AHI. In a study by Ljunggren a dose-response relationship between the severity of sleep apnea during the night and the levels of BNP in the morning was seen [27] while other studies found no correlation between OSA severity and NT-proBNP concentration [22,28-30].

The present study did have some limitations that deserve comment. First the number of patients is small due to a high drop out of patients because of insufficient desaturation (≤ 80%) at polysomnography. Second it is possible that the chosen time point for analysis of ST-segment depression after maximum oxygen desaturation might not represent the time of most severe myocardial ischemia, since other studies suggest that the main cause of ischemia is not an inadequate oxygen supply, but an increase in oxygen demand due to tachycardia and sympathetic activation following the rebreathing phase after an apnea event [18]. We also did not take into account the duration of hypoxemia. Third a single night of CPAP treatment might be too short to have a measureable impact on hs-cTnT and NT-proBNP concentrations in spite of the short half-life of the markers.

Conclusion

Our study showed that in patients suffering from T2DM and concomitant severe OSA, repeated oxygen desaturation ≤80% did not result in myocardial necrosis based on elevation of hs-cTnT and NT-proBNP serum concentrations after sleep. At the time of maximum oxygen desaturation during sleep we found no significant ST-segment depression. Patients with T2DM and concomitant OSA had higher hs-cTnT serum levels than patients with OSA alone, but hs-cTnT concentrations were neither influenced by severe nocturnal hypoxia nor by CPAP. The mechanism of cardiovascular injury in these patients seems to be independent of direct ischemia-induced myocardial necrosis due to nocturnal oxygen desaturation.

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