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<tr>
<td>Citation</td>
<td>The American Journal of Cardiology, 101(12), pp.1796-1800; 2008</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2008-06-15</td>
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<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10069/16401">http://hdl.handle.net/10069/16401</a></td>
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Effect of Nasal Continuous Positive Airway Pressure in Men on Global Left Ventricular Myocardial Performance in Patients with Obstructive Sleep Apnea Syndrome

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Running head: Nasal-CPAP recovers cardiac dysfunction in OSAS.

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Abstract

The influence of obstructive sleep apnea syndrome (OSAS) on left ventricular function remains controversial. We examined the influence of OSAS on global left ventricular function using the myocardial performance index (Tei-index) and plasma brain natriuretic peptide (BNP) level, and investigated the effect of nasal continuous positive airway pressure (nCPAP) on these parameters. We obtained echocardiographic indices including the Tei-index and BNP concentrations from 27 patients with OSAS whose mean apnea-hypopnea index (AHI) was 42.2 ± 21.5 events/hour and who were undergoing nCPAP, as well as from 22 control individuals. We defined global left ventricular dysfunction (GLVD) as a Tei-index of ≥ 0.50, and high BNP as ≥ 20 pg/ml. Compared with controls, the Tei-index of OSAS patients was significantly increased (P < 0.01) and the prevalence of GLVD was high (19%, P < 0.05). The correlation between the Tei-index and AHI was significant (r = 0.447, P < 0.05). Although BNP levels were higher in OSAS patients than in controls, the difference did not reach significance. The BNP level was high in 37% of OSAS patients and in only 9% of controls (P < 0.05). The Tei-index of OSAS patients was significantly decreased after 1 and 3 months of nCPAP (P < 0.01), and the prevalence of GLVD significantly decreased from 19% to 4% (P < 0.05). In contrast, BNP significantly decreased at 3 months after nCPAP (P < 0.05). In conclusion, patients with moderate to severe OSAS frequently have impaired global left ventricular myocardial performance, which can be reversed at the early stage after starting nCPAP.

Key words: sleep apnea, echocardiography, natriuretic peptide
**Introduction**

Whether brain natriuretic peptide (BNP) is affected by obstructive sleep apnea syndrome (OSAS), and whether the effect can be reversed using nasal continuous positive airway pressure (nCPAP) remains unknown. Moreover, the association between the Tei-index and BNP in OSAS has not been evaluated. The present study clarifies the influence of OSAS on global left ventricular function using the Tei-index and BNP, and defines the short-term effects of nCPAP on these parameters.

**Materials and methods**

We enrolled 27 consecutive patients diagnosed with moderate to severe OSAS, an apnea-hypopnea index (AHI) of $\geq 20$ events/hour according to overnight polysomnography, and who had started nCPAP therapy. We also enrolled 22 age-matched control men without apparent excessive daytime sleepiness (Epworth sleepiness scale $< 10$ points\(^1\)). The exclusion criteria for both groups comprised apparent lung diseases, daytime hypoxemia (arterial oxygen pressure $< 80$ mmHg), atrial fibrillation, bundle branch block, atrioventricular block and implantable pacemaker, left ventricular dysfunction (ejection fraction $< 50\%$), ischemic or valvular heart disease, and cardiomyopathy determined from medical history or a physical examination, electrocardiography, chest radiography, and echocardiography; and renal insufficiency (serum creatinine $> 2.0$ mg/dl). Withdrawal criteria comprised changes in medical treatment, clinical exacerbation or hospital admission and $< 3.5$ hours/night of average nCPAP usage by OSAS patients. The Institutional Ethics Committee at our hospital approved the study and we obtained written, informed consent from all participants to be involved in all procedures associated with the study. The protocol of this study was registered at ClinicalTrials.gov (ID number,
Hypertension was defined as systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg, or the use of anti-hypertensive agents. Body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$). Overweight and obesity were defined as a 30 kg/m$^2$ > BMI $\geq 25$ kg/m$^2$ and a BMI of $\geq 30$ kg/m$^2$, respectively.

Overnight polysomnography (EMBLA S7000; Medcare Flaga, Iceland) proceeded as described in the manufacturer’s protocol. Data were analyzed using a semi-automatic system (Rembrandt; Medcare Flaga). Arterial oxygen saturation using pulse oximetry and AHI were measured as described$^2$. Patients with OSAS whose AHI was $\geq 20$ events/hour were prescribed nCPAP (PV10; Breas, Sweden), and the effects of nCPAP were confirmed by polysomnography or by monitoring arterial oxygen saturation while asleep.

Transthoracic echocardiography was performed using an SSD-5500 echocardiograph (Aloka, Japan) and echocardiographic parameters were obtained as described$^3$. Left ventricular ejection fraction was calculated using the Teichholz method, and left ventricular mass and left ventricular mass index were calculated using the formula reported by Devereux et al$^4$. We obtained peak flow velocity in early diastole (E), peak flow velocity at atrial contraction (A), ratio of E/A, and mitral deceleration time from the mitral inflow velocity. The Tei-index was calculated from (a-b)/b, where ‘a’ is the interval between cessation and onset of mitral inflow, and ‘b’ is the ejection time of left ventricular outflow (Figure 1)$^5$. Five consecutive beats were measured and averaged for each parameter. The normal adult Tei-index of $0.39 \pm 0.05$ increases with worsening left ventricular dysfunction$^5$. Global LV dysfunction (GLVD) was defined as a Tei index $\geq 0.50$. The same experienced echocardiographer who was blinded to the patients’ data obtained all
Plasma BNP concentrations were measured using an industry-standard analytical platform (SRL, Japan), and the reference value was within 18.4 pg/ml. High BNP was defined as ≥ 20 pg/ml. Echocardiographic parameters and BNP concentrations were determined before and at 1 and 3 months after CPAP initiation in the OSAS group, and only once for the controls at the time of enrollment.

Data are expressed as means ± standard deviation. Control and OSAS groups were compared using the unpaired *t* test or Mann-Whitney U-test. Relationships between variables were determined by Pearson’s correlation analysis. Changes at 1 and 3 months after nCPAP initiation were compared using the one-way repeated measures ANOVA, followed by the Bonferroni post hoc test. We compared changes in GLVD or High BNP between baseline and at 3 months after nCPAP using the Wilcoxon signed rank test. A *P* value of < 0.05 was considered statistically significant. Data were statistically analyzed using SPSS version 11.0 (SPSS Inc., USA).

Results

Table 1 shows the patients’ characteristics. The BMI as well as the prevalence of obesity and hypertension were higher in patients than in controls. Blood pressure value did not significantly differ between the two groups, possibly because of the high prevalence of treatments for hypertension in OSAS. Polysomnography revealed an AHI of 42.2 ± 21.5 events/hour, 94 ± 3% mean arterial oxygen saturation, and 78 ± 7% minimum arterial oxygen saturation in the patients.

Table 2 shows baseline data for BNP and echocardiographic parameters. Although the BNP concentrations were higher in patients than in controls, the difference did not reach significance. Values for ventricular septum and posterior wall thickness, left ventricular mass and left
ventricular mass index, were significantly higher in the patients with OSAS, whereas those for left ventricular end-diastolic dimension, end-systolic dimension and left ventricular ejection fraction did not significantly differ. The patients had a significantly lower E/A ratio, as well as longer deceleration, isovolumic relaxation and isovolumic contraction times than controls, even though their values remained within the normal range. The Tei-index was significantly increased in OSAS patients (Table 2) and in OSAS patients without hypertension compared with controls (0.42 ± 0.08 vs. 0.35 ± 0.05, P < 0.01).

Figure 2 shows that GLVD and High BNP were more obvious in 5 (19%) and 10 (37%) of the 27 OSAS patients, respectively, than in normal individuals (P < 0.05).

Table 3 shows that the Tei-index significantly and negatively correlated with the E/A ratio, and positively with AHI (Figure 3), BMI, ventricular septum and posterior wall thickness. Levels of BNP significantly and positively correlated with deceleration time and negatively with BMI. The Tei-index and BNP did not significantly correlate.

All studied parameters of sleep significantly improved after nCPAP with a mean pressure of 9.1 ± 1.8 cmH₂O: AHI decreased to 6.7 ± 7.6 events/hour, and minimum and average arterial oxygen saturation increased to 91 ± 4% and 96 ± 1%, respectively. Table 4 shows changes in BNP and echocardiographic parameters after nCPAP initiation. None of BMI, blood pressure, and heart rate significantly differed between baseline and after nCPAP. Although ventricular septum and posterior wall thickness, left ventricular mass and left ventricular mass index significantly decreased at 3 months after nCPAP, left ventricular end-diastolic dimension and end-systolic dimension and left ventricular ejection fraction did not significantly change. The E/A ratio, ejection time and reduction in deceleration time and isovolumic relaxation time tended
to increase after nCPAP, whereas isovolumic contraction time was significantly reduced. The Tei-index significantly decreased from 1- to 3-months after nCPAP, and the prevalence of GLVD also significantly decreased from 5 (19%) to 1 (4%) in 27 OSAS patients after nCPAP (P < 0.05). The BNP concentrations significantly decreased after 3 months of nCPAP, and the prevalence of High BNP tended to decrease from 10 (37%) to 7 (26%) (p = 0.08).

Discussion

The main findings of this study were that the Tei-index and BNP levels are frequently increased in OSAS patients, and that nCPAP can reverse these changes at the early stage.

Indices of diastolic function including the E/A ratio, deceleration time and isovolumic relaxation time, and left ventricular hypertrophy, were more frequently disordered among OSAS patients than controls. The elevated Tei-index in OSAS may be partly explained by these findings. Elevated nocturnal blood pressure and sympathetic nervous system activity during OSA create ventricular pressure overload, which leads to left ventricular hypertrophy and impaired ventricular relaxation. Futile inspiratory efforts against an occluded pharynx during OSA cause exaggerated negative intrathoracic pressure, and also increase left ventricular transmural pressure and hence afterload. Venous return is also enhanced, resulting in right ventricular distension and a leftward shift of the ventricular septum. Thus, the exaggerated negative intrathoracic pressure can affect left ventricular filling. These mechanisms might lead to diastolic left ventricular dysfunction, resulting in an elevated Tei-index. Hypertension and obesity may also affect the Tei-index. Since the Tei-index was also elevated in our OSAS patients without hypertension compared with controls, we considered that the influence of hypertension was minimal. The influence of obesity or being overweight cannot be denied.
because we had no BMI-matched controls. However, the Tei-index was significantly reduced after nCPAP without affecting the BMI, suggesting that the influence of obesity was also minimal.

A few reports have described the effect of nCPAP on the Tei-index in OSAS and the effect is still controversial\textsuperscript{11,12}. We discovered here that 1 and 3 months of nCPAP improved the left ventricular Tei-index. Among the parameters included in the formula for calculating the Tei-index, only isovolumic contraction time significantly shortened, which can reflect the reduction in left ventricular afterload after nCPAP. The Tei-index is preload dependent\textsuperscript{3,13} and nCPAP also reduces left ventricular preload by reducing end-diastolic volume and pressure\textsuperscript{14,15}. Thus, the nCPAP-induced improvement in the Tei-index may be due, at least in part, to the reduction of pre- and after-load in the left ventricle. Another possible mechanism is that left ventricular hypertrophy regressed after nCPAP, since left ventricular hypertrophy is associated with an elevated Tei-index\textsuperscript{16}. The indices of diastolic function, such as deceleration time and isovolumic relaxation time, tended to be decreased, but not significantly, after nCPAP, which might contribute to the change. In the present study, Tei-index indicated improvements in left ventricular function after nCPAP earlier than other indices. This might be due to the higher sensitivity of the Tei-index, because the formula could identify changes in cardiac function by amplifying systolic and diastolic dysfunction\textsuperscript{17}.

We showed that the BNP level tended to increase and that the prevalence of High BNP was significantly higher in OSAS patients than in controls. Moreover, 3 months of nCPAP reduced BNP levels. Svatikova et al.\textsuperscript{18} reported that OSAS is not associated with increased BNP during sleep and that nCPAP did not elicit any acute changes. In contrast, Kita et al.\textsuperscript{19} discovered
increased BNP levels during sleep in OSAS that were reduced by nCPAP. Why these and the present findings differ is unclear. However, differences in the backgrounds of the studies including severity of OSAS, BMI and duration of nCPAP therapy might be contributing factors. Most BNP is secreted from both ventricles in response to pressure and volume overload or stretch\textsuperscript{20}, and its presence reflects systolic and/or diastolic ventricular dysfunctions\textsuperscript{21}. OSA induces pressure overload and hypertrophy in the left ventricle as well as dilation and reduces the performance of the right ventricle. Moreover, nCPAP can recover these changes in both ventricles. Thus, BNP levels might be higher in OSAS patients than in controls and reduced by 3 months of nCPAP.

Although Ono et al.\textsuperscript{22} found a positive correlation between the Tei-index and BNP in various heart diseases, the present study did not. Wang et al.\textsuperscript{23} reported that obese individuals have lower BNP levels than individuals with a normal BMI. Table 3 shows that BMI correlated positively with the Tei-index, but negatively with BNP levels. Furthermore, the Tei-index also correlated positively with AHI (Figure 3). These findings might explain why our patients with severe OSAS had low BNP levels despite an increased Tei-index.

This study has some limitations. The study cohort was small and most of our OSAS patients were hypertensive. We did not have BMI-matched controls because obese, middle-aged individuals are rarely healthy. Although some controls with asymptomatic OSAS might have introduced bias against the present findings, all of our controls scored < 10 on the Epworth sleepiness scale, which excluded at least moderate to severe OSAS\textsuperscript{1}. We did not measure serum or urinary catecholamines and blood pressure during sleep, and thus were unable to evaluate nocturnal changes in sympathetic nervous system activity.
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