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SHORT COMMUNICATION

Effect of CPAP treatment on plasma high sensitivity troponin levels in patients with obstructive sleep apnea☆

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Summary
Background: Obstructive sleep apnea (OSA) is associated with an increased prevalence of cardiovascular diseases. New generations of highly sensitive assays for cardiac troponin (hs-cTnT) have been introduced recently, and a number of clinical observations have challenged the notion that troponins are only increased in blood following irreversible necrosis.
Objective: The aims of this study were to compare the levels of hs-cTnT between a group of healthy controls and a group of patients with OSA without co-existent coronary artery disease, and to assess the possible influence of the treatment with Continuous positive airway pressure (CPAP) on these levels.
Methods: The study population included 200 male participants. The case ($n = 133$) or control ($n = 67$) status was defined by an apnea–hypopnea index of 10 or greater. The hs-cTnT assay was validated as reported previously, with a limit of detection of 3 ng/L and an upper reference limit (99th percentile) of 14 ng/L.
Results: The proportion of subjects with detectable plasma hs-cTnT was higher in patients with OSA than in controls (61 vs 75%, $p = 0.04$). In patients, a significant increase in hs-cTnT levels was observed after an effective treatment with CPAP (7.3 ± 3.4 vs 10.1 ± 4.9 ng/L; $p < 0.01$).

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Conclusion: This study shows that the percentage of subjects with detectable hs-cTnT is associated with the presence of OSA. It also evidences that treatment with CPAP is followed by a rise in hs-cTnT concentrations. It is reasonable to suggest that CPAP therapy might induce a potential degree of cardiac stress, resulting in deleterious consequences for the heart.

Obstructive sleep apnea (OSA) is associated with an increased prevalence of cardiovascular diseases [1]. Continuous positive airway pressure (CPAP) treatment reduces cardiovascular risk in OSA and recent evidence suggests that early signs of atherosclerosis as well as endothelial dysfunction and cardiac remodeling are partially reversed after treatment with CPAP [2–4].

Cardiac troponins (cTnI and cTnT) are components of the myofibrillar contractile apparatus of cardiomyocytes and are considered the most sensitive and specific biochemical markers of myocardial damage [5]. Traditionally, it was thought that any release of detectable concentrations of cardiac troponins (cTn) was equivalent to irreversible myocardial injury. However, new generations of highly sensitive for cTn (hs-cTn) have been introduced recently and there have been a number of clinical observations that have challenged the notion that troponins are only increased in blood following irreversible necrosis [6,7].

A recent approach demonstrates that hs-cTnT levels increase in proportion to OSA severity, but in a multivariate model, OSA was not an independent predictor of hs-cTnT, suggesting that a clustering of cardiovascular risk factors explains this association [8]. However, the clinical significance and mechanism of the increase in hs-cTnT in patients with OSA remain unclear. It is unknown whether treatment of OSA with CPAP would modify the release of cardiac troponins.

The aim of this study was to assess the possible influence of the treatment with CPAP on hs-cTnT in a group of patients with OSA without co-existent coronary artery disease.

The study population included 200 male participants recruited from subjects consecutively admitted to the sleep unit of our institution. The case ($n = 133$) or control ($n = 67$) status was defined by the apnea–hypopnea index (AHI) threshold of 10 or greater (case are subjects with an AHI ≥ 10 and controls those with an AHI < 10). Patients with cardiovascular disease (myocardial infarction, unstable angina, coronary bypass or coronary angioplasty, stroke or transient ischemic attack) were excluded. No participant suffered from any other chronic disease (diabetes, chronic obstructive pulmonary disease (COPD), liver cirrhosis, thyroid dysfunction, chronic renal failure and/or psychiatric disorders). Participants were recruited from subjects who attended our sleep unit. We initially excluded participants (controls or patients) who were taking hypoglycemic, antihypertensive, hypolipemiant and/or anti-inflammatory agents.

Patients were studied at diagnosis and after effective treatment with CPAP (REM Star, Respironics®, Murrysville, PA, USA) during 12 months. Patients with detectable hs-cTnT levels and who used the device for a minimum of 4 h/night were included in the follow-up analysis ($n = 95$).

The study was approved by the Ethics Committee of our institution, and all participants signed their consent after being fully informed of its goal and characteristics.

The diagnosis of OSA was established by full polysomnography (E-Series Compumedics, Abbotsford, Australia) that included recording of oronasal flow, thoracoabdominal movements, electrocardiography, submental and pretibial electromyography, electrooculography, electroencefalography and trancutaneous measurement of arterial oxygen saturation. Apnea was defined by the absence of airflow for more than 10 s. Hypopnea was defined as any airflow reduction that last more than 10 s and resulted in arousal or oxygen desaturation. We considered desaturation a decrease in SaO_2 greater than 3%. The apnea–hypopnea index (AHI) was defined as the sum of the number of apneas plus hypopneas per hour of sleep. Excessive daytime sleepiness (EDS) was quantified subjectively by the Epworth sleepiness scale (ESS).

After fasting overnight, venous blood samples were obtained between 8 and 10 am. Blood was centrifuged and serum was immediately separated in aliquots and stored at −80 °C until analysis. Glucose, triglycerides, total cholesterol, HDL cholesterol (HDLc), and creatinine were determined by standard methods on a Hitachi Modular analyzer (Roche Diagnostics, Indianapolis, USA). The plasma levels of hs-cTnT were measured on the Cobas e 411 using the highly sensitive fifth generation cTnT assay (Roche Diagnostics). The hs-cTnT was validated as reported previously with the upper reference limit (99th percentile) at 14 ng/L, limit of detection at 3 ng/L and 10% coefficient of variation cut-off at 13 ng/L [9].

Results are presented as percentages, median or mean ± standard deviations. Parametric (Student *t* test) and non-parametric test (Wilcoxon test) were performed to assess the statistical significance of differences between groups. The effects of CPAP therapy were analyzed using paired *t*-tests.

Correlations between variables were explored using the Spearman-rank test. Separate multiple regression analyses were used to identify the independent variables associated with hs-cTnT. A p value lower than 0.05 was considered significant.

Characteristics of the study population are summarized in Table 1.

BMI, waist circumference, systolic (SBP) and diastolic (DBP) pressure were significantly higher in patients with OSA than in subjects without OSA. Compared to control subjects, OSA patients showed abnormal plasma levels of glucose and triglycerides.

The proportion of subjects with detectable hs-cTnT was higher in patients with OSA than in controls (61 vs 75%, $p = 0.04$). Nevertheless, the levels of hs-cTnT in patients with detectable hs-cTnT levels were not higher than in

Table 1 Baseline characteristics and sleep profiles in controls and OSA patients.

	Controls ($n = 67$)	OSA ($n = 133$)
Age (years)	48 ± 11	51 ± 9
BMI (kg m^{-2})	26 ± 4	31 ± 6*
Waist circumference (cm)	96 ± 13	110 ± 13*
AHI (h^{-1})	5 ± 2	56 ± 25*
Arousal index (h^{-1})	22 ± 4	59 ± 23*
Mean sat O_2 (%)	97 ± 2	94 ± 3*
Minimal sat O_2 (%)	90 ± 3	82 ± 3*
Epworth scale	8 ± 2	9 ± 3
SBP (mm Hg)	123 ± 16	134 ± 15*
DBP (mm Hg)	75 ± 10	83 ± 12*
Glucose (mg/dL)	98 ± 17	108 ± 20*
Triglycerides (mg/dL)	119 ± 46	167 ± 74*
Cholesterol (mg/dL)	194 ± 44	207 ± 37
HDLc (mg/dL)	51 ± 12	49 ± 7
Creatinine (mg/dL)	0.89 ± 0.2	0.96 ± 0.3

*$p < 0.05$.

controls with detectable hs-cTnT levels (7.3 ± 3.4 vs 6.9 ± 2.3 ng/L, $p = 0.163$).

The baseline characteristics of OSA patients with detectable hs-cTnT levels (75%, $n = 100$), were not different than those with no detectable hs-cTnT (25%, $n = 33$).

hs-cTnT were significantly related to apnea–hypopnea index ($r = 0.165$, $p = 0.0132$), age ($r = 0.411$, $p < 0.001$), SBP ($r = 0.290$, $p < 0.001$), DBP ($r = 0.197$, $p = 0.008$), BMI ($r = 0.188$, $p = 0.010$) and waist circumference ($r = 0.330$, $p < 0.001$). Multivariate analysis showed that the independent variables associated with hs-cTnT were age ($p = 0.018$) and BMI ($p = 0.038$). A statistically significant elevation was observed in the levels of hs-cTnT in patients after CPAP treatment (10.1 ± 4.9 vs 7.3 ± 3.4 ng/L, $p < 0001$) (Fig. 1). They also manifested a significant increase in HDLc cholesterol compared to baseline despite similar BMI. There were no significant changes in waist circumference, SBP, DBP, glucose and triglyceride levels.

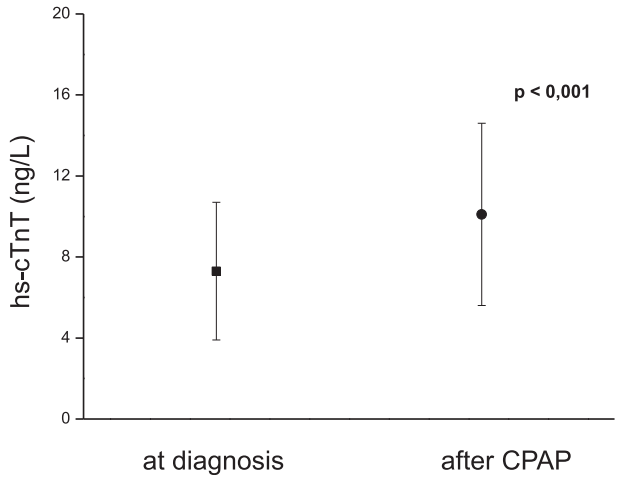

Figure 1 Mean values of hs-cTnT at diagnosis and after treatment with CPAP.

This study shows that the percentage of subjects with detectable cTnT is associated with the presence of OSA. It also evidences that treatment with CPAP is followed by a rise in the concentrations of hs-cTnT.

The mechanisms that support a relationship between OSA and increased hs-cTnT levels are not known. Recent findings may explain why plasma troponin concentrations are detected in patients with OSA in absence of myocardial necrosis. Mechanical stretch of cardiomyocytes due to increased sympathetic activity and intrathoracic pressure changes during respiratory events may lead to release of intact troponins [10,11]. A different approach provides evidence for a positive relationship between OSA and hs-cTnT, but the authors conclude that this association is likely to be caused by a clustering of cardiovascular risk factors among patients with OSA [8].

In the current study, the relationship between OSA and hs-cTnT was also attenuated after controlling for age, BMI, waist circumference and mean arterial pressure suggesting that the concentration of hs-cTnT may vary in OSA according to the degree of obesity and metabolic disturbances. Therefore, it is possible that the consequences of sleep apnea on the release of hs-cTn become apparent in the presence of co-morbidities such as obesity, hypertension or metabolic syndrome.

A significant elevation was observed in the levels of hs-cTnT after CPAP therapy. We observed that this increase was not dependent on obesity unlike the independent relationship detected between basal BMI and hs-cTnT. The underlying mechanisms responsible for CPAP induced troponin release are unclear.

On the one hand, it is reasonable to suggest that CPAP therapy has a potential degree of cardiac stress that results in deleterious consequences for the heart, thus inducing the release of troponin. By contrast, some recent studies have demonstrated a progressive improvement in cardiovascular remodeling in patients with OSA receiving CPAP therapy [3,4].

On the other hand, there is increasing evidence of a slow continuous turnover of cardiomyocytes and minor elevations of troponin could be a consequence of a cardiac adaptation to CPAP [12]. Although a direct effect of CPAP therapy on release of hs-cTnT is questionable, we speculate that this release could represent a reversible change in membrane permeability of the cardiomyocyte and reflect part of a regulatory process of repair leading to enhanced structure and function. An adaptive response to CPAP, including fiber regeneration and connective tissue changes might protect against further cardiac injury. In any case, quantitative measures of myocardial function and perfusion would be helpful in elucidating the cellular and physiologic bases.

Several limitations should be considered. First, despite patients with diagnosed cardiovascular disease were excluded, objective measures of myocardial function, including echocardiographic assessments are necessary to define standard levels of hs-TnT. Second, hs-cTnT changes observed in this study might have other potential causes that are not investigated. It is possible that other physical and environmental factors have either adverse or favorable effects on the release of troponin. Third, the lack of randomization and the absence of data about those

patients with undetectable hs-TnT levels before CPAP starting limited our study. Follow up of patients under CPAP including serial measurements of hs-cTnT is necessary to determine the mechanisms responsible for the release of troponin in patients with OSA and their clinical significance.

Author contributorship

AB accepts final responsibility for the integrity of the work as a whole, and had full access to all data in the study and takes responsibility for the accuracy of data analysis. AAF, MDLP, JP and MA collected patient information; AB, MDLP, CE and FB developed the initial plan of analysis and statistics; finally all authors including JMB and MST discussed data results, proposed new analyses, helped drafting the first manuscript, and finally approved this submission.

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