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Effect of nasal continuous positive airway pressure on global right ventricular myocardial performance in patients with obstructive sleep apnea syndrome

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Aim: The myocardial performance index (Tei index), plasma N-terminal pro B-type natriuretic peptide (NT-proBNP), and ischemia-modified albumin (IMA) were used to investigate the effect of obstructive sleep apnea syndrome (OSAS) on right ventricular function.

Materials and methods: Twenty-three patients diagnosed with OSAS (moderate or severe AHI > 15) by polysomnography at Karadeniz Technical University Medical Faculty Chest Disease Clinic between September 2009 and September 2010 were included. The Tei index, Nt-proBNP, and IMA were measured in all patients before CPAP treatment and 3 months after the diagnosis.

Results: Patients with OSAS had statistically significantly higher right ventricular Tei indices than the control group ($P < 0.05$). There was no significant difference between the groups in terms of NT-proBNP or IMA values. The systolic blood pressure of the patient group was significantly lower ($P < 0.05$) after CPAP treatment, but there was no difference in the Tei index, NT-proBNP, or IMA values.

Conclusion: We conclude that plasma NT-proBNP and IMA levels are not effective as the Tei index for showing myocardial damage in patients with OSAS, and that these parameters are inadequate to show the effect of CPAP treatment on right ventricular myocardial function.

Key words: Obstructive sleep apnea syndrome, Tei index, plasma N-terminal pro B-type natriuretic peptide, ischemia-modified albumin

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by repeated upper respiratory tract obstruction during sleep and frequently by a decrease in oxygen saturation (1). The most common symptoms in OSAS are severe snoring, daytime sleepiness, and reported apnea. Complications developing in OSAS patients during apnea and hypopnea are pulmonary hypertension, systemic hypertension, coronary insufficiency heart failure, left/right ventricular (LV/RV) dysfunction, and arrhythmia (2,3).

The gold standard in mild or moderate–severe OSAS with a cardiovascular or cerebrovascular disease is nasal continuous positive airway pressure (nCPAP) treatment (4,5). Using echocardiography, previous studies have shown that this treatment has a positive effect on right and left ventricular functions (6,7). We investigated the correlation between the right ventricular Tei index and the degree of OSAS.

N-terminal pro B-type natriuretic peptide (NT-proBNP) is a marker of systolic and diastolic dysfunction released from both ventricles in association with volume overload and distension (8). The literature contains various studies evaluating NT-proBNP levels before and after CPAP treatment, but this issue has conflicting results (9–11). Ischemia-modified albumin (IMA) is formed as a result of the normal human albumin N-terminal region undergoing alteration during ischemia (12). Elevated IMA showing myocardial ischemia has been identified not only in coronary diseases, but also in pulmonary edema with hypoxemia (13). Therefore, this marker may be expected to be high in OSAS patients because of nocturnal hypoxemia. This study investigated the effect of OSAS on global right ventricular function using the myocardial performance index (Tei index), plasma NT-proBNP, IMA, and nCPAP on these parameters.

2. Materials and methods

Twenty-three adult (≥18 years) patients diagnosed with moderate–severe OSAS by polysomnography who were admitted to the Karadeniz Technical University Medical

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Faculty Chest Disease Clinic between September 2009 and September 2010 and scheduled for nCPAP treatment were included in this study. There were no exclusion criteria. An age-matched control group of 23 individuals with no excessive daytime sleep and an Epworth sleepiness score of less than 10 was also established. Individuals in either group who had a sleep-related respiratory disease other than OSAS, diagnosed pulmonary disease, atrial fibrillation, branch block or atrioventricular block, left ventricular dysfunction (EF < 50%), ischemic or valvular heart disease, or renal insufficiency (serum creatinine > 2 mg/dL), or who were fitted with pacemakers, were excluded.

Polysomnography tests were performed using an ALICE Sleepware (Respironics Inc.) device at the KTU Medical Faculty Sleep Unit under the supervision of a technician with the patient in spontaneous sleep (Respironics Inc.). PSG records were scored in 30-s epochs on the basis of international classification of sleep disorders criteria (AASM-2007) (14). CPAP titration was commenced at a pressure of 4 cm H_2O in 2nd-night records, and pressure was gradually raised until no abnormal respiratory events were observed. The most appropriate CPAP pressure eliminating all abnormal respiratory events sleep was determined for each patient during sleep. The use of CPAP devices for at least 3.5 h per night and for 70% of nights was accepted as effective use.

The Epworth sleepiness scale was completed for each patient enrolled in the study. Total scores can range from 0 to 24; scores of 0–8 were evaluated as normal sleepiness, 9–12 as mild, 13–16 as average, and above 16 as severe. Subjects with an Epworth sleepiness score of below 10 were enrolled as the control group.

Echocardiography, using 2-dimensional pulse-waved Doppler and tissue Doppler imaging, was performed on patients before beginning nCPAP treatment and at the 3rd month after treatment, and once during the study in the control group. Examinations were performed at the KTU Medical Faculty Department of Cardiology by a cardiologist blinded to patients' clinical and laboratory data using a Vivid 7 (GE Vingmed Ultrasound, Horten, Norway) echocardiography device with the patient in the left lateral decubitus position. Doppler recording was performed at a speed of 100 mm/s with simultaneous single derivation ECG recording. All measurements were taken at 3 consecutive cycles and the averages of these were recorded. In order for the parameters not to be affected by respiration and to be more consistent, Doppler measurements were taken at the end of expirium. For right ventricular systolic functions, ejection fraction (EF) was calculated using Simpson's method. Systolic artery pressure was measured with the addition of mean right atrial pressure to the transtricuspid gradient calculated using the maximum velocity of the tricuspid regurgitation jet. Tricuspid flow was obtained with the pulsed wave Doppler sample volume in the apical 4-chamber view being placed on the ends of the tricuspid valve. In short axis views, Doppler trace of flow was obtained from the exit pathway of the right ventricle by placing the sample volume immediately beneath the pulmonary valves. The Tei index was calculated with the ejection process obtained from the right ventricular exit pathway flow sample with pulsed wave Doppler in the parasternal short axis view subtracted from the tricuspid regurgitation flow duration in the apical 4 chamber view (or the period from the end of one diastolic flow at transtricuspid Doppler tracing to the start of the next diastolic flow) being divided into the remaining ejection duration.

Serum NT-proBNP tests were performed using original kits on a Roche Cobas 6000 autoanalyzer (proBNP II Cobas, Roche Diagnostics). The NT-proBNP cutoff value was < 125 pg/mL. At IMA testing, reduced cobalt to albumin binding capacity was measured using the rapid and colorimetric method developed by Bar-Or et al. (15). Values above 0.400 ABSU were regarded as low cobalt binding and therefore exhibiting ischemia, while values below 0.400 ABSU were regarded as nonischemic, as recommended by those authors. Echocardiographic parameters, NT-proBNP, and IMA concentration, were analyzed before the start and at the 3rd month of nCPAP treatment in the OSAS group and once at the beginning of the study in the control group.

2.1. Statistical analysis

The chi-square test was used in the analysis of data obtained by counting. The compatibility with normal distribution of data obtained by measurement was analyzed using the Kolmogorov–Smirnov test. Normally distributed data were analyzed with Student's t-test and nonnormally distributed data with the Mann–Whitney U test. Correlation between NT-proBNP, IMA, and Tei index with AHI score, BMI TA, EF, PAB, and Epworth sleepiness scale was investigated using Spearman correlation analysis. Patient group pre- and posttreatment echocardiography findings were analyzed using the McNemar test.

3. Results

Patients' demographic characteristics are summarized in Table 1. The prevalence of obesity and hypertension, smoking year, BMI, and systolic blood pressure values were higher in patients than in the control group. Data for basal NT-proBNP, IMA, and echocardiographic parameters are listed in Table 2. Although higher NT-proBNP concentrations were determined in the patients than in the control group, the difference was not significant. No significant difference was determined between the groups in terms of IMA values. The right ventricular Tei index

Table 1. Basal characteristics of patients.

Variables	Patient (n = 23) (Mean ± SD)	Control (n = 23) (Mean ± SD)	P
Age (years)	53.6 ± 7.1	53.7 ± 6.5	0.983
Sex (F/M)	9/14	9/14	1.000
Body mass index (kg/m²)	34.8 ± 7.8†	25.8 ± 1.7	**<0.0005***
Obesity	17 (73.91%)	1 (4.34%)	**<0.0005***
Respiratory rate (/min)	13.1 ± 1.2	12.5 ± 0.09	0.127
Systolic blood pressure (mmHg)£	133.7 ± 8.7	126.3 ± 5.7	**0.002***
Diastolic blood pressure (mmHg)£	81.3 ± 6.4	80.2 ± 3.5	0.288
Antihypertension treatment	15 (65%)	2 (8.7%)	**<0.0005***
Diabetes mellitus	4 (17.4%)	0 (0%)	0.109

Data are expressed as mean ± SD or number of patients (percentage)
† Body mass index > 30 kg/m²
£ Systolic blood pressure ≥ 140 mmHg; diastolic blood pressure ≥ 90 mmHg
* P < 0.01

Table 2. Basal NT-proBNP, ischemia-modified albumin, and echocardiographic parameters.

Variables	OSAS (n = 23) (Mean ± SD)	Control (n = 23) (Mean ± SD)
Epworth sleepiness score	9.17 ± 5.10	0.26 ± 0.54*
Tei index	0.323 ± 0.095	0.251 ± 0.010*
NT-proBNP (pg/mL)	89.3 ± 128.7	33.8 ± 21.5
IMA (ABSU)	0.493 ± 0.052	0.453 ± 0.092
Pulmonary arterial pressure (mmHg)	21.8 ± 5.9	22.1 ± 4.4
EF	63.6 ± 3.9	65 ± 1.4

Data are expressed as mean ± SD
* P < 0.05

was significantly higher in the patients than in the control group (0.32 ± 0.09 vs. 0.25 ± 0.01, P < 0.01). No significant difference was determined between the 2 groups in terms of pulmonary artery pressure or ejection fraction.

The basal and posttitration values of polysomnography in patients are summarized in Table 3. Desaturation index, AHI, duration of sleep time spent below 90%, and arousal index were statistically significantly higher than basal values. Oxygen level during sleep and minimum oxygen levels were significantly lower than basal values. After treatment, none of the patients reported complaints of snoring, apnea, or daytime sleepiness.

Correlations between NT-proBNP, IMA, and Tei index with BMI, TA, EF, PAB, oxygen level during sleep, arousal index, and basal Epworth sleepiness scale are shown in Table 4. A significant positive correlation was determined between basal NT-proBNP values and basal AHI (r = 0.442; P = 0.039). A significant positive correlation was determined between basal IMA values and basal desaturation index (r = 0.860; P = 0.025). A significant negative correlation was determined between basal oxygen level during sleep values and basal IMA level (r = –0.598; P = 0.003). A significant negative correlation was determined between basal minimum oxygen level and

Table 3. Basal and posttitration values in patient group.

Variables	Basal (Mean ± SD)	After CPAP titration (Mean ± SD)
AHI (events/h)	50.5 ± 26.6	3.9 ± 4.3*
Desaturation index	48.08 ± 24.2	2.50 ± 1.7*
Oxygen level during sleep (%)	89.13 ± 6.01	93.65 ± 2.05*
Duration of sleep time that was spent below 90% (min)	58.98 ± 106.56	1.76 ± 5.74*
Minimum oxygen levels (%)	74.43 ± 17.99	89.78 ± 6.99*
Arousal index (min)	29.85 ± 14.98	8.76 ± 6.32*

* $P < 0.01$

Table 4. Correlations between Tei index, NT-proBNP, and IMA, and apnea-hypopnea index, body mass index, blood pressure, echocardiographic parameters, oxygen values, and arousal index.

Variables	Correlation coefficients		
	Tei index	NT-proBNP	IMA
Body mass index	–0.141	0.416	0.352
Systolic blood pressure	0.068	0.22	0.379
Diastolic blood pressure	0.047	0.191	0.198
Pulmonary arterial pressure	–0.109	0.279	0.25
Right ventricular ejection fraction	0.046	0.033	–0.024
Tei index	—	0.242	–0.240
IMA	–0.24	0.412	—
NT-proBNP	0.242	—	0.412
AHI	–0.412	0.442*	0.348
Epworth sleepiness score	0.243	0.392	0.385
Arousal index	0.135	0.299	0.483*
Oxygen level during sleep	–0.246	–0.259	–0.598**
Desaturation index	–0.051	0.393	0.254
Duration of sleep time that was spent below 90%	0.294	0.274	0.626**
Minimum oxygen levels	–0.061	–0.229	–0.591**

* $P < 0.05$, **$P < 0.01$

baseline IMA level (r = –0.591; P = 0.003). A significant positive correlation was determined between basal IMA values and baseline duration of sleep time spent below 90% (r = 0.6.26; P = 0.001).

Although posttreatment diastolic blood pressure (81.3 ± 6.4 vs. 79.8 ± 4.1 mmHg), posttreatment NT-proBNP (89.3 ± 128.7 vs. 71.7 ± 79.8 pg/mL), posttreatment IMA (0.49 ± 0.05 vs. 0.51 ± 0.08 ABSU), posttreatment Tei index (0.32 ± 0.09 vs. 0.31 ± 0.08), and posttreatment pulmonary arterial pressure (21.8 ± 5.9 vs. 20.3 ± 5.8 mmHg) were decreased, these differences did not reach statistically significant levels compared to basal values. There was no change in right ventricular ejection fraction (63.6 ± 3.9 vs. 63.5 ± 3.5) after treatment. Systolic blood pressure (133.7 ± 8.7 vs. 130.4 ± 6.7 mmHg) and heart rate (78.3 ± 3.7 vs. 75.4 ± 2.8/min) decreased significantly compared to basal values (Figures 1 and 2).

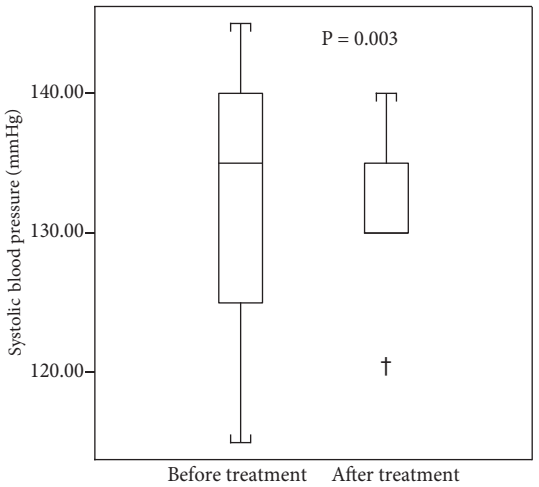

Figure 1. Basal and systolic blood pressure values of patients.

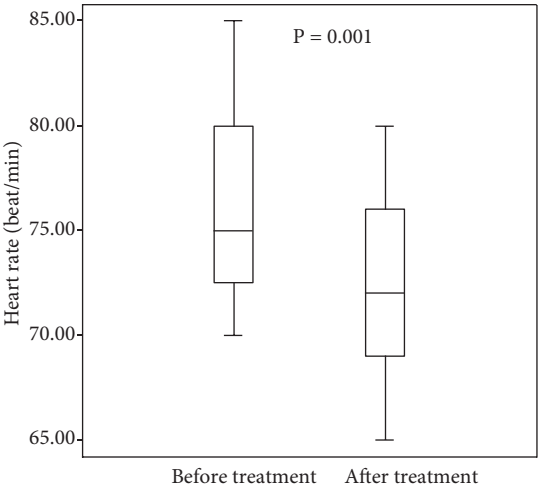

Figure 2. Basal and posttreatment heart rate values of patients.

4. Discussion

The right ventricle structure and function in OSAS patients is negatively affected by several factors, including obesity, elevations in the intrathoracic negative pressure related to apneic events, and nocturnal increases in pulmonary vascular resistance. All of these factors have been related to impaired right ventricular filling and diastolic dysfunction (16–18). Obesity is an important risk factor for the development of OSAS. The Cleveland Family Study has shown that an increase in bodyweight over time increases the risk for and accelerates the progression of OSAS (19). In our study, the patient group was overweight and had a high body mass index. We found that the oxygen levels during sleep and the minimum oxygen levels of patients were low. İnönü et al. compared 71 patients with OSAS and 12 with complex sleep apnea syndrome (SAS) (20). The study showed that the level of oxygen saturation was lower in the complex SAS group than in the OSAS group.

CPAP is the most effective treatment for the prevention of cardiac complications in OSAS patients. Bayram et al. compared 28 moderate–severe OSAS patients with 18 control cases. According to parameters determined by tissue Doppler echocardiography, right ventricular systolic and diastolic dysfunction was present in the OSAS group, and there was an improvement in these parameters after 6 months of CPAP treatment (21). Dursunoğlu et al. included 18 moderate–severe OSAS patients in a study intended to investigate the effects of CPAP treatment on right ventricular myocardial performance. Patients underwent echocardiography at the beginning of the study and after 6 months of CPAP treatment. At the end of the study, the right atrial and ventricular end diastolic diameters were unchanged after treatment, while the right ventricular free wall diameter and right ventricular Tei index were decreased in comparison to initial levels (7). The mean right ventricular Tei index our OSAS patients was 0.32 ± 0.09, and 0.25 ± 0.01 in the control group; it was higher in the former group, in accordance with other studies. Patients' mean right ventricular Tei index at the start of our study was 0.32 ± 0.09, and although this declined to 0.31 ± 0.08 after treatment, this decrease was not significant. In addition, the patients in other studies were evaluated with echocardiography after 6 months of CPAP treatment, while in the present study patients were evaluated after 3 months of CPAP treatment. Patients with hypertension were also included in our study, and our study period was shorter than those of other studies, which might be the reason for the lack of any significant difference in right ventricular Tei index values after CPAP treatment.

In a multicenter, double-blinded, randomized study by Cantolla et al., the effect of CPAP on systemic hypertension was investigated with CPAP given to 169 out of 340 OSAS patients with BMI > 15, and placebo to the other 171. At the end of the study, a 2.1 mmHg decrease in mean systolic blood pressure and a 1.33 mmHg decrease in diastolic blood pressure were observed in the 3-month CPAP treatment group (22). Our patients' mean systolic blood pressure before treatment was 133.7 ± 8.7 mmHg, compared to 130.4 ± 6.7 mmHg after CPAP. As with other studies, we found a significant decrease in systolic blood pressure in OSAS patients after CPAP treatment. Our patients' mean initial diastolic blood pressure was 81.3 ± 6.4 mmHg. Despite contracting to 79.8 ± 4.1 mmHg after CPAP treatment, in contrast to other studies, the difference was not statistically significant. We think that

the reasons for this difference might be the presence of systemic hypertension in all cases in the studies examining the effects of CPAP on systemic hypertension, and the greater number of cases in these studies than in our study.

Studies have shown that BNP rises in various cardiac conditions, including coronary insufficiency, coronary artery disease, and cardiac hypertrophy. Left ventricular capacity decreases in parallel to increased BNP and has been correlated with a poor prognosis (23). Maeder et al. reported that a high serum NT-proBNP level in OSAS patients is an appropriate marker for cardiovascular system injury independent of increased oxygen consumption (24). Koga et al. compared 27 moderate–severe OSAS patients with 22 controls; the left ventricle Tei index was higher in the OSAS group, but they determined no significant difference between plasma BNP levels. Moreover, that study determined that there was a significant decrease in OSAS patients' Tei index and BNP values after 3 months of CPAP treatment (6). Kita et al. determined that plasma BNP levels rose throughout sleep in OSAS patients, but that this was not correlated with patients' clinical and polysomnographic parameters. They also observed that CPAP treatment reduced BNP levels (25). Tasci et al. reported no significant difference between hypertensive and normotensive OSAS patients' plasma NT-proBNP levels, but showed that NT-proBNP levels declined with CPAP treatment (26). Similarly to Kita et al., Hübner et al. showed no significant correlation between serum NT-proBNP levels and AHI, BMI, mean and minimal saturation, left ventricle ejection fraction, and left ventricular Tei index. Contrary to other studies, however, they showed that there was no change in NT-proBNP level after CPAP treatment (10,25). Similarly, Çifçi et al. failed to establish a correlation between OSAS severity and plasma NT-proBNP levels, and reported that NT-proBNP levels were not altered with CPAP treatment (11). In the light of these few studies with conflicting results, it is still unclear what kind of correlation exists between CPAP treatment and serum BNP levels. The mean NT-proBNP level in our OSAS patients was 89.3 ± 128.7 pg/mL, and 33.8 ± 21.5 pg/mL in the control group. In addition, and similarly to Hübner and Çifçi's studies, although mean serum NT-proBNP values fell to 71.7 ± 79.8 pg/mL after CPAP treatment, this decrease was not statistically significant.

Elevated IMA levels have been shown in such ischemic events and hypoxemia (13,27,28). Previous studies have shown that IMA reflects the magnitude and duration of ischemia induced during percutaneous coronary intervention and exercise test for coronary syndrome, and that it is a sensitive marker for the identification of acute cardiac ischemia (29–32). The most important characteristic that differentiates IMA from other cardiac ischemia markers is that it increases in the early phase. Therefore, IMA could be considered to be an applicable diagnostic marker for OSAS. Our scan of the literature revealed no publications regarding IMA levels in OSAS cases. No significant difference was determined in our study between the IMA levels of the OSAS patients and those of the control group. OSAS patients' IMA values did not change with CPAP treatment. However, the negative correlation between baseline oxygen level during sleep values, minimum oxygen level, and baseline IMA level was significant. From the point of view of these relationships, IMA could be a hypoxemic marker in OSAS patients.

In the light of existing findings, our study supports the idea that plasma NT-proBNP and IMA levels are not as sensitive as the Tei index in showing myocardial injury developing in OSAS, and that these parameters are inadequate in determining the effect of CPAP treatment on right ventricular myocardial function. The limited number of cases and the absence of an OSAS patient group are the main limitations of the present study. However, since patients diagnosed with OSAS without any cardiac insufficiency were included in our study, the patient population is a more appropriate one in terms of investigating the cardiac effects of intermittent hypoxia compared to those of other studies. In the light of the study data, we think that more research on different markers is needed to show cardiac injury developing in OSAS patients before clinical findings develop.

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