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Original Research Article

Systemic prostacyclin and thromboxane production in obstructive sleep apnea

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ABSTRACT

Purpose: Obstructive sleep apnea increases the risk of cardiovascular diseases. Alternations in prostacyclin and thromboxane concentrations and balance could constitute one of mechanisms linking sleep apnea and cardiovascular events. Thus we aimed to assess the concentrations of 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) (metabolite of prostacyclin) and thromboxane B_2 (TXB_2) (metabolite of thromboxane A_2) in urine and blood of obstructive sleep apnea patients and controls (snoring subjects with otherwise normal polysomnogram).

Material and methods: Overnight urine and morning blood samples were taken from subjects and controls at baseline and in sleep apnea group during continuous positive airway pressure (CPAP) treatment. Samples were analyzed using mass chromatography/gas spectrometry.

Results: We analyzed data from 26 obstructive sleep apnea subjects (mean apnea–hypopnea index 45.4 ± 17.3) and 22 well-matched controls. At baseline sleep apnea patients, when compared to controls, have higher 6-keto-$PGF_{1\alpha}$ in urine (0.89 ± 0.15 vs 0.34 ± 0.06, $p = 0.01$) and blood (24.49 ± 1.54 vs 19.70 ± 1.77, $p = 0.04$). TXB_2 levels in urine and blood were not different across groups. CPAP treatment significantly decreased 6-keto-$PGF_{1\alpha}$ in urine (0.92 ± 0.17 vs 0.22 ± 0.10, $p = 0.04$), but not in blood. TXB_2 levels during CPAP treatment did not change significantly.

Conclusions: These results suggest augmented systemic prostacyclin production in obstructive sleep apnea patients, which potentially could constitute a protective mechanism against detrimental effects of sleep apnea.

1. Introduction

Obstructive sleep apnea (OSA) increases the risk of several cardiovascular diseases [1,2]. Multiple studies have confirmed relationship between OSA and systemic hypertension [3,4]. OSA increases the risk of ischemic stroke, myocardial infarction and cardiac arrhythmias [5]. Less often recognized clinically, yet important is association between OSA and pulmonary hypertension [6]. Proposed mechanisms linking sleep apnea and cardiovascular disorders include hypoxemia during apnea/hypopnea episodes, activation of sympathetic mechanisms and sleep fragmentation [5,7]. Recently, the role of systemic inflammation [8] and metabolic changes [9] has received growing attention. Systemic inflammation and oxidative stress could possibly act through impaired endothelial function [10–12]. Alternations in prostacyclin (PGI_2) and thromboxane (TXA_2) concentrations/balance could be one of the mechanisms linking OSA, impaired endothelial function and increased risk of cardiovascular diseases. Prostacyclin (prostaglandin I2 – PGI_2) its best known as a potent vasodilator and an inhibitor of platelet aggregation, but it also holds some pro-inflammatory properties. Its physiological influences opposites those of thromboxane A2, which has vasoconstrictor and thrombogenic properties [13]. Few studies tried to address this issues, but included small number of subjects, differed in inclusion criteria and their results were contradictory [14,15]. Thus in this study we aimed to assess the concentrations of stable metabolites of prostacyclin and thromboxane A_2 in urine and blood of severe OSA patients and snoring controls, before and during continuous positive airway pressure (CPAP) treatment.

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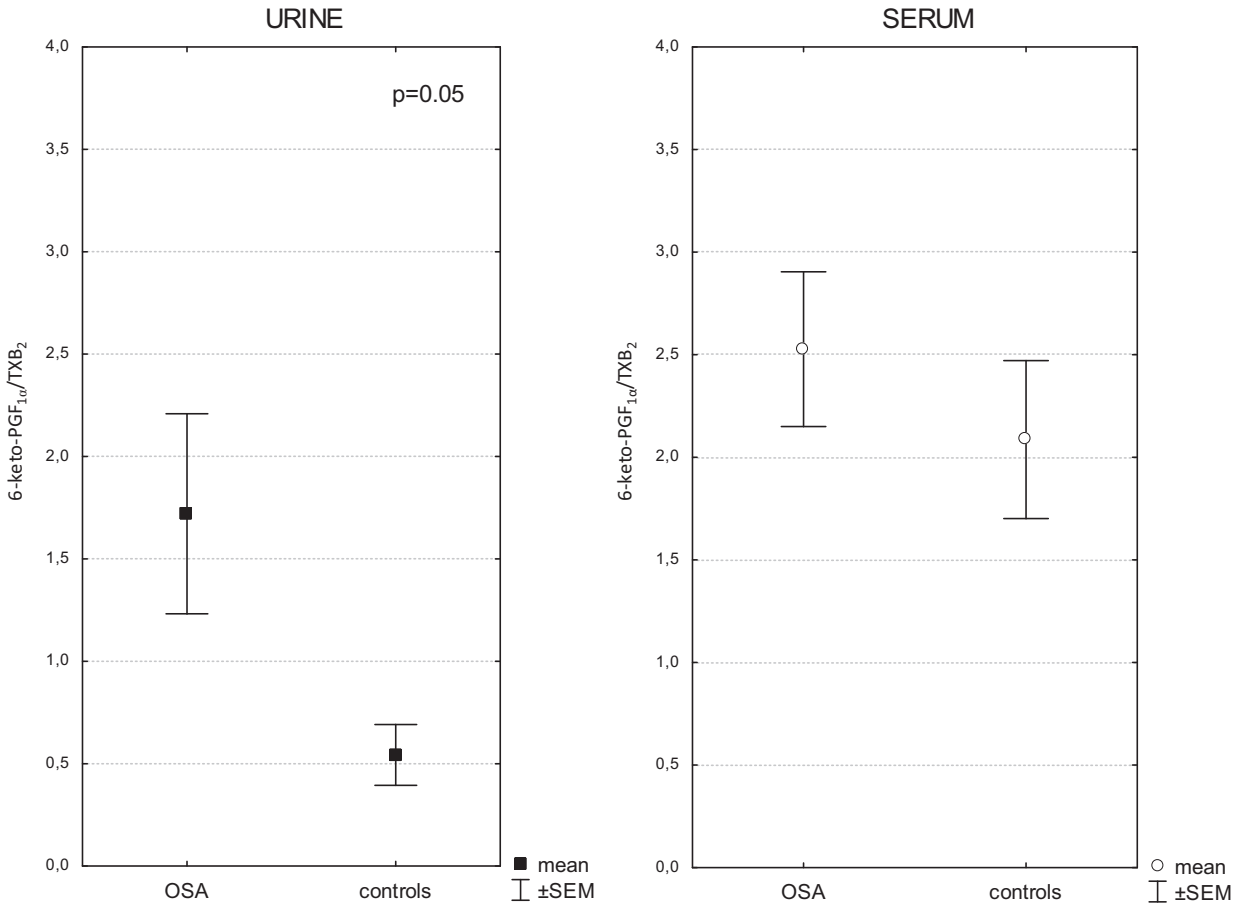

Fig. 1. 6-Keto-$PGF_{1\alpha}/TXB_2$ ratio in OSA and controls.

2. Material and methods

2.1. Screening

Subjects sent to our Sleep Clinic were screened on an outpatient basis. Those thought to have sleep disordered breathing were assessed with full-night polysomnography (Somnolab, Weinmann, Germany) or polygraphy (PolyMESAM, MapMed, Germany). All consecutive patients diagnosed with severe obstructive sleep apnea and fulfilling entry criteria specified below as well as healthy snoring subjects were offered to enter the study. Those willing to participate after giving written informed consent were scheduled for the first study visit.

2.2. Subjects

Inclusion criteria were: male or female aged 30–70 years, body mass index (BMI) at least 25 kg/m^2, severe OSA defined as apnea/hypopnea index (AHI) $\geq 30\ h^{-1}$ of sleep.

Multiple exclusion criteria were applied: cardiovascular diseases other than hypertension, diabetes mellitus, dyslipidemia (based on lipid profile or prior medical diagnosis), renal disease/failure, abnormal liver tests or known liver disease, asthma, chronic obstructive pulmonary disease or any other lung disease, allergic rhinitis, any other significant co-morbidities, current smoking ($\geq$1 cigarette smoked in 2 weeks prior to inclusion), medication other than anti-hypertensives (β-blocking agents, calcium channel blockers, ACE inhibitors and diuretics in hypertensive subjects were allowed).

Those qualified to CPAP treatment had to demonstrate compliance with CPAP (defined as at least 240 min of sleep time with CPAP) and the effectiveness of treatment (defined as reduction in AHI > 70% and AHI < 10 h^{-1} of sleep).

2.3. Protocol

Subjects were admitted to hospital in the morning before the sleep study. They were asked to abstain from sleep during that day and from consuming caffeine containing beverages after 1 p.m. At the first study visit during the night (10 p.m. till 6 a.m.) polysomnography was performed. From 10 p.m. till the first miction in the morning patient's urine was collected as an overnight sample. Subjects were woken at 6 a.m., and then samples of blood were taken. OSA subjects were scheduled for the 2nd study visit and all the procedures were repeated as described above, but during the night with auto-titrating CPAP device. Samples of blood and urine were deep-frozen (−80 °C) for further analyses. Later on the samples were defrosted and analyzed with gas chromatography/mass spectrometry (Engine 5989b, Hewlett-Packard, USA). We were measuring 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) – stable metabolite of prostacyclin and thromboxane B_2 (TXB_2) – stable metabolite of thromboxane A_2. The values measured in urine samples were expressed as ng/mg of creatinine and those in blood samples as pg/ml.

2.4. Sleep study and CPAP treatment

Polysomnography was performed with SomnoLab polysomnograph (Weinmann, Germany). Recorded signals included 2 channel electroencephalogram, 2 channel electrooculogram, 1 channel electromyogram, nasal and oral airflow (thermal probe) or pressure in CPAP mask during CPAP treatment night, hemoglobin