Journal of Sleep Disorders & Therapy
ISSN: 2167-0277

Demir et al., J Sleep Disorders Ther 2013, 2:1
DOI: 10.4172/2167-0277.1000105

Research Article Open Access

The Association of Troponin I Levels with Severity of Obstructive Sleep Apnea Syndrome

Nalan Demir[1],Oğuz Köktürk[2], Tansu Ulukavak Ciftçi[2], Ozlem Gülbahar[3], Neslihan Celik Bukan[3] and Kenan Köse[4]

[1]*Department of Chest Diseases, School of Medicine, Ankara University, Ankara, Turkey*
[2]*Department of Chest Diseases, School of Medicine, Gazi University, Sleep Medicine Unit, Ankara, Turkey*
[3]*Department of Biochemistry, School of Medicine, Gazi University, Ankara, Turkey*
[4]*Department of Statistics, School of Medicine, Ankara University, Ankara, Turkey*

Abstract

Background: As a result of repeated nocturnal hypoxemia, pulmonary arterial vasoconstriction, acute right ventricular dilatation and hypokinesia and myocardial injury may occur in patients with Obstructive Sleep Apnea Syndrome (OSAS). As it is known, Cardiac Troponin I (cTnI) is an important marker of myocardial injury.

Objectives: The aim of this study is to investigate the degree of myocardial injury which is created with nocturnal hypoxemia by measuring cTnI levels in patients with OSAS and to evaluate the association between cTnI levels and severity of OSAS.

Methods: Seventy-six subjects who had OSAS symptoms were examined with standard polysomnography (PSG) and classified according to their Apnea-Hypopnea Index (AHI). Forty-seven patients with AHI ≥ 5 were considered as OSAS and 29 subjects with AHI<5 were included into control group. OSAS patients were divided into three groups according to their AHI values as mild (AHI=5-15) (n:13), moderate (AHI=15-30) (n:14) and severe (AHI>30) OSAS (n:20). Serum cTnI levels were measured twice in all subjects after the PSG.

Results: When the levels of cTnI were compared, there was no significant difference between patients and controls (OSAS=3.6 ± 2.7 ng/ml and controls=3.1 ± 1.8 ng/ml, p=0.3). Also no significant difference was detected between mild-moderate OSAS (2.93 ± 1.67 ng/ml), severe OSAS (4.57 ± 3.47 ng/ml) and controls comparing with their cTnI levels (p=0.053). But cTnI levels in severe OSAS patients were significantly higher than controls (p=0.01). According to the logarithmic transformation, log-cTnI was 0.49 ± 0.21 ng/ml and 0.47 ± 0.21 ng/ml in OSAS subjects and controls, respectively (p=0.74). Severe OSAS patients had higher log-cTnI levels (0.59 ± 0.22 ng/ml) than mild-moderate OSAS subjects and controls (p=0.018, f=4.26). There was a positive correlation between AHI and cTnI levels in patients with OSAS (r=0.276, p=0.019, R^2=0.076).

Conclusion: Cardiac troponin I measurements may be useful to show the degree of myocardial injury in severe OSAS.

Keywords: Cardiac troponin I; Obstructive sleep apnea syndrome; Polysomnography; Apnea-hypopnea index; Myocardial injury

Introduction

Obstructive sleep apnea syndrome (OSAS), characterized by repeated upper airway obstruction episodes and nocturnal desaturation is a common disorder that occurs at least 2% to 4% of the adult population. The severity of OSAS is described according to the apnea-hypopnea index (AHI) [1].

The relationship of OSAS with cardiovascular diseases including hypertension, congestive heart failure, arrhythmias, and Coronary Artery Disease (CAD) is well known [2,3]. The acute hemodynamic changes of OSAS include systemic and pulmonary hypertension, increased right and left ventricle after load, and increased cardiac output [4]. Recent studies have shown that at the end of the repeated nocturnal hypoxemia, pulmonary arterial vasoconstriction may be observed in OSAS. In addition, Right Ventricle (RV) dilatation and hypokinesia due to repetitive hypoxemia may lead to myocardial injury and ischemia without CAD [5-8].

Cardiac troponins are high sensitive biochemical markers of acute myocardial infarction [9]. Serum troponins are also increased in a number of clinical settings such as acute and chronic heart failure, cardioversion, ablation, cardiac arrest, sepsis/septic shock and SIRS, end stage renal failure, acute pulmonary embolism, cardiac trauma and acute stroke in addition to acute coronary syndrome [10-16]. Recently, cardiac troponin testing is increasingly used in non-coronary diseases to indicate cardiac injury [17,18]. Cardiac troponin I (cTnI) levels may also be elevated in patients with OSAS who occurred myocardial injury due to repeated nocturnal hypoxemia [19].

The aim of this study is to evaluate the degree of myocardial injury in patients with OSAS and to determinate association between AHI values and cTnI levels.

Material and Methods

Study subjects

A total number of 76 patients admitted to Gazi University Sleep Medicine Unit were included in this study, prospectively. The study

***Corresponding author:** Nalan Demir, MD, Department of Pulmonary Medicine, School of Medicine, Ankara University 06100 Cebeci-Ankara, Turkey, Tel: 903125957077; Fax: 903123190046; E-mail: dr.ndemir@gmail.com

Received November 20, 2012; **Accepted** December 26, 2012; **Published** January 02, 2013

Citation: Demir N, Köktürk O, Ciftçi TU, Gülbahar O, Bukan NC, et al. (2013) The Association of Troponin I Levels with Severity of Obstructive Sleep Apnea Syndrome. J Sleep Disorders Ther 2: 105. doi:10.4172/2167-0277.1000105

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was approved by the local ethics review board. Inclusion criteria were as follows: being older than 18 years, having OSAS symptoms (snoring, witnessed apneas, excessive daytime sleepiness) on admission, to give informed consent for the study, performing full-night polysomnography. Exclusion criteria were accepted as: having acute coronary syndrome, renal and heart failure, sepsis, chronic obstructive pulmonary diseases, recent cardiac trauma or intervention.

Sleep study

Overnight Polysomnography (PSG) was performed in all patients by a computerized system (Somnostar alpha; Sensormedics, USA) and included the following variables: electrooculogram (2 channels), electroencephalogram (4 channels), electromyogram of submental muscles (2 channels), electromyogram of the anterior tibialis muscle of both legs (2 channels); electrocardiogram and airflow (with a nasal cannule). Chest and abdominal efforts (2 channels) were recorded using inductive plethysmography, arterial oxyhemoglobin saturation (SaO_2: 1 channel) by pulse oximetry with a finger probe. The recordings were conducted at a paper speed of 10 mm/s, and sleep stage were scored according to the standard criteria of Rechtschaffen and Kales [20]. Arousals were scored according to accepted definitions [21]. The AHI was obtained by dividing the total number of apneas and hypopneas by the Total Sleep Time (TST). Apneas were defined as complete cessation of airflow ≥ 10 s. Hypopneas were defined as reduction of >50% in one of three respiratory signals, airflow signal or either respiratory or abdominal signals of respiratory inductance plethysmography, with an associated fell of ≥ 3% in oxygen saturation or an arousal [22]. According to the recently updated International Classification of Sleep Disorders published by the American Academy of Sleep Medicine, a diagnosis of OSAS was made if the AHI is ≥ 15, independent of occurrence of symptoms, or whenever an AHI>5 is associated with any of the following: 1) sleep attacks excessive daytime sleepiness (EDS), 2) unrefreshing sleep, fatigue or insomnia, or 3) witnessed heavy snoring and/or breathing pauses referred by the partner [23]. Patients with sleep disorders, except OSAS, such as Upper Airway Resistance Syndrome (UARS), Periodic Legs Movements' Syndrome (PLMs) or narcolepsy were excluded.

Study design

Totally 76 patients who had performed PSG due to OSAS symptoms (snoring, witnessed apneas, excessive daytime sleepiness) without acute coronary syndrome were included to this study, prospectively. In 47 cases of all OSAS diagnoses were confirmed by PSG. The remaining 29 patients without OSAS were evaluated as control group (AHI<5). The cases with OSAS were also divided in 3 groups according to severity of disease: Mild OSAS (AHI: 5-15), moderate OSAS (AHI: 15-30) and severe OSAS (AHI>30).

For all patients, clinical data (symptoms, physical examination findings, body mass index, X-ray, electrocardiography, lung function tests, complete blood count, routine biochemical analysis and thyroid hormone levels) were obtained on admission. According to the body mass index, the patients classified as normal, overweight (BMI ≥ 25), obese (BMI ≥ 30), and morbid obese (BMI ≥ 40). After the sleep study, the findings of PSG, AHI values, and cTnI levels were recorded.

Laboratory analyses

In all patients, the venous blood samples were obtained after the PSG for cTnI measurements. Blood samples were centrifuged at 3000 rpm for 15 minutes and saved at -80°C. All samples were analyzed with cTnI ELISA test (solid phase enzyme-linked immunosorbent assay) (specificity: 87.5%, sensitivity: 100%, CI: 95%). The lower limit of cTnI ELISA=0.48 ng/ml; upper limit=1.0 ng/ml.

Statistical analysis

Data were analyzed by using SPSS for Windows release 10.0.1 (SPSS, Chicago, IL). Values were expressed as mean ± SD. The chi-square test was used to compare categorical variables. The *t*-test was used to compare the mean differences in independent samples. In addition, case summary reports and frequency charts were used to analyze the group variables. Kruskal wallis one way analysis was used for comparison of mild, moderate, severe OSAS subjects and controls. The comparison of groups was performed by ANOVA test. Pearson correlation was used to evaluate an association between AHI and cTnI values. All p values were two-tailed and a p value<0.05 was considered statistically significant.

Results

In the analysis of all cases (n: 76, female/male: 28/48), the mean age was 50.2 ± 10.9 (27-76) years. Mean body mass index (BMI) was 30.5 ± 6.1 kg/m^2. According to the BMI, 14 (18.4%) cases were normal. Thirty (39.5%) of them was overweight. Obesity and morbid obesity were seen in 23 (30.3%) and 9 (11.8%) of all cases. Thirty-three patients (43.4%) were active smoker on admission. Existing co-morbidities were hypercholosterolemia (n:29, 38.2%), hypertension (n:17, 22.4%), diabetes mellitus (n:10, 13.2%), artymia (n:5, 6.6%), coronary artery disease (n:5, 6.6%), and chronic heart failure (n: 2, 2.6%).

OSAS was detected in 47 (61.8%) (M/F:27/20) of all cases, and these cases were subdivided to the three groups as mild (n:13), moderate (n:14) and severe OSAS (n:20), according to the their AHI values. The remaining 29 (38.2%) patients of all who had normal PSG were accepted as controls (Figure 1).

When demographic data of subjects and controls were analyzed; sex, mean body mass index (BMI-kg/m^2), smoking history, existing co-morbidities, first SaO_2 levels and electrocardiographic changes (left and right bundle block, arytmia) on PSG were similar between subjects and controls (p>0.05). Nonetheless, OSAS subjects were older than controls (p=0.01), and obesity was more frequent in cases with OSAS (p=0.03). At the sleep study, mean AHI values and minimum SaO_2 were different for each group as expected (p=0.00). First SaO_2, mean was 94.9 ± 1.5

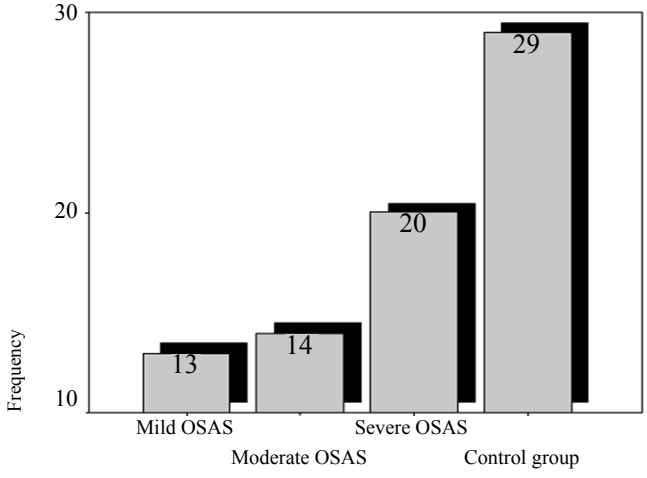

Figure 1: The frequency of OSAS subjects and controls that had normal polysomnography.

and 94.8 ± 5.4 in subjects and controls, respectively (p=0.8 and 0.0). Whereas mean AHI values in cases with OSAS were 38.5 ± 36.7, it was 2.1 ± 1.3 in controls. The levels of cTnI were similar in both groups (OSAS=3.6 ± 2.7 ng/ml and controls=3.1 ± 1.8 ng/ml, p=0.3) (Table 1).

At the comparison of mild-moderate and severe OSAS and controls, females were predominant in controls than mild-moderate and severe OSAS (p=0.04). In OSAS subjects min SaO_2 levels were gradually decreased according to the severity of OSAS during the PSG (p=0.00). When cTnI levels were compared between mild-moderate OSAS (2.93 ± 1.67 ng/ml), severe OSAS (4.57 ± 3.47 ng/ml) and controls (3.13 ± 1.83 ng/ml), there was no significant difference (p=0.053). But levels of cTnI in patients with severe OSAS were significantly higher than controls (p=0.01) (Table 2).

In present study, logaritmic transformation was used for normalization of cTnI levels. According to this analysis, log-cTnI was 0.49 ± 0.21 ng/ml and 0.47 ± 0.21 ng/ml in OSAS subjects and controls, respectively (p=0.74) (Table 3). When mild and moderate OSAS were compared with severe OSAS and controls, the patients with severe OSAS had higher log-cTnI levels (0.59 ± 0.22 ng/ml) than mild-moderate OSAS subjects and controls (p=0.018, f=4.26, Kruskal wallis one way analysis) (Table 4).

At the analysis of demographic features according to the log-cTnI; smoker patients had higher log-cTnI levels (0.52 ± 0.25 ng/ml) than non-smokers (0.44 ± 0.16 ng/ml), statistically (p=0.01) (Table 5), there was no relation between smoking and AHI values (p=0.8). Age, BMI, and min SaO_2 during the sleep study were no associated with log-cTnI as given in table 6 (p>0.05, Pearson correlation). When the presence of comorbidity was compared with AHI and cTnI values, there was no statistically significance (p>0.05).

There was a positive correlation between AHI and cTnI levels in patients with OSAS (r=0.276, p=0.019, R^2=0.076, Pearson correlation) (Table 7; Figure 2).

Discussion

This study showed that cardiac troponin I is a detectable marker in OSAS patients and high levels of cTnI might be observed in severe OSAS.

Obstructive sleep apnea syndrome is an important risk factor for cardiovascular diseases [2,3,24-28]. In literature, angina-like symptoms and ischemic changes on electrocardiogram have been detected in patients without CAD previously [1,5,29]. Whether nocturnal ischemic events in patients with OSAS has not been clear adequately, previous studies have suggested that OSAS is associated with myocardial injury without CAD due to possible mechanisms such as repeated hypoxemia and related sympathetic activation [24,30]. Acute hemodynamic changes involving the pulmonary artery and RV during apneic episodes are well

	OSAS subjects	Controls	p
Sex (F/M)	20/27	8/21	0.2
Mean age (year)	52.5 ± 10.5	46.3 ± 10.6	0.01
Body mass index (BMI-kg/m²), mean	31.3 ± 6.4	29.1 ± 5.5	0.1
According to BMI Normal Overweight Obesity Morbid obesity	 9 13 19 6	 5 17 4 3	 0.03
Smoking history	19	14	0.6
Co-morbidities Hypercholosterolemia Hypertension Diabetes mellitus Arytmia Coronary artery disease Chronic heart failure	 18 12 7 4 4 1	 11 5 3 1 1 1	 1.0 0.5 0.7 0.6 0.6 1.0
Polisomnography AHI, mean First SaO_2, mean Min SaO_2, mean ECG changes	 38.5 ± 36.7 94.9 ± 1.5 74.9 ± 12.2 15	 2.1 ± 1.3 94.8 ± 5.4 85.8 ± 6.0 8	 0.0 0.8 0.0 0.7
cTnI, mean	3.6 ± 2.7	3.1 ± 1.8	0.3

Table 1: The comparison of OSAS subjects and controls according to the clinical characteristics, polysomnographic findings and mean troponin (cTnI) values.

	Controls	Mild+Moderate OSAS	Severe OSAS	F	p
Age, mean	46.25 ± 10.62	50.30 ± 9.53	55.55 ± 11.15	4.67	**0.012**
Sex **Female** **Male**	 21 8	 8 19	 12 8		**0.04**
Smoking history **Smokers** **Non-smokers**	 14 15	 12 15	 7 13		0.64
BMI, mean	29.06 ± 5.48	29.95 ± 6.19	33.19 ± 6.29	2.98	0.057
ECG changes **+** **-**	 8 21	 7 20	 8 12		0.53
Min SaO_2 on PSG	85.85 ± 6.04	79.37 ± 9.22	68.90 ± 13.32	18.39	0.00
$cTnI_{mean}$ (ng/ml)	3.13 ± 1.83	2.93 ± 1.67	4.57 ± 3.47	3.06	0.053

Table 2: The clinical and laboratory findings in patients with mild-moderate and severe OSAS, and controls (ANOVA test).

	Log-cTnI, mean ± SD	p
OSAS subjects	0.49 ± 0.21	0.74
Controls	0.44 ± 0.19	
Total	0.47 ± 0.21	

Table 3: The comparison of OSAS subjects and controls according to the log-cTnI levels.

	Log-cTnI, mean ± SD	F	p
Mild+Moderate OSAS	0.44 ± 0.19	4.26	0.018
Severe OSAS	**0.59 ± 0.22**		
Controls	0.44 ± 0.19		
Total	0.47 ± 0.21		

Table 4: The evaluation of the OSAS subjects and controls according to the log-cTnI levels.

	Log-cTnI	p
Female **Male**	0.42 ± 0.16 0.50 ± 0.22	0.18
Smokers **Non-smokers**	0.52 ± 0.25 0.44 ± 0.16	0.01
Hypertension **+** **-**	 0.53 ± 0.24 0.46 ± 0.20	0.91
ECG changes **+** **-**	 0.47 ± 0.17 0.47 ± 0.22	0.92

Table 5: The demographic features according to the Log-cTnI levels in all subjects.

	r	p
Age and Log-cTnI	-0.033	0.78
BMI and Log-cTnI	0.014	0.90
SaO_2 min and Log-cTnI	-0.141	0.24

Table 6: The comparison of age, BMI, min SaO_2 and Log-cTnI in study subjects.

	Log-AHI
Log-cTnI	r=0.28 p=0.019 R^2=0.076

Table 7: The correlation of Log-AHI and Log-cTnI in patients.

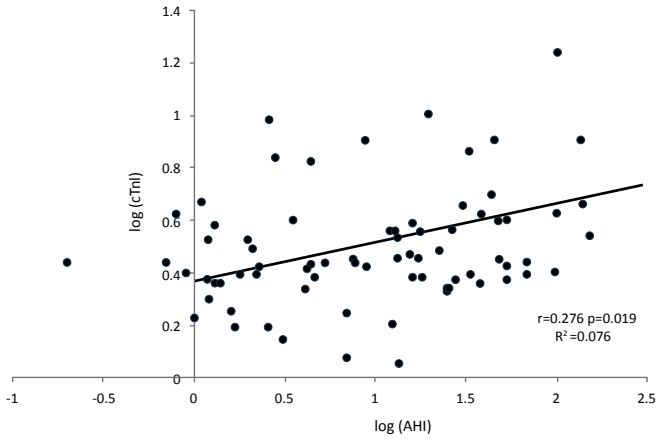

Figure 2: The association of log-AHI and log-cTnI in OSAS subjects.

recognized so far. It is known that pulmonary hypertension and RV dysfunction may occur in OSAS patients due to nocturnal hypoxemia. Hypoxemia-induced endothelial cell dysfunction is a critical factor in pulmonary artery remodeling because of the repeated apnea-related hypoxic events may induce oxidative stress of vascular endothelium [6,8,31-33]. Chronic Intermittent Hypoxia (CIH) is considered to be one of the most important causes of cardiovascular diseases in OSAS patients. The repeated hypoxia and reoxygenation cycle in sleep is similar to hypoxia-reperfusion injury, which initiates oxidative stress. In animal OSA models, there have been shown that CIH induced to myocardial injury, and cardiac troponin I levels was significantly higher in the CIH [34,35]. Thus cTnI levels might be elevated in OSAS patients due to possible factors such as RV dysfunction and repeated nocturnal hypoxemia as reported earlier studies.

The Sleep Heart Health Study showed a modest increase in the odds ratio of coronary artery disease in patients with severe OSAS compared with controls and the other studies showed that patients with OSAS have nocturnal ST segment changes that correlate with oxyhemoglobin desaturation and severity of OSA [5,29,30,36]. In our study, cTnI levels were detected higher in severe OSAS than mild, moderate OSAS and controls, too. This result was compatible with the results of previous studies which ischemic changes were found to be associated with severity of disease. The significant difference in cTnI between mild, moderate and severe OSAS groups considered that myocardial injury induced by repeated nocturnal hypoxemia and apnea-hypopnea. However, there was no statistically significance between nocturnal desaturation during the PSG and cTnI values in our study. In a study which cardiac troponin T levels were studied of 15 OSAS patients without CAD, there was observed that cardiac troponin T levels was not detectable marker in OSAS [37]. In another study performing to establish cardiac damage related to nocturnal ischemia in fifty OSAS patients, cTnI levels were found similar to the controls [38]. However, recently published a study has been shown that high sensitivity cardiac troponin T levels were associated with severity of OSAS [39]. As compatible with this, although cTnI levels were detected similar between OSAS patients and controls, cTnI levels were increased with severity of diseases in our study.

As emphasized in previous studies, myocardial injury without CAD can be detected in OSAS by cardiac troponins or another biomarker [30,33,40]. The presence of any possible contribution of cardiac troponins to the pathophysiology of OSAS because of cardiac troponins might be useful in detection of myocardial injury in patients with OSAS and CAD could be prevented by CPAP therapy in early stage. Considering the cardiovascular morbidity and mortality rates, myocardial injury in OSAS should be diagnosed immediately and the decision of CPAP therapy should be made as early as possible [29,30].

In a recent study which was evaluated the association between severity of OSAS and coronary vasoconstriction there was significant correlation between AHI values and endothelial function of coronary arteries [41]. The results of our study were confirmed to this opinion.

One of the limitations of our study is that histopathologic diagnosis could not be performed for subclinical coronary artery disease in patients. But the patients included to the study had no symptoms suggesting acute coronary syndrome and there was no relation found between troponin I values and existing cardiovascular diseases, statistically. However, further imaging techniques are needed to determine underlying coronary artery disease. Another limitation of our study is that control group consisted of patients who admitted to sleep clinic, therefore may not reflect healthy controls.

In conclusion, high levels of cTnI were observed in severe OSAS. This study has been thought that cardiac troponin I measurements may be may be useful to show the degree of myocardial injury in severe OSAS.

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