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Oral-appliance therapy obstructive sleep apnea-hypopnea syndrome

Hoekema, Aarnoud

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Chapter 4.3

Left ventricular structure and function and natriuretic peptides in obstructive sleep apnea-hypopnea: effects of oral appliances and continuous positive airway pressure

This chapter is based on the following publication:

* Hoekema A, Voors AA, Wijkstra PJ, Stegenga B, van der Hoeven JH, Tol CG, de Bont LGM. Left ventricular structure and function and natriuretic peptides in obstructive sleep apnea-hypopnea: effects of oral appliances and continuous positive airway pressure (submitted for publication).

Summary

Background In patients without cardiovascular disease, the obstructive sleep apnea-hypopnea syndrome (OSAHS) is associated with an increased incidence of both systolic and diastolic cardiac dysfunction and left ventricular hypertrophy. Continuous positive airway pressure (CPAP) therapy has been shown to improve left ventricular structure and function and natriuretic peptides. The effects of oral-appliance therapy on cardiac function are largely unknown. The aims of this study were to determine the left ventricular structure and function and natriuretic peptides in untreated OSAHS patients without cardiovascular disease, and to compare the effects of oral-appliance with CPAP therapy.

Methods In 28 moderate to severe OSAHS patients echocardiography and measurements of concentrations of the amino-terminal fragment of pro-brain natriuretic peptide (NT-pro-BNP) were performed. Fifteen patients were randomized to oral-appliance and 13 to CPAP therapy. After two to three months of treatment, echocardiography and NT-pro-BNP measurements were repeated.

Results Of the 28 patients, seven had left ventricular hypertrophy, six had left ventricular dilatation, and three had elevated NT-pro-BNP values. No significant improvements in echocardiographic outcomes were observed. The NT-pro-BNP values improved significantly following oral-appliance therapy (median: baseline 52 pg/ml versus follow-up review 22 pg/ml) whereas values did not improve significantly following CPAP therapy (median: 31 pg/ml versus follow-up review 37 pg/ml).

Conclusions This study demonstrates that 50% of patients with moderate to severe OSAHS, without cardiovascular disease, have left ventricular hypertrophy, left ventricular dilatation or elevated natriuretic peptides. Significant changes in the NT-pro-BNP values indicate an improvement of cardiac function as a result of effective oral-appliance therapy.

Introduction

The obstructive sleep apnea-hypopnea syndrome (OSAHS) is a prevalent sleep-related breathing disorder characterized by disruptive snoring and repetitive upper airway collapse.¹ Cardiovascular sequelae of OSAHS include hypertension and an increased risk of ischemic heart disease, congestive heart failure and stroke.^{2,3} Especially in patients with severe OSAHS there is a higher risk of fatal and non-fatal cardiovascular events.⁴ In patients without cardiovascular disease OSAHS is associated with an increased incidence of both systolic and diastolic dysfunction and left ventricular hypertrophy.⁵⁻¹⁰

Continuous positive airway pressure (CPAP) prevents upper airway collapse during sleep, and is currently regarded as the treatment of choice.¹ The effectiveness of CPAP in improving hypertension has been demonstrated.¹¹ More circumstantial evidence suggests favorable effects of CPAP on myocardial ischemia¹² and congestive heart failure.² It has also been shown that CPAP therapy improves left ventricular structure and function in OSAHS patients without cardiac disease.⁶⁻⁹ In addition, natriuretic peptides, which are believed to reflect left ventricular wall stress,¹³ improved following successful CPAP therapy.¹⁴ Although CPAP is usually very effective, treatment may be compromised by poor compliance.¹⁵

Over the past decade, oral-appliance therapy has emerged as an increasingly popular alternative for CPAP. An oral appliance aims at relieving upper airway collapse during sleep by modifying the position of the mandible, the tongue and pharyngeal structures. Current research clearly shows that oral appliances are beneficial for the treatment of OSAHS.^{16,17} In addition, two randomized trials have demonstrated favorable effects of oral-appliance therapy on blood pressure when compared with control and CPAP therapy.^{17,18} However, the effects of oral-appliance therapy on cardiac function are largely unknown.¹⁶

The increased incidence of systolic and diastolic dysfunction and left ventricular hypertrophy in OSAHS patients is an important risk factor for developing cardiovascular disease. The aims of this study were to determine the left ventricular structure and function and natriuretic peptides in untreated OSASH patients without cardiovascular disease, and to compare the effects of oral-appliance with CPAP therapy.

Methods

Patient selection

A group of 51 patients over age 20 who were diagnosed with moderate to severe OSAHS (apnea-hypopnea index [AHI] >20) were screened for inclusion in the

present study.¹⁹ All patients were recruited via the Department of Home Mechanical Ventilation of the University Medical Center Groningen (The Netherlands) in the period of June 2004 to April 2005. The study population was part of a larger group of patients that was recruited for a randomized trial comparing the effects of oral-appliance and CPAP therapy. In contrast to the present study, this group also included OSAHS patients with an AHI ≤ 20 .

To screen for any underlying disease all eligible patients were subjected to a comprehensive physical evaluation, spirometry, thoracic radiography, electrocardiography and blood testing. Patients were excluded in case of previous treatment of OSAHS (one patient uvulopalatopharyngoplasty, two patients CPAP), morphological airway abnormalities (one patient adenotonsillar hypertrophy, one patient upper airway malignancy), endocrine dysfunction, a reported or documented history of severe pulmonary disease (four patients daytime respiratory insufficiency), a reported or documented history of cardiovascular disease (one patient congestive heart failure, one patient severe mitral valve insufficiency), moderate or severe periodic limb movement disorder or a psychological condition precluding informed consent. Also excluded were patients with a dental status that could complicate oral-appliance therapy (three patients had an insufficient number of teeth, three patients had extensive periodontal disease or dental decay).²⁰ Because six of the remaining 34 patients refused participation, 28 patients could eventually be enrolled. The randomized trial was approved by the Groningen University Medical Center's ethics committee (METc 2002/032). Written informed consent was obtained from patients before enrollment.

Study design

Of the 28 patients, 15 were allocated to oral-appliance therapy and 13 to CPAP therapy by means of block randomization.²¹ It was not possible to blind the patients or clinicians to treatment assignment. At baseline the following measurements were performed in all patients: echocardiography, concentration of the amino-terminal fragment of pro-brain natriuretic peptide (NT-pro-BNP), and the Epworth sleepiness scale.²²

The oral appliance used in this study (Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) positioned the patient's mandible in a forward and downward position. By turning a propulsion screw incorporated anteriorly in the appliance, patients could adjust mandibular advancement in 0.2-mm increments. When commencing oral-appliance therapy the mandible was set at approximately 50% of the patient's maximum advancement capacity. After having accustomed to this protrusive position during a two-week period, patients were allowed to further adjust their appliance during a six-week period. To do so, patients were instructed to advance the mandible each night with one to two

increments (*i.e.*, 0.2 to 0.4 mm) whenever OSAHS-symptomatology persisted (*e.g.*, snoring, apneas, hypopneas, or excessive sleepiness). This “titration” of the appliance was continued until symptoms abated or until further advancement caused discomfort.

CPAP-titration was performed during an afternoon nap. This technique, aimed at abolishing: all signs of apneas, hypopneas, and snoring—has been shown an appropriate procedure for the effective titration of CPAP.²³ Following titration an eight-week follow-up period was arranged that allowed for habituation and, if necessary, adjustments of CPAP therapy.

After patients had used an oral appliance or CPAP for eight weeks, the treatment effect was assessed with a second polysomnographic study. For patients whose AHI was still ≥ 5 , treatment was adjusted, if possible, to improve effectiveness. For this purpose oral appliance treated patients were instructed to maximally protrude their mandible with the appliance. In CPAP treated patients, the pressure was raised with 1 or 2 cm H₂O (depending on the severity of residual OSAHS with CPAP). In these patients, the follow-up period was extended with another four weeks. The effect was then assessed with a third polysomnographic study. This adjustment sequence was continued until the AHI was < 5 or until the adjustments became uncomfortable for the patient. Follow-up review ended with a patient’s final polysomnographic evaluation. At their final follow-up review the echocardiography, NT-pro-BNP measurement and the Epworth sleepiness scale were repeated. In addition, treatment usage was evaluated at this stage by asking patients how many nights per week and how many hours per night they used their treatment.

Treatment was considered effective when the AHI either was < 5 or showed “substantial reduction”,¹⁶ defined as reduction in the index of at least 50% from the baseline value to a value of < 20 in a patient who had no symptoms while using therapy. Patients not meeting these criteria at their final review were considered “nonresponsive” to treatment.

Polysomnography

Polysomnography (Embla® A10 digital recorder, Medcare, Reykjavik, Iceland) for baseline and follow-up evaluations was conducted ambulatory in the patient’s home situation. Each study started 11 AM and stopped 9 AM the next morning. Outcomes were limited to the time in bed part of the study. Standardized criteria were used to score apneas and hypopneas,¹⁹ arousals,²⁴ sleep stages²⁵ and periodic limb movements.²⁶ All polysomnographic studies were evaluated and scored by one neurophysiologist (J.H. van der Hoeven) who was unaware of the patient’s treatment assignment.

Echocardiography

Echocardiography was performed using conventional equipment (Vingmed System Five, Sonotron, Horten, Norway). Measurements of left ventricular posterior wall diastolic thickness (LVPW), diastolic interventricular septal thickness (LVIVS), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were obtained from a standard parasternal long axis view. Mean values of three recordings were used. To estimate the left ventricular mass the formula of Devereux and Reichek was used: left ventricular mass (gr) = $1.04 \times ([LVEDD + LVIVS + LVPW]^3 - LVEDD^3) - 13.6$.²⁷ Left ventricular mass was divided by body surface area to calculate left ventricular mass index (LVMI). Left ventricular ejection fraction (LVEF) was calculated according to a modification of Simpson's method.²⁸ All echocardiographs were evaluated by one cardiologist (A.A. Voors) who was unaware of the patient's treatment assignment.

Left ventricular structure and function were determined according to three separate parameters. First, left ventricular hypertrophy was defined by a LVPW or LVIVS ≥ 12 mm, or an LVMI ≥ 110 gr/m² for women or ≥ 134 gr/m² for men.²⁹ Secondly, left ventricular dilatation was defined by a LVEDD ≥ 55 mm or a LVESD ≥ 40 mm.^{30,31} Thirdly, left ventricular systolic dysfunction was defined by a LVEF $< 50\%$.

NT-pro-BNP measurements

Measurements of concentrations NT-pro-BNP were determined from venous blood samples that were drawn after an overnight fast between 8 and 10 AM. During sampling patients remained in a sitting position. No exercise was allowed half an hour before sampling. Samples were collected in a 5-ml tube containing ethylene-diamine-tetra-acetate (1 mg/ml). NT-pro-BNP was measured with use of a commercially available immunoassay based on the sandwich technique (Elecsys proBNP, Roche Diagnostics, Almere, The Netherlands). The lower limit of detection was 5 pg/ml.

NT-pro-BNP values were compared with the age and gender specific upper reference values as reported by Galasko et al.³² In subjects < 60 years these values are 100 and 164 pg/ml for males and females, respectively. In subjects ≥ 60 years, these values are 172 and 225 pg/ml for males and females, respectively. If the NT-pro-BNP exceeded these reference values patients were considered to have functional cardiac impairment.

Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 12.0, SPSS Inc, Chicago, IL, USA). Means and standard deviations, or medians and interquartile ranges in skewed distributions, are reported. At baseline, the number of patients with left ventricular hypertrophy, left ventricular

TABLE 1. Baseline characteristics of OSAHS patients.

Variable	OSAHS patients* (n = 28)
Male / female ratio	25 / 3
Age (years)	50 ± 10
Body-mass index (kg/m ²)	33 ± 5
AHI (no/hour)	52 ± 24
minSaO ₂ (%)	75 ± 8
Epworth sleepiness scale	14 ± 5
Blood pressure (mm Hg): - systolic	149 ± 19
- diastolic	93 ± 9
Antihypertensive medication (no. patients)	17
- Angiotensin-receptor-blockers	2
- Beta-blockers	8
- angiotensin converting enzyme-inhibitor	10
- Calcium-antagonist	7
- Diuretics	2
Hypertension (no. patients)†	26

* Plus-minus values are means ± standard deviations.

† Hypertension was defined as either the use of antihypertensive medication or a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg.³³

Abbreviations: AHI = apnea-hypopnea index, minSaO₂ = lowest oxyhemoglobin saturation during sleep, OSAHS = obstructive sleep apnea-hypopnea syndrome.

dilatation, left ventricular systolic dysfunction, or elevated NT-pro-BNP values was determined. To examine the effects of oral-appliance and CPAP therapy changes in the echocardiographic outcomes and NT-pro-BNP values were evaluated. Differences between baseline and follow-up variables were compared with paired Student's t-tests (Wilcoxon's signed ranks tests for variables with skewed distributions). To compare outcomes between the two groups independent sample t-tests were used (Mann-Whitney U tests for variables with skewed distributions). A significance level of $p < 0.05$ was predefined in all cases.

Results

Baseline outcomes

Most of the 28 patients included were middle-aged, moderately obese men with severe OSAHS (Table 1). The Epworth sleepiness scale indicated moderate

TABLE 2. Baseline left ventricular structure and function and NT-pro-BNP values of OSAHS patients.

Variable	OSAHS patients	
	n	outcome*
LVPW (mm)	n = 25	9.7 ± 1.4
LVIVS (mm)	n = 25	10.1 ± 1.7
LVESD (mm)	n = 26	49 ± 5
LVESD (mm)	n = 25	31 ± 5
LVMI (gr/m ²)	n = 25	95 ± 27
LVEF (%)	n = 21	58 ± 3
NT-pro-BNP (pg/ml)	n = 24	40 (17–60)

* Plus-minus values are means ± standard deviations, values with additives in parentheses are medians with interquartile ranges.

Abbreviations: LVESD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, LVIVS = diastolic interventricular septal thickness, LVMI = left ventricular mass index, LVPW = left ventricular posterior wall diastolic thickness, NT-pro-BNP = amino-terminal fragment of pro-brain natriuretic peptide, OSAHS = obstructive sleep apnea-hypopnea syndrome.

excessive daytime sleepiness in most of the patients included. In patients both mean systolic and diastolic blood pressures were elevated, and 26 subjects were classified as hypertensive.³³

Echocardiography was technically challenging in the obese subjects, and complete baseline measurements were only possible in 20 patients (Table 2). Left ventricular wall thickness could be assessed in 25 patients of whom seven were classified as having left ventricular hypertrophy. Left ventricular diameters could be assessed in 25 patients of whom six were classified as having left ventricular dilatation. LVEF values were available in 21 patients. Left ventricular systolic dysfunction was observed in none of these patients. NT-pro-BNP values were obtained in 24 patients. NT-pro-BNP values were elevated in three patients (*i.e.*, 104, 108 and 444 pg/ml). One patient with the highest NT-pro-BNP values had been successfully treated for atrial fibrillation. Of the 28 patients included, left ventricular structure was abnormal in 11 patients and another three patients were considered to have functional cardiac impairment according to their NT-pro-BNP values.

Effects of oral-appliance and CPAP therapy

Of the 15 patients that were allocated to oral-appliance therapy, two patients were lost to follow-up review. Another patient discontinued treatment due to discomfort of the oral appliance. Therefore, follow-up outcomes were available in 12 and 13 patients in the oral-appliance and CPAP group, respectively. At final follow-up

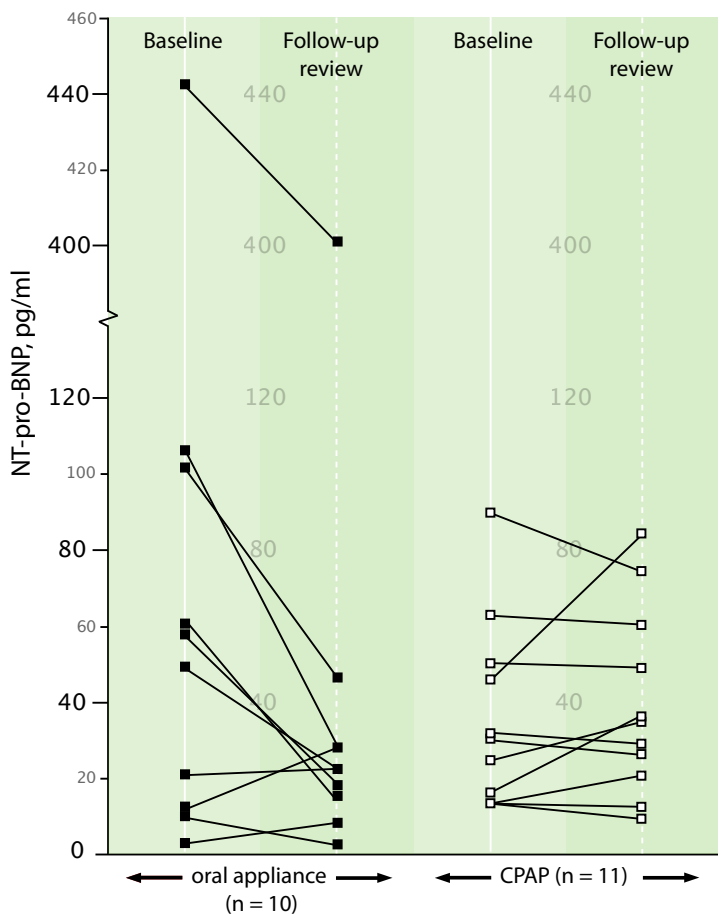


FIGURE 1. Individual values of the concentration NT-pro-BNP of OSAHS patients treated with an oral appliance and CPAP.

NT-pro-BNP values are reported at baseline and at follow-up review after treatment with oral appliance or CPAP therapy. The median period to final follow-up review was 69 (interquartile range 69–82) days in the oral-appliance group and 69 (interquartile range 64–83) days in the CPAP group ($p>0.05$).

Abbreviations: CPAP = continuous positive airway pressure, NT-pro-BNP = amino-terminal fragment of pro-brain natriuretic peptide, OSAHS = obstructive sleep apnea-hypopnea syndrome.

review, the mean advancement of the mandible with the oral appliance was $82 \pm 21\%$ of the maximum advancement. The mean CPAP pressure was 8.8 ± 1.9 cm H₂O at final review. The median period to final review was 69 (interquartile range 69–82) days in the oral-appliance group and 69 (interquartile range 64–83) days in the CPAP group ($p>0.05$).

TABLE 3. Changes in baseline characteristics and treatment usage of OSAHS patients treated with an oral appliance and CPAP.

Variable	Oral appliance* (n = 12)	CPAP* (n = 13)	Difference†
Body-mass index (kg/m ²)			
- baseline	32 ± 6	34 ± 5	NS
- follow-up review‡	32 ± 6	34 ± 5	NS
- Δ	0 ± 1	0 ± 1	NS
Epworth sleepiness scale			
- baseline	13 (9-17)	14 (12-18)	NS
- follow-up review‡	5 (2-9)	5 (3-10)	NS
- Δ	-7 (-9--3)**	-7 (-11--4)‡	NS
AHI (no./hour)			
- baseline	32 (24-37)	55 (51-74)	p=0.005
- follow-up review‡	2 (1-10)	2 (0-6)	NS
- Δ	-23 (-35--20)¶	-54 (-68--45)	p=0.002
minSaO ₂ (%)			
- baseline	77 ± 8	72 ± 8	NS
- follow-up review‡	89 ± 5	89 ± 4	NS
- Δ	12 ± 9	17 ± 7§	NS
Treatment usage			
- treatment use: nights per week	6.9 ± 0.4	6.9 ± 0.3	NS
- treatment use: hours per night	6.8 ± 1.3	7.0 ± 0.7	NS

* Plus-minus values are means ± standard deviations, values with additives in parentheses are medians with interquartile ranges.

† Significance for the difference in baseline, follow-up review or Δ outcomes between treatment groups.

‡ The median period to final follow-up review was 69 (interquartile range 69-82) days in the oral-appliance group and 69 (interquartile range 64-83) days in the CPAP group (p>0.05).

§ p=0.000 for difference between baseline and follow-up outcomes within treatment group.

|| p=0.001 for difference between baseline and follow-up outcomes within treatment group.

¶ p=0.002 for difference between baseline and follow-up outcomes within treatment group.

p=0.003 for difference between baseline and follow-up outcomes within treatment group.

** p=0.005 for difference between baseline and follow-up outcomes within treatment group.

Abbreviations: AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, NS = not significant, minSaO₂ = lowest oxyhemoglobin saturation during sleep, OSAHS = obstructive sleep apnea-hypopnea syndrome.

Treatment was effective in all patients completing the final follow-up review. Following treatment, both groups showed significant improvements in the Epworth sleepiness scale, AHI and lowest oxyhemoglobin saturation during sleep (minSaO₂) (Table 3). No significant differences were seen between the groups at baseline and final review, except for the AHI. Patients in the CPAP group had significantly higher AHI values at baseline. Although changes in the AHI were more pronounced with

CPAP, no significant differences were observed between both groups at final review. There were no significant differences between the treatment modalities with regard to treatment usage (Table 3). In addition, only one patient in both the oral-appliance and CPAP group reported using treatment less than seven nights per week, and one patient reported using the oral appliance less than five hours per night.

Echocardiography yielded complete baseline and follow-up measurements in 16 patients (eight patients in both groups). No significant changes in the echocardiographic outcomes were observed. In addition, no significant differences in the baseline and follow-up outcomes were noted between the groups (Table 4). Baseline and follow-up measurements of NT-pro-BNP were obtained in ten and 11 patients in the oral-appliance and CPAP group, respectively. In the oral-appliance group, the median NT-pro-BNP values decreased significantly following treatment. In the CPAP group, the median NT-pro-BNP values increased following treatment. Changes in NT-pro-BNP values were more pronounced with oral-appliance therapy when compared with CPAP (Table 4). The differences in NT-pro-BNP remained significant for the oral-appliance group after excluding one outlier (patient with NT-pro-BNP of 444 pg/ml at baseline). In two patients in the oral-appliance group with elevated baseline NT-pro-BNP values, normalization was observed at final review (Figure 1).

Discussion

This study demonstrates that 50% of the patients with moderate to severe OSASH, without known cardiovascular disease, display left ventricular hypertrophy, left ventricular dilatation or elevated NT-pro-BNP values. We could not establish significant improvements in any of the echocardiographic outcomes as a result of oral-appliance or CPAP therapy. However, significant changes in the NT-pro-BNP values indicate an improvement of cardiac function as a result of effective oral-appliance therapy.

Left ventricular hypertrophy was seen in seven of 25 OSAHS patients in whom left ventricular wall thickness could be determined. Patients with left ventricular hypertrophy have an increased risk of developing a variety of cardiovascular sequelae, including angina pectoris, myocardial infarction, stroke, heart failure, and sudden death.³⁴ The prevalence of left ventricular hypertrophy on echocardiography in the general population is reported variably and may range from 14 to 15% for men and from 9 to 20% for women.^{35,36} These numbers suggest an increased prevalence of left ventricular hypertrophy in the OSAHS patients in our study. This is confirmed by other studies that also demonstrated an increased prevalence of left ventricular hypertrophy, and increased left ventricular mass and wall thickness in severe OSAHS patients without cardiac disease.^{8,10} Hypertension and obesity are

TABLE 4. Left ventricular structure and function and NT-pro-BNP values of OSAHS patients treated with an oral appliance and CPAP.

Variable	n	Oral appliance*	n	CPAP*	Difference†
LVPW (mm)	n = 8		n = 11		
- baseline		9.1 ± 1.6		10.5 ± 1.0	NS
- follow-up review‡		10.1 ± 0.8		10.5 ± 1.9	NS
- Δ		1.0 ± 1.2		0.0 ± 1.1	NS
LVIVS (mm)	n = 8		n = 11		
- baseline		9.8 ± 1.3		10.7 ± 1.6	NS
- follow-up review‡		9.9 ± 1.0		11.1 ± 2.0	NS
- Δ		0.1 ± 0.6		0.4 ± 1.4	NS
LVEDD (mm)	n = 9		n = 11		
- baseline		49 ± 3		48 ± 6	NS
- follow-up review‡		48 ± 5		48 ± 4	NS
- Δ		-1 ± 3		-1 ± 5	NS
LVESD (mm)	n = 9		n = 11		
- baseline		31 ± 5		28 ± 4	NS
- follow-up review‡		30 ± 5		29 ± 6	NS
- Δ		-1 ± 5		1 ± 7	NS
LVMl (gr/m ²)	n = 8		n = 11		
- baseline		90 ± 22		97 ± 29	NS
- follow-up review‡		91 ± 19		98 ± 29	NS
- Δ		2 ± 15		2 ± 19	NS
LVEF (%)	n = 10		n = 9		
- baseline		57 ± 4		59 ± 2	NS
- follow-up review‡		61 ± 5		60 ± 1	NS
- Δ		4 ± 6		1 ± 2	NS
NT-pro-BNP (pg/ml)	n = 10		n = 11		
- baseline		52 (13-105)		31 (17-53)	NS
- follow-up review‡		22 (15-33)		37 (21-61)	NS
- Δ		-32 (-46-3) [§]		-2 (-6-11)	p=0.035

* Plus-minus values are means ± standard deviations, values with additives in parentheses are medians with interquartile ranges.

† Significance for the difference in baseline, follow-up review or Δ outcomes between groups.

‡ The median period to final follow-up review was 69 (interquartile range 69-82) days in the oral-appliance group and 69 (interquartile range 64-83) days in the CPAP group (p>0.05).

§ p=0.037 for difference between baseline and follow-up outcomes within treatment group.

Abbreviations: CPAP = continuous positive airway pressure, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, LVIVS = diastolic interventricular septal thickness, LVMl = left ventricular mass index, LVPW = left ventricular posterior wall diastolic thickness, NS = not significant, NT-pro-BNP = amino-terminal fragment of pro-brain natriuretic peptide, OSAHS = obstructive sleep apnea-hypopnea syndrome.

well known determinants for left ventricular hypertrophy.^{6,8,34} Our study population in general included moderately obese men with hypertension. However, in OSAHS patients the consequences of upper airway collapse, including an increased transmural pressure, hypoxemia and increased sympathetic activity, have also been implicated in the development of left ventricular hypertrophy.⁸ Because we did not recruit a matched control group without OSAHS, we cannot conclude whether the high prevalence of left ventricular hypertrophy is pathognomonic for OSAHS or represents the sequelae of obesity and hypertension.

Left ventricular dilatation was observed in six of the 25 OSAHS patients in whom left ventricular diameters could be determined. Left ventricular dilatation is considered a risk factor for the development of congestive heart failure and cardiovascular disease events.^{37,38} When comparing OSAHS patients and control subjects, the prevalence of left ventricular dilatation has been reported at least 17% and 18%, respectively.⁵ Moreover, left ventricular diameters are generally similar when comparing OSAHS patients with mild, moderate and severe disease.¹⁰ Although we found left ventricular dilatation in a substantial proportion of our patients, this condition does not appear pathognomonic for OSAHS. Our results also indicate normal left ventricular systolic function in untreated OSAHS patients. Some studies have suggested these patients seem to develop left ventricular systolic dysfunction.⁷ However, the results from the present study are in keeping with other reports that have demonstrated normal LVEF values in OSAHS patients without cardiovascular disease.^{6,8}

Three patients in our study sample had elevated NT-pro-BNP values at baseline.³² In one patient, with the highest values, the elevated NT-pro-BNP could be explained by the presence of atrial fibrillation this patient had been treated for. Although baseline NT-pro-BNP values were within the normal range in most of our patients, significant improvements were seen following oral-appliance therapy. The small improvements in NT-pro-BNP values indicate a decrease in left ventricular wall stress that may have resulted from an improvement in left ventricular systolic or diastolic function.¹³ This suggestion is supported by the fact that we did observe a small and non-significant improvement in left ventricular systolic function with oral-appliance therapy. It has been suggested that brain natriuretic peptides values reflect functional cardiac impairment better than the LVEF.³⁹ This may explain why the reduction NT-pro-BNP values were not accompanied by a significant improvement in the LVEF. However, at baseline the LVEF, which is an expression of systolic function, was within normal range in all our patients. Because NT-pro-BNP values reflect both the degree of systolic and diastolic function,⁴⁰ improvements in the NT-pro-BNP may also have been affected by changes in left ventricular diastolic function. CPAP therapy has been demonstrated to partially reverse left ventricular diastolic dysfunction in OSAHS patients without cardiovascular disease.⁹ This

aspect of left ventricular function was not evaluated and should be addressed in future studies.

Only few studies have evaluated the effects of OSAHS treatment on natriuretic peptides. A previous study demonstrated improvements of both atrial and brain natriuretic peptides as a result of CPAP therapy in severe OSAHS patients without heart failure.¹⁴ Another uncontrolled study has demonstrated significant improvements of brain natriuretic peptides following oral-appliance therapy in OSAHS patients with stable congestive heart failure.⁴¹ The present study is the first to evaluate the effects of oral-appliance therapy on natriuretic peptides in OSAHS patients without cardiovascular disease.¹⁶ We not only demonstrated a significant decrease of NT-pro-BNP following oral-appliance therapy, but the change in NT-pro-BNP was also significantly larger compared to CPAP therapy. This may be explained by the increased work of breathing and intrathoracic pressure associated with CPAP therapy.⁴² The latter two phenomena may have resulted in a relative increase in ventricular wall stress with CPAP therapy when compared with oral-appliance therapy. However, differences in improvements of NT-pro-BNP values should be interpreted with caution. At baseline, the AHI was significantly higher in the CPAP group whereas NT-pro-BNP values were higher in the oral-appliance group. These differences in baseline characteristics preclude any definite conclusions on the differences in effect of both treatments on cardiac function.

We could not demonstrate significant changes in echocardiographic outcomes after therapy. Previous studies have demonstrated that especially patients with abnormal LVEF values show improvements in left ventricular function following CPAP therapy.⁶⁻⁹ Left ventricular function was normal in all our patients. Moreover, an appreciable subset of our patients had normal left ventricular structure at baseline. The expectancy of normal baseline outcomes to improve would have been unrealistic in these patients. However, other factors may also account for the non-significant changes in echocardiographic outcomes. First, the follow-up period of approximately two to three months may have been too short to observe any significant improvements of, for instance, left ventricular hypertrophy. In OSAHS patients without cardiovascular disease significant changes in left ventricular structure and function are generally seen after six months of CPAP therapy.^{7,8} Secondly, the echocardiographic “abnormalities” may be attributed to other factors than OSAHS (e.g., left ventricular hypertrophy in obese OSAHS patients). Finally, we studied the effects of oral-appliance and CPAP therapy in a relative small population. Our study was of an explorative character and not based on a power calculation. Therefore, it is possible that a larger study sample would have yielded significant changes in some echocardiographic parameters.

From the present investigation we conclude that patients with moderate to severe OSAHS without established cardiovascular disease often have abnormal left ventricular structure and elevated natriuretic peptides. Left ventricular hypertrophy and dilatation were observed most frequently. Although we cannot draw definite conclusions whether these abnormalities are pathognomonic for OSAHS, they should be considered an ominous sign for future cardiac health. OSAHS patients without established cardiovascular disease therefore appear at risk for developing cardiovascular sequelae. Significant improvements in echocardiographic parameters of left ventricular structure and function could not be demonstrated following oral-appliance or CPAP therapy. However, the significant changes in the NT-pro-BNP values indicate an improvement of cardiac function following effective oral-appliance therapy. Additional studies with larger sample sizes and longer follow-up periods should elucidate the specific effects of oral-appliance and CPAP therapy on left ventricular structure and function.

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