INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Effects of Nasal Continuous Positive Airway Pressure on Left Ventricular Concentric Hypertrophy in Obstructive Sleep Apnea Syndrome

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Abstract

Objective Abnormal left ventricular (LV) geometry, especially concentric hypertrophy, is associated with cardiovascular morbidity and mortality. The aim of this study was to evaluate the impact of obstructive sleep apnea syndrome (OSAS) and the effects of nasal continuous positive airway pressure (CPAP) on the LV geometric patterns.

Methods The LV morphological parameters, including the LV mass index (LVMI) and the relative wall thickness (RWT), were evaluated using echocardiography in 37 patients with OSAS diagnosed on polysomnography and 34 control subjects. Based on the values of LVMI and RWT, the LV geometry was classified as normal, concentric remodeling, concentric hypertrophy or eccentric hypertrophy. The echocardiographic parameters were reassessed after three months of CPAP treatment.

Results Compared with the controls, the OSAS patients had a higher proportion of concentric hypertrophy patterns (54% vs. 0%, $p<0.001$) and a lower proportion of normal geometric patterns (5% vs. 62%, $p<0.001$). A univariate logistic regression analysis showed the apnea-hypopnea index, lowest oxygen saturation, hypoxemia index and body mass index to each be significantly associated with the presence of concentric hypertrophy. In a multivariate analysis of these factors, the apnea-hypopnea index was found to be a significant independent factor associated with the presence of concentric hypertrophy (odds ratio: 1.06, $p=0.008$). Three months of CPAP treatment resulted in significant decreases in LVMI and the proportion of cases with concentric hypertrophy (both $p=0.025$).

Conclusion In our limited study population, OSAS patients were found to be associated with a high prevalence of concentric LV hypertrophy patterns that were able to be reversed with three months of CPAP treatment.

Key words: obstructive sleep apnea syndrome, continuous positive airway pressure, left ventricular hypertrophy

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Introduction

Left ventricular (LV) hypertrophy is associated with an increased risk of cardiovascular morbidity and death (1-4). The LV geometric pattern also influences cardiovascular mortality. LV geometry is classified into four patterns, including normal, concentric remodeling, concentric and eccentric hypertrophy. Among these patterns, concentric hypertrophy is associated with the most adverse cardiac events and the highest mortality rate (2, 5). Obstructive sleep apnea syndrome (OSAS), as well as hypertension and obesity, have been shown to be critical risk factors for the development of LV hypertrophy (6-9). Several studies have indicated that severe OSAS is associated with a high prevalence of concentric hypertrophy through sympathetic activation, vasoconstriction and the elevation of blood pressure (7, 10, 11); however, this hypothesis still remains con-

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troversial.

Nasal continuous positive airway pressure (CPAP) is the most popular modality for improving nocturnal desaturation, decreasing blood pressure and improving symptoms such as headaches, snoring and daytime sleepiness in patients with moderate to severe OSAS. Furthermore, the use of CPAP protects against death from cardiovascular diseases and can improve mortality among patients with OSAS (12, 13). Several reports have shown that CPAP causes a regression of LV hypertrophy in patients with OSAS (9, 14). However, the effects of CPAP on the patterns of LV geometry are less well known.

The aim of our study was to assess the prevalence of LV geometry patterns in patients with OSAS and to examine the effects of three months of CPAP treatment on LV geometry.

Materials and Methods

Patient population

We enrolled 37 consecutive men with OSAS diagnosed based on a history of snoring and daytime sleepiness with an apnea-hypopnea index of ≥5 events/hour according to overnight polysomnography. We also enrolled 34 age-matched healthy men as controls. None of the controls had hypertension. The control patients did not undergo polysomnography; however, all of them scored 0 on the Epworth sleepiness scale (15). For each participant, a complete medical history was obtained and a physical examination and echocardiographic study were performed. The exclusion criteria comprised apparent lung disease, daytime hypoxemia (arterial oxygen pressure <80 mmHg), atrial fibrillation, left ventricular dysfunction (ejection fraction <50%), ischemic or valvular heart disease, changes in medications during the follow-up period and previous CPAP use. The Institutional Ethics Committee of our hospital approved the study, which also conformed to the Declaration of Helsinki. Informed consent was obtained from each of the patients prior to their enrollment in the study.

Polysomnography and CPAP

All patients underwent overnight polysomnography (EMBLA S7000; Medcare Flaga, Reykjavik, Iceland). Polysomnography consisted of 4-channel electroencephalography, electrooculography, submental and leg electromyography, electrocardiography and measurement of oronasal airflow (thermistors), chest and abdominal respiratory movements, snoring (using a microphone) and body position. Oxygen saturation was measured using a pulse oximeter. Apnea was defined as air flow cessation for >10 seconds. Hypopnea was defined as a >50% reduction in respiratory signals for at least 10 seconds with 3% desaturation from baseline. A total number of incidents of obstructive apnea/hypopnea exceeding five per hour (apnea-hypopnea index: AHI) and the presence of clinical symptoms of OSAS were required for a diagnosis of OSAS. The lowest nocturnal oxygen saturation and the mean apnea duration were measured. The hypoxemia index was defined as the percentage of sleep time at an oxygen saturation of <90%. Patients with OSAS with an AHI of ≥20 events/hour were prescribed with CPAP (PV10; Breas, Molnlycke, Sweden) in fixed pressure mode. Automatic pressure titration was performed using the auto-adjusting CPAP system with overnight attending polysomnography. Patients with an average CPAP usage of <3.5 hours/night were considered non-compliant and excluded. Patients underwent clinical reassessment and echocardiographic study after three months of CPAP use.

Echocardiography

Transthoracic echocardiograms were obtained using an SSD-5500 echocardiograph (Aloka, Tokyo, Japan). The interventricular septum thickness (IVST), posterior wall thickness (PWT), LV end-diastolic dimension (LVDd), LV end-systolic dimension (LVDs) and left atrial diameter (LAD) were measured according to the recommendations of the American Society of Echocardiography (16). The LV ejection fraction (LVEF) was calculated using the Teichholz method. The ratio of early peak filling velocity (E) to atrial peak velocity (A) (E/A ratio) and the deceleration time (DT) were calculated based on mitral inflow velocities determined with Doppler echocardiography (17). The LV mass was calculated as $0.8\times \{1.04\times [(\text{interventricular septal wall thickness} + \text{posterior wall thickness} + \text{LV end-diastolic dimension})^3 - (\text{LV end-diastolic dimension})^3]\} + 0.6$, and the LV mass index (LVMI) was calculated as the LV mass divided by $\text{height}^{2.7}$ (16). An LVMI of ≥49 $g/m^{2.7}$ indicated LV hypertrophy (16). The relative wall thickness (RWT) was calculated as (2× PWT)/LVDd, for which the normal limit is < 0.43 (16). Based on LVMI and RWT, the LV geometry was classified as normal (normal LVMI and RWT), concentric remodeling (normal LVMI and increased RWT), concentric hypertrophy (LV hypertrophy with increased RWT) or eccentric hypertrophy (LV hypertrophy with normal RWT) (18). All of the echocardiographic recordings and measurements were obtained by one experienced cardiologist blinded to the clinical status of the patients and the presence and magnitude of OSAS.

Definition of clinical characteristics

Hypertension was defined as an office sphygmomanometer systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) ≥90 mmHg and/or the use of antihypertensive medications. The body mass index (BMI) of each participant was calculated as weight/height^2 (kg/m^2). Patients with a fasting plasma glucose level exceeding 126 mg/dL and/or those under medication for diabetes or who were diagnosed with diabetes were defined as having diabetes mellitus.

Statistical analysis

All values are expressed as the mean ± standard deviation for continuous variables and as numbers and percentages for

Table 1. Clinical Characteristics

	Controls (n = 34)	OSAS (n = 37)	p
Age (years)	53.6 ± 10.9	54.4 ± 9.8	0.75
BMI (kg/m^2)	22.9 ± 2.4	28.2 ± 4.4	<0.001
Hypertension	-	21 (57%)	-
Anti-hypertension treatment	-	19 (51%)	-
Calcium-channel blocker		13 (35%)	
ACE inhibitor		6 (16%)	
Angiotensin II-receptor blocker		12 (32%)	
β-blocker		0	
α-blocker		5 (14%)	
Diuretics		0	
SBP (mmHg)	116 ± 11	126 ± 16	0.002
DBP (mmHg)	71 ± 8	79 ± 10	0.001
HR (beats/min)	71 ± 9	70 ± 11	0.51
Smoking			
No	17 (50%)	20 (54%)	
Current smoker	12 (35%)	10 (27%)	0.73
Ex-smoker	5 (15%)	7 (19%)	
Alcohol drinking	15 (44%)	17 (46%)	0.88
Polysomnographic data			
AHI (events/hour)	-	38.5 ± 22.2	-
Lowest oxygen saturation (%)	-	79.4 ± 8.2	-
Hypoxemia index (%)	-	8.2 ± 12.8	-

OSAS: obstructive sleep apnea syndrome, BMI: body mass index, ACE: angiotensin converting enzyme, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, AHI: apnea-hypopnea index

Table 2. Baseline Echocardiographic Data

	Controls (n = 34)	OSAS (n = 37)	p
IVST (mm)	9.9 ± 1.3	12.2 ± 1.5	<0.001
PWT (mm)	9.6 ± 1.2	12.0 ± 1.1	<0.001
LVMI (g/m$^{2.7}$)	39.8 ± 7.0	55.1 ± 14.7	<0.001
RWT	0.42 ± 0.07	0.51 ± 0.07	<0.001
LVDd (mm)	46.8 ± 4.2	47.3 ± 5.5	0.63
LVDs (mm)	28.9 ± 3.4	29.1 ± 4.1	0.77
LAD (mm)	32.7 ± 4.1	36.7 ± 4.2	<0.001
LVEF	0.68 ± 0.05	0.68 ± 0.05	0.86
E velocity (m/s)	0.59 ± 0.15	0.61 ± 0.14	0.51
A velocity (m/s)	0.57 ± 0.12	0.63 ± 0.12	0.039
E/A ratio	1.05 ± 0.29	0.98 ± 0.24	0.34
DT (ms)	184.1 ± 22.7	208.8 ± 32.9	0.004

OSAS: obstructive sleep apnea syndrome, IVST: interventricular septum thickness, PWT: posterior wall thickness, LVMI: left ventricular mass index, RWT: relative wall thickness, LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, LAD: left atrial diameter, LVEF: left ventricular ejection fraction, DT: deceleration time

categorical variables. Correlations between two variables were assessed using a Pearson correlation analysis. Univariate and multivariate logistic regression analyses were used to determine the independent factors associated with concentric hypertrophy. Specified variables with p<0.05 in the univariate model were entered into the multivariable model. Differences before and after CPAP were compared using the paired t-test or the Wilcoxon signed-rank test. A p-value of <0.05 was considered to represent a statistically significant difference. The data were analyzed using a statistical software package (SPSS 11.0; SPSS Inc., Chicago, IL, USA).

Results

The clinical characteristics of the patients with OSAS and the controls are listed in Table 1. The patients with OSAS had significantly higher values of BMI, SBP and DBP. No significant differences were observed regarding age or heart rate. The results of polysomnography in the OSAS patients are also listed in Table 1.

The results of baseline echocardiographic examinations are shown in Table 2. In the patients with OSAS, the values of IVST, PWT, LVMI, RWT and LAD were significantly larger, the DTs were significantly prolonged and the A velocities were significantly higher than those observed in the controls. No significant differences were detected between the groups in the values of LVDd, LVDs, LVEF, E velocity or the E/A ratio.

Fig. 1 shows a comparison of LV geometric patterns between the OSAS patients and the controls. The proportion of patients with concentric hypertrophy was significantly higher (54% vs. 0%, p<0.001) and that of patients with normal geometry was significantly lower in the OSAS group than in the control group (5% vs. 62%, p<0.001). The proportion of patients with concentric remodeling or eccentric hypertrophy did not differ between the groups.

The results of the correlation analyses conducted in the OSAS patients are shown in Table 3. LVMI was found to correlate positively with the AHI, hypoxemia index, and BMI and negatively with the lowest oxygen saturation. No correlations were observed between LVMI and age, SBP or DBP. Significant positive correlations were found between RWT and the hypoxemia index. No significant correlations were detected between RWT and the other variables. The results of the logistic regression analysis of concentric hypertrophy in the OSAS patients are listed in Table 4. A univariate analysis showed that the AHI, lowest oxygen saturation, hypoxemia index and BMI were each significantly associated with the presence of concentric hypertrophy. The multivariate logistic analysis revealed that, among these factors, the AHI was a significant independent factor associated with concentric hypertrophy.

Thirty-two of the original 37 OSAS patients had an AHI ≥20 events/hour and were prescribed CPAP. Five of those patients were not compliant with the CPAP treatment and withdrew from the study. The remaining 27 compliant patients were reassessed after three months of CPAP treatment. All polysomnographic data improved (Table 5). None of the values of BMI or blood pressure changed after CPAP treatment.

Table 6 shows the changes in echocardiographic data obtained before and three months after the use of CPAP treatment. The values of IVST, PWT, LVMI and DT significantly decreased and the E/A ratios significantly increased after three months of CPAP therapy. Fig. 2 shows the

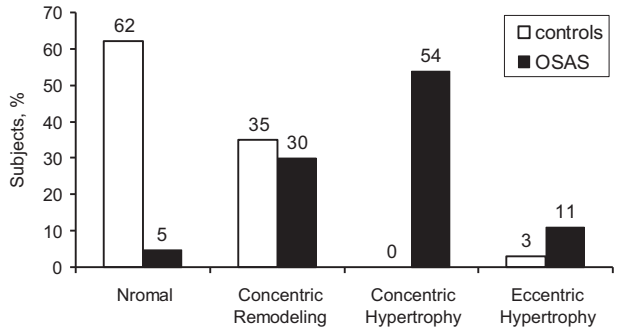

Figure 1. A comparison of the left ventricular geometric patterns in patients with obstructive sleep apnea syndrome (OSAS) and controls.

Table 3. Correlation Analysis for LVMI and RWT

	LVMI		RWT	
	r	p	r	p
AHI	0.46	0.004	0.26	0.13
Lowest oxygen saturation	-0.44	0.006	-0.31	0.61
Hypoxemia index	0.45	0.006	0.46	0.005
Age	-0.16	0.36	-0.10	0.54
BMI	0.37	0.023	0.28	0.089
SBP	0.13	0.45	-0.20	0.23
DBP	-0.07	0.69	-0.10	0.58

LVMI: left ventricular mass index, RWT: relative wall thickness, AHI: apnea-hypopnea index, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 4. Univariate and Multivariate Analysis for Concentric Hypertrophy in OSAS

	Univariate			Multivariate		
Variables	OR	95%CI	p	OR	95%CI	p
AHI	1.05	1.01-1.09	0.014	1.06	1.01-1.10	0.008
Lowest oxygen saturation	0.87	0.78-0.97	0.011			
Hypoxemia index	1.18	1.02-1.36	0.022			
BMI	1.36	1.05-1.77	0.02			

OR: odds ratio, CI: confidence interval, AHI: apnea-hypopnea index, BMI: body mass index

changes in LV geometric patterns before and after CPAP treatment. The proportion of patients with concentric hypertrophy significantly decreased from 44% to 26% (p= 0.025), whereas the proportion of patients with other patterns did not significantly change.

Discussion

The main finding of our study is that the most prevalent type of LV geometry in OSAS patients is concentric hypertrophy, which is regressed by three months of CPAP treatment.

The present study showed that LVMI correlates positively with the AHI, hypoxemia index and BMI and negatively with the lowest oxygen saturation. Avelar et al. (19) reported that severe nocturnal hypoxemia, increasing SBP and BMI are each independently associated with increased LV mass. OSAS can contribute to LV hypertrophy through increased blood pressure, increased sympathetic tone, intermittent hypoxemia and large negative intrathoracic pressure changes during periods of airway obstruction (20, 21). Obesity and hypertension often coexist in patients with OSAS and can also influence LV hypertrophy. Indeed, we found here that BMI is closely associated with the LVMI. However, we could not demonstrate the presence of a correlation between blood pressure and the LVMI. This might be due to the high percentage of patients undergoing anti-hypertension treatment (57%) with already well controlled blood pressure (SBP: 126±16 and DBP: 79±10 mmHg). Therefore, our findings cannot completely exclude the influence of hypertension on the LVMI.

In the present study, we demonstrated that the most prevalent pattern of LV geometry in OSAS patients is concentric hypertrophy. Furthermore, the multivariate logistic regression analysis showed that the AHI is an independent factor associated with the presence of concentric hypertrophy. Our results are similar to those of the study by Cioffi et al. (11) who reported that moderate to severe OSAS and higher BMIs are associated with a high prevalence of concentric hypertrophy. In contrast, Chami et al. (22) showed that the frequency of eccentric hypertrophy is higher than that of concentric hypertrophy in OSAS patients and that this prevalence increases in association with higher AHIs. These variable findings may relate to heterogeneity in the degree of obesity and hypertension and the duration of having OSAS. Obesity induces a state similar to volume overload due to increased blood circulation through a large and relatively low resistance depot of adipose tissue (19). The increased blood volume results in an elevated preload in the LV, which leads to LV dilation. According to LaPlace's law, LV dilation increases ventricular wall stress and therefore afterload (23). The LV adapts to this burden by increasing its muscle mass, causing the myocardial wall to thicken. The increase in myocardial mass remains proportional to chamber dilatation. Therefore, LV adaptation to obesity is associated with eccentric hypertrophy. Meanwhile, the predomi-

Table 5. Patient Data before and 3 Months after Treatment with CPAP

	Baseline	After CPAP	p
Polysomnographic data			
AHI (events/hour)	41.8 ± 19.8	5.7 ± 6.3	<0.001
Lowest oxygen saturation (%)	77.9 ± 7.7	89.4 ± 5.7	<0.001
Hypoxemia index (%)	10.2 ± 14.6	0.5 ± 1.2	0.004
BMI (kg/m^2)	28.6 ± 4.5	27.9 ± 4.2	0.11
SBP (mmHg)	126.6 ± 14.9	128.1 ± 16.5	0.56
DBP (mmHg)	79.1 ± 10.7	78.1 ± 8.4	0.60

CPAP: continuous positive airway pressure, BMI: body mass index, AHI: apnea-hypopnea index, SBP: systolic blood pressure, DBP: diastolic blood pressure

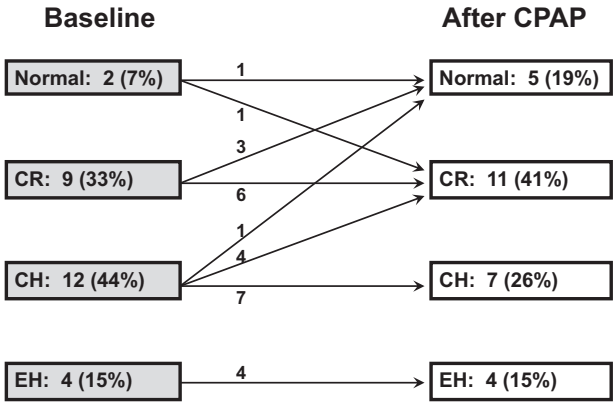

Figure 2. Changes in the left ventricular geometric patterns at baseline and three months after nasal continuous positive airway pressure (CPAP) treatment in patients with obstructive sleep apnea syndrome (n = 27). The data are expressed as numbers and percentages. CR: concentric remodeling, CH: concentric hypertrophy, EH: eccentric hypertrophy

nance of concentric hypertrophy suggests the presence of sympathetic activation and elevated blood pressure (23), especially during night-time/sleep (18). Elevated night-time/sleep blood pressure is a feature of OSAS. In addition, the duration of OSAS may be also a confounding factor influencing LV geometry. These complex situations might therefore alter the LV geometry in patients with OSAS.

The second important finding of the present study is that LVMI and the proportion of patients having concentric hypertrophy significantly decreased after three months of CPAP treatment. The effects of CPAP on LV hypertrophy are controversial. Neither Arias et al. (24) nor Moro et al. (25) found any significant changes in LVMI after three or six months of CPAP therapy, whereas Cloward et al. (9) and Shivalkar et al. (14) identified significantly reduced IVST values after six months of CPAP therapy. In general, LV hypertrophy can regress due to decreases in blood pressure brought about by appropriate anti-hypertension medication and decreases in BMI (26, 27). In the present study, since the levels of blood pressure and BMI remained unchanged before and after CPAP treatment, we assume that these conditions do not induce changes in LVMI or LV geometry. Although we did not have any data on the duration of hypertension and/or anti-hypertensive medication use, the medications were not altered during this study period. Therefore, a long-term effect of anti-hypertensive medications on regression of LVMI cannot be excluded completely; however, we believe that this effect is small. Alternatively, the observed improvements might have been caused by the CPAP treatment itself. CPAP abolishes apneic and/or hypopneic episodes, maintains normal oxygenation, corrects sympathetic activity and reduces both pre-load and after-load in the LV, which might result in the regression of LVMI and concentric hypertrophy. Our data are somewhat unique in that changes in echocardiographic parameters were seen within a very short term of three months. This is earlier than that reported by others (5, 9, 14) and might be explained by the lower severity of OSAS, obesity, hypertension and LV hypertrophy in the present study compared with other studies.

Table 6. Changes of Echocardiographic Data before and 3 Months after Treatment with CPAP

	Baseline	After CPAP	p
IVST (mm)	11.7 ± 1.3	11.0 ± 1.3	0.001
PWT (mm)	11.6 ± 1.1	10.8 ± 1.3	<0.001
LVMI (g/m$^{2.7}$)	51.9 ± 13.8	48.4 ± 12.9	0.025
RWT	0.50 ± 0.07	0.48 ± 0.10	0.42
LVDd (mm)	47.4 ± 5.7	48.2 ± 5.7	0.31
LVDs (mm)	29.6 ± 4.1	29.9 ± 4.2	0.51
LAD (mm)	36.3 ± 4.6	34.9 ± 5.3	0.15
LVEF	0.67 ± 0.04	0.68 ± 0.04	0.87
E velocity (m/s)	0.60 ± 0.16	0.61 ± 0.14	0.83
A velocity (m/s)	0.62 ± 0.12	0.58 ± 0.11	0.11
E/A ratio	0.99 ± 0.27	1.07 ± 0.27	0.033
DT (ms)	205.2 ± 33.9	191.9 ± 29.0	<0.001

CPAP: continuous positive airway pressure, IVST: interventricular septum thickness, PWT: posterior wall thickness, LVMI: left ventricular mass index, RWT: relative wall thickness, LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, LAD: left atrial diameter, LVEF: left ventricular ejection fraction, DT: deceleration time

There are several limitations associated with our study. First, this study was small, non-randomized and did not include BMI- and blood pressure-matched control patients. Second, since the controls did not undergo polysomnography, some might have had subclinical OSAS or other sleep-disordered breathing patterns. However, all of the controls scored 0 on the Epworth sleepiness scale. Therefore, patients with at least moderate to severe OSAS were excluded. Third, the levels of serum and urinary catecholamines and blood pressure during sleep using ambulatory blood pressure monitoring were not measured. Therefore, the effects of nocturnal changes on sympathetic nervous system activity remain unknown. Fourth, we did not measure the level of brain natriuretic peptide as an objective marker of LV overload. Fifth, because all of the patients were men, the results cannot be applied to women. Sixth, the echocardiographic recordings and measurements were obtained by one cardi-

ologist, which might have biased the echocardiographic data. Finally, echocardiographic data should have also been obtained during three months in untreated OSAS patients to compare untreated OSAS patients with OSAS patients treated with CPAP. However, it is difficult not to treat moderate to severe OSAS patients for long periods due to ethical considerations.

In conclusion, in our limited study population, the patients with OSAS exhibited a high prevalence of concentric LV hypertrophy, and the AHI was found to be an independent factor associated with the presence of concentric LV hypertrophy. The prevalence of concentric LV hypertrophy decreased following three months of CPAP treatment.

The authors state that they have no Conflict of Interest (COI).

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