

# N-terminal pro-B-type natriuretic peptide and functional capacity in patients with obstructive sleep apnea

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**Abstract** The obstructive sleep apnea syndrome (OSAS) is associated with cardiovascular abnormalities including left ventricular hypertrophy, left ventricular diastolic dysfunction, and endothelial dysfunction. The present study evaluated whether N-terminal pro-B-type natriuretic peptide (NT-proBNP) and peak oxygen consumption (peak  $\text{VO}_2$ ), both integral markers of cardiovascular function, are related to OSAS severity. In addition, we tested whether NT-proBNP levels depend on body composition in OSAS patients, similar to what has been reported in patients without OSAS. Eighty-nine patients with untreated OSAS underwent NT-proBNP measurement, dual X-ray absorpti-

ometry, and cardiopulmonary exercise testing. In a representative subgroup ( $n=32$ ), transthoracic echocardiography was performed. The severity of OSAS was classified based on apnea–hypopnea index (AHI) values as mild (AHI 5–15  $\text{h}^{-1}$ ), moderate (AHI 15–30  $\text{h}^{-1}$ ), and severe (AHI >30  $\text{h}^{-1}$ ). OSAS was mild in 19 (21%), moderate in 21 (24%), and severe in 49 (55%) patients. NT-proBNP levels did not differ among patients with mild [30 (10–57)], moderate [37 (14–55)], and severe [24 (13–49)  $\text{pg/ml}$ ;  $p=0.8$ ] OSAS and were not related to body mass index ( $r=0.07$ ;  $p=0.5$ ), percent lean body mass ( $r=-0.17$ ;  $p=0.1$ ), and percent fat mass ( $r=0.18$ ;  $p=0.1$ ). Percent predicted peak  $\text{VO}_2$  was on average normal and did not differ among patients with mild ( $115\pm 26$ ), moderate ( $112\pm 23$ ), and severe OSAS ( $106\pm 29\%$ ;  $p=0.4$ ). Body weight-indexed peak  $\text{VO}_2$  did not differ among patients with mild ( $31.9\pm 10.3$ ), moderate ( $32.1\pm 7.9$ ), and severe OSAS ( $30.0\pm 9.9 \text{ ml kg}^{-1} \text{ min}^{-1}$ ;  $p=0.6$ ) either. Lower NT-proBNP ( $\beta=-0.2$ ;  $p=0.02$ ) was independently but weakly associated with higher body weight-indexed peak  $\text{VO}_2$ . In the echocardiography subgroup, NT-proBNP was not significantly related to left ventricular mass index ( $r=0.26$ ;  $p=0.2$ ). In conclusion, NT-proBNP and peak  $\text{VO}_2$  are not related to OSAS severity, and NT-proBNP poorly reflects left ventricular hypertrophy in OSAS. The lack of a relationship between NT-proBNP and OSAS severity is not due to a significant influence of body composition on NT-proBNP. There is an association between higher NT-proBNP and lower peak  $\text{VO}_2$ , indicating that NT-proBNP is a marker of cardiorespiratory fitness in patients with OSAS. However, the association is too weak to be clinically useful.

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## Introduction

The obstructive sleep apnea syndrome (OSAS) is associated with various cardiovascular abnormalities, including increased sympathetic nerve activity [1], subclinical atherosclerosis [2], endothelial dysfunction [3], left ventricular hypertrophy [4, 5], and left ventricular diastolic dysfunction [4, 6, 7]. There is an association between OSAS and hypertension [8], and OSAS has also been recognized as a risk factor for the development and progression of heart failure [9]. These cardiovascular abnormalities appear to depend on the severity of OSAS [5, 7, 8, 10], and many of them are attenuated or reversed after treatment with continuous positive airway pressure ventilation [2, 3, 6, 11].

B-type natriuretic peptide (BNP) and the N-terminal fragment of its precursor peptide (N-terminal pro-B-type natriuretic peptide; NT-proBNP) are markers of cardiomyocyte stretch and, thereby, cardiac dysfunction. There is an association between BNP and/or NT-proBNP and left ventricular hypertrophy [12, 13], left ventricular diastolic dysfunction [14, 15], and impaired functional capacity [16–18]. Thus, BNP and NT-proBNP might be suitable biomarkers to detect subclinical cardiovascular stress induced by OSAS, and given the relationship between OSAS severity and cardiac dysfunction [5, 7, 10], BNP and NT-proBNP might be related to the presence and severity of OSAS. However, previous studies failed to identify such an association [19–22]. All these studies, however, were either comparatively small or had other limitations, including a long time interval between sleep study and hormone measurement [19] and the use of BNP instead of NT-proBNP [19, 20], the former having a much shorter half-life (20 min) than NT-proBNP (several hours) [23, 24]. Furthermore, apart from testing the association between BNP/NT-proBNP and the presence and severity of OSAS, no attempts have been made to establish the relationship between circulating BNP or NT-proBNP levels and cardiovascular abnormalities in OSAS. In particular, it is unknown whether BNP and NT-proBNP levels are related to exercise capacity, similar to what had been reported in subjects with heart failure [17, 18]. In patients not limited by pulmonary disease or musculoskeletal problems, exercise capacity is an integral measure of cardiovascular performance. Interestingly, data on exercise testing in patients with OSAS but without overt cardiovascular disease are quite sparse [25–27].

Assuming more severe cardiovascular dysfunction and thus increased myocyte stretch at rest and impaired cardiac output during exercise in patients with more severe OSAS, we hypothesized that NT-proBNP levels and peak oxygen consumption (peak  $\text{VO}_2$ ) depend on disease severity expressed as the apnea–hypopnea index (AHI) in a native OSAS population without obvious cardiac disease. Furthermore, we hypothesized that NT-proBNP and peak  $\text{VO}_2$

would also be related in OSAS patients. Finally, as a previous study revealed a relationship between NT-proBNP and body mass index and body composition [28], we evaluated whether this also applies for OSAS patients and thereby might influence the relationship between NT-proBNP levels, measures of OSAS severity, and cardiovascular performance.

## Materials and methods

### Patients and protocol

We studied 96 outpatients with a new diagnosis of OSAS established by polysomnography. Only patients with a normal electrocardiogram (sinus rhythm, absence of significant Q waves, or left-bundle-branch-block) were eligible. Patients with a history of heart failure, significant pulmonary disease, anemia, peripheral arterial occlusive disease, or other conditions limiting exercise capacity were excluded. All patients underwent measurement of NT-proBNP and serum creatinine, cardiopulmonary exercise testing with gas exchange techniques, and dual X-ray absorptiometry. Due to the relationship between NT-proBNP and renal function [29], patients with an estimated glomerular filtration rate [30]  $<30 \text{ ml/min/1.73 m}^2$  were not included in the analysis. In the last 32 consecutive patients included in the study, an echocardiogram was also performed to verify that only patients with preserved left ventricular systolic function were studied as attempted by the inclusion criteria and to test the association between NT-proBNP and left ventricular hypertrophy and measures of left ventricular diastolic dysfunction. All examinations were performed within 1 to 3 days before institution of continuous positive airway pressure ventilation. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Participants gave written informed consent, and the local ethics committee approved the study protocol.

### Polysomnography

Fully supervised polysomnography was performed in all patients using a commercially available monitoring system (Mepal, MAP Medizin-Technologie, Martinsried, Germany). Minimum time spent in the laboratory was 6 h. Sleep was measured with the three standard electroencephalographic channels. Electromyographic signals were collected for eye movements, chin activity, and leg movements. Respiration was traced with thoracic and abdominal piezoelectric bands, and air flow was measured with nasal pressure prongs. All studies were analyzed by an experienced sleep technologist supervised by a physician specialized in sleep medicine. Apnea was defined as complete ( $>80\%$ ) reduction in the

flow signal (assessed via nasal pressure prongs) lasting for  $\geq 10$  s, and hypopnea was defined as  $>50\%$  reduction in the airflow signal lasting for  $\geq 10$  s accompanied by a decrease in oxygen saturation  $>3\%$  or an arousal. The AHI was defined as the number of episodes of apnea and hypopnea per hour of sleep monitored. The diagnosis of OSAS was based on symptoms of daytime sleepiness (according to the Epworth sleepiness scale [31]) and an AHI  $\geq 5$   $\text{h}^{-1}$  [32]. The severity of OSAS was classified based on AHI values as mild (AHI 5–15  $\text{h}^{-1}$ ), moderate (AHI 16–30  $\text{h}^{-1}$ ), and severe (AHI  $>30$   $\text{h}^{-1}$ ). As additional measures of the severity of OSAS, arousal index and desaturation index were assessed.

#### Assessment of body composition

Weight was measured to the nearest 0.1 kg on a calibrated scale, and height was determined using a wall-mounted stadiometer. Body mass index was calculated as weight (in kg) divided by height to the power of two, and body surface area was calculated using the Mosteller formula [33]. Lean body mass was determined by dual X-ray absorptiometry [34] using a commercially available scanner (Lunar DPX-NT, Lunar, General Electrics Healthcare, Munich, Germany). We used the scanner-installed software package (Encore Version 6.7). The subjects were measured in light clothing. The scanner was calibrated every morning, and three times a week, a bone phantom scan was used to determine scan quality.

#### Laboratory analysis

After an overnight fast, serum samples were collected at 7:00 A.M. into EDTA tubes and stored at  $-70^\circ\text{C}$  for later analysis. NT-proBNP was measured in 2006 using a commercially available highly sensitive and specific immunoassay based on double antibody sandwich technique (Elecys proBNP, Roche Diagnostics, Basel, Switzerland) [35, 36]. The technicians involved in NT-proBNP analysis were blinded to clinical data.

#### Cardiopulmonary exercise testing

Participants underwent cardiopulmonary exercise testing on a treadmill ergometer (CS-200, Schiller, Baar, Switzerland). All tests were performed between 3:00 and 7:00 P.M. under regular medication. Before the test, the tightness of the facemask was adjusted manually to avoid leakage. To allow familiarization with the test mode, the protocol started with a warm-up period of 6 min of constant work load (speed 1.6 km/h, inclination 6%), followed by an individualized ramp protocol, which was selected according to the patient's subjective estimate of physical fitness from a set of 12 ramp protocols for exercise capacities ranging from 4 to 17 metabolic equivalents (as estimated from speed and

grade of the treadmill) to achieve a test duration of approximately 10 min (ramp portion of the test) [37]. During the tests, subjects were verbally encouraged to exercise until exhaustion. A 12-lead electrocardiogram was recorded continuously, and blood pressure (by indirect arm-cuff sphygmomanometry) was assessed every 2 min. Expired gases were acquired continuously, and oxygen consumption and carbon dioxide output ( $\text{VCO}_2$ ) were recorded in rolling 30-s averages (ErgoScope, Ganshorn, Niederlauer, Germany). Calibration of the system was performed before each test.

Functional capacity was expressed as peak  $\text{VO}_2$  (absolute, percent predicted from age, gender, and height [38], and indexed to body weight). For each test, the relation between minute ventilation (VE) and  $\text{VCO}_2$  was plotted to determine the VE/ $\text{VCO}_2$  slope. All data points from the beginning to the end of exercise were included to determine the VE/ $\text{VCO}_2$  slope [39]. To ensure appropriate effort, only subjects achieving a respiratory exchange ratio (i.e.,  $\text{VCO}_2$  divided by oxygen consumption)  $\geq 1.0$  at peak exercise were included in the analysis.

#### Echocardiography

Echocardiographic studies (Toshiba Powervision 8000, Osaka, Japan) were performed by one single operator using standard techniques [40]. Measures of left ventricular and left atrial dimensions were obtained in the parasternal long axis view. Left ventricular mass was calculated based on an anatomically validated formula [41]. All measurements were indexed to body surface area. Left ventricular hypertrophy was defined as a left ventricular muscle mass index (LVMI)  $>125$   $\text{g}/\text{m}^2$  in men and  $>110$   $\text{g}/\text{m}^2$  in women, which is the definition employed in a previous study showing a relationship between BNP and left ventricular mass index in patients with hypertension [13] to allow comparison with that study. Left ventricular ejection fraction (LVEF) was determined from the apical view by biplane calculation or visual estimation in case of a poor acoustic window. The pulse-wave Doppler sample was placed at the tips of mitral valve leaflets in the apical four-chamber view, and the ratio of the peak flow velocity in early diastole and the peak flow velocity at atrial contraction ( $E/A$  ratio) and deceleration time were determined.

#### Statistical analysis

Statistical analysis was performed using a commercially available software package (SPSS, Version 10.1, Chicago, IL, USA). Categorical data were expressed as numbers and percentages. Continuous data were expressed as the mean  $\pm$  SD or the median (interquartile range) where appropriate. The chi-square test was used to compare categorical data.

For comparison of continuous data, the unpaired *t* test or the Mann–Whitney *U* test was used as appropriate. For comparison of several groups, the chi-square test, analysis of variance (ANOVA), or the Kruskal–Wallis test was applied. Pearson's or Spearman's rank correlation coefficients were calculated to identify associations between parameters of interest.

Multiple linear regression analysis was performed to identify pretest predictors of peak  $\text{VO}_2$ . For variables with a skewed distribution, ln-transformed values were employed. Variables with a *p* value <0.1 at the univariate analysis were included in the multivariate model (forward stepwise technique). A receiver operator characteristics (ROC) curve was constructed for the ability of NT-proBNP to predict a peak  $\text{VO}_2$  <20 ml  $\text{kg}^{-1} \text{min}^{-1}$ , a widely used cut-off for an impaired exercise capacity [42], and the area under the

ROC curve was determined. A *p* value <0.05 was considered statistically significant.

## Results

### Patients

Of 96 patients undergoing cardiopulmonary exercise testing, seven were excluded because of a respiratory exchange ratio <1.0, leaving 89 patients for the present analysis. Patient characteristics are shown in Table 1.

OSAS was mild in 19 (21%), moderate in 21 (24%), and severe in 49 (55%) patients. Patients with severe OSAS were more likely to be male and had higher absolute lean body mass than those with mild and moderate OSAS. Body

**Table 1** Patient characteristics

	All	AHI 5–15 $\text{h}^{-1}$	AHI 15–30 $\text{h}^{-1}$	AHI >30 $\text{h}^{-1}$	<i>p</i> value
Number	89	19	21	49	
Age (years)	49.5±9.7	48.4±9.1	47.6±8.4	50.1±10.5	0.4
Gender (female)	11 (12%)	6 (32%)**	4 (19%)***	2 (4%)**	0.002
Body composition					
Height (cm)	173±8	171±8	173±7	175±8	0.1
Weight (kg)	91±14	85±12**	87±10	94±15**	0.02
Body mass index ( $\text{kg}/\text{m}^2$ )	30.2±4.6	29.4±5.1	29.3±4.1	30.9±4.5	0.3
Lean body mass (kg)	55.6 (51.6–60.6)	53.0 (47.0–55.2)**	53.7 (50.7–58.9)***	58.5 (54.7–63.1)***	<0.001
Lean body mass (%)	65 (59–68)	64 (56–68)	65 (58–68)	64 (60–68)	0.8
Fat mass (kg)	27.9 (23.5–35.6)	25.7 (23.1–33.3)	25.9 (22.7–34.0)	29.1 (24.3–36.2)	0.6
Fat mass (%)	33 (29–39)	33 (29–41)	32 (30–40)	34 (29–39)	0.8
Cardiovascular risk factors					
Hypertension	56 (63%)	11 (58%)	8 (38%)***	37 (76%)***	0.01
Hypercholesterolemia	73 (82%)	13 (68%)	18 (86%)	42 (86%)	0.2
Diabetes	9 (10%)	1 (5%)	1 (5%)	7 (14%)	0.4
Smoking	52 (58%)	10 (53%)	12 (57%)	30 (61%)	0.9
Medication					
ACEI or ARB	19 (21%)	2 (11%)	2 (10%)	15 (31%)	0.06
β-blockers	11 (12%)	3 (16%)	2 (10%)	6 (12%)	0.8
Diuretics	15 (17%)	2 (11%)	2 (10%)	11 (22%)	0.3
Calcium channel blockers	9 (10%)	0	2 (10%)	7 (14%)	0.2
Aspirin	8 (9%)	1 (5%)	1 (5%)	6 (12%)	0.5
Statin	15 (17%)	1 (5%)	2 (10%)	11 (22%)	0.2
OSAS severity					
Epworth sleepiness score	13 (9–15)	14 (9–17)	13 (10–15)	11 (9–15)	0.4
AHI ( $\text{h}^{-1}$ )	34 (17–53)	11 (8–12)* **	25 (18–27)* **	52 (38–74)** **	<0.001
Arousal index ( $\text{h}^{-1}$ )	44 (28–63)	23 (17–35)**	34 (28–41)***	60 (46–80)** **	<0.001
Desaturation index ( $\text{h}^{-1}$ )	15 (7–37)	5 (3–7)* **	10 (6–15)* **	36 (21–48)** **	<0.001
GFR ( $\text{ml}/\text{min}/1.73 \text{ m}^2$ )	92.9±14.1	92.0±8.6	96.3±15.5	91.7±15.2	0.5

The *p* values are given for the results of ANOVA, chi-square, or Kruskal–Wallis test, respectively.

AHI Apnea–hypopnea index, ACEI angiotensin-converting-enzyme inhibitors, ARB angiotensin-receptor blockers, OSAS obstructive sleep apnea syndrome, GFR glomerular filtration rate

\**p*<0.05 for AHI 5–15 vs AHI 15–30  $\text{h}^{-1}$  (results of post hoc testing)

\*\**p*<0.05 for AHI 5–15 vs AHI >30  $\text{h}^{-1}$  (results of post hoc testing)

\*\*\**p*<0.05 for AHI 15–30 vs AHI >30  $\text{h}^{-1}$  (results of post hoc testing)

weight was higher in patients with severe than those with mild OSAS. Patients with severe OSAS were more likely to have hypertension as compared to patients with moderate OSAS. As expected, the groups differed with respect to objective measures of OSAS severity. However, they were similar with respect to the Epworth sleepiness scale and other characteristics.

#### NT-proBNP and OSAS severity

The median NT-proBNP value was 24 (13–49) pg/ml. NT-proBNP values did not differ across different AHI categories ( $p=0.8$ ) as shown in Fig. 1. There was no significant relationship between NT-proBNP and Epworth sleepiness score ( $r=0.17$ ;  $p=0.1$ ), arousal index ( $r=0.03$ ;  $p=0.7$ ), or desaturation index ( $r=-0.05$ ;  $p=0.7$ ).

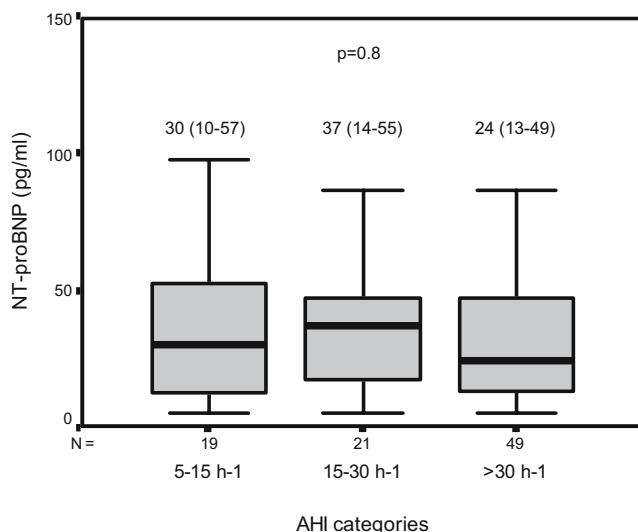
As there were significant gender differences across the AHI categories, analysis was repeated after exclusion of the 11 female subjects. However, NT-proBNP values did not differ among men with mild [18 (8–38) pg/ml], moderate [23 (14–52) pg/ml], and severe [24 (13–49) pg/ml] OSAS ( $p=0.57$ ).

#### NT-proBNP and body composition

NT-proBNP was not related to body mass index ( $r=0.07$ ;  $p=0.5$ ) nor absolute ( $r=-0.13$ ;  $p=0.2$ ) or percent lean body mass ( $r=-0.17$ ;  $p=0.1$ ) nor total ( $r=0.14$ ;  $p=0.2$ ) or percent fat mass ( $r=0.18$ ;  $p=0.1$ ).

#### Functional capacity and OSAS severity

Data from cardiopulmonary exercise testing are shown in Table 2. No patients showed an ischemic response. Patients



**Fig. 1** Boxplots showing NT-proBNP values in different AHI categories. Boxes indicate median values and interquartile ranges

with mild OSAS had higher diastolic blood pressure at rest as compared to patients with moderate OSAS, and patients with moderate OSAS had lower systolic blood pressure at peak exercise as compared to the other two AHI groups. However, peak heart rate, absolute peak  $\text{VO}_2$ , percent predicted peak  $\text{VO}_2$ , and peak  $\text{VO}_2$  indexed for body weight did not differ across the AHI categories. Among the whole study population, 11 (12%) patients had a peak  $\text{VO}_2 < 20 \text{ ml kg}^{-1} \text{ min}^{-1}$ . Values for the  $\text{VE}/\text{VCO}_2$  slope were generally very low and did not differ across the AHI categories.

If the 11 female subjects were excluded from the analysis, absolute ( $p=0.41$ ) and percent predicted ( $p=0.31$ ) peak  $\text{VO}_2$  did not differ among men with mild, moderate, and severe OSAS either. Percent predicted peak  $\text{VO}_2$  was on average normal in men with mild ( $116 \pm 26\%$ ), moderate ( $111 \pm 19\%$ ), and severe ( $105 \pm 28\%$ ) OSAS. ANOVA revealed lower body weight-indexed peak  $\text{VO}_2$  in men with more severe OSAS ( $p=0.02$ ), but body mass index was higher in more severe OSAS ( $p=0.02$ ). Further analysis by post hoc testing (Bonferroni) revealed only borderline differences with respect to body weight-indexed peak  $\text{VO}_2$  ( $p=0.055$ ) and body mass index ( $p=0.062$ ) in subjects with AHI between 5 and  $15 \text{ h}^{-1}$  and those with  $\text{AHI} > 30 \text{ h}^{-1}$ . Otherwise, no differences were obtained.

#### Exercise capacity and NT-proBNP

There was a moderate correlation between  $\ln$  NT-proBNP and peak  $\text{VO}_2$  (Fig. 2). In the univariate analysis, peak  $\text{VO}_2$  was also associated with age ( $r=-0.42$ ;  $p<0.001$ ), gender ( $r=-0.32$ ;  $p=0.02$ ), body mass index ( $r=-0.50$ ;  $p<0.001$ ), resting heart rate ( $r=-0.30$ ;  $p=0.004$ ),  $\ln$  arousal index ( $r=0.25$ ;  $p=0.02$ ), and  $\ln$  desaturation index ( $r=-0.23$ ;  $p=0.03$ ). There was no significant association between peak  $\text{VO}_2$  and  $\ln$  AHI ( $r=-0.15$ ;  $p=0.17$ ). In the multivariate model, male gender ( $\beta=0.23$ ;  $p=0.008$ ), younger age ( $\beta=-0.29$ ;  $p=0.001$ ), lower body mass index ( $\beta=-0.35$ ;  $p<0.001$ ), lower resting heart rate ( $\beta=-0.24$ ;  $p=0.004$ ), and lower NT-proBNP ( $\beta=-0.2$ ;  $p=0.02$ ) were independently associated with higher peak  $\text{VO}_2$ . However, the area under the ROC curve for the ability of NT-proBNP to predict a peak  $\text{VO}_2 < 20 \text{ ml kg}^{-1} \text{ min}^{-1}$  was only 0.55 ( $p=0.6$ ). An optimal NT-proBNP cut-off of 24 pg/ml had sensitivity of 73% and a specificity of 50% for the prediction of a peak  $\text{VO}_2 < 20 \text{ ml kg}^{-1} \text{ min}^{-1}$ .

#### Left ventricular mass and function

Patients undergoing echocardiography ( $n=32$ ) and patients not doing so ( $n=57$ ) were similar with respect to age ( $49.1 \pm 8.4$  vs  $49.8 \pm 10.5$  years;  $p=0.7$ ), body mass index ( $29.4 \pm 5.7$  vs  $30.6 \pm 3.8 \text{ kg/m}^2$ ;  $p=0.2$ ), AHI [ $32 (16-57)$  vs  $37 (24-52) \text{ h}^{-1}$ ;

**Table 2** Cardiopulmonary exercise testing results

	All	AHI 5–15 h <sup>-1</sup>	AHI 15–30 h <sup>-1</sup>	AHI >30 h <sup>-1</sup>	<i>p</i> values
Number	89	19	21	49	
Exercise time (s)	517 (463–597)	517 (459–573)	481 (447–598)	527 (467–614)	0.7
Heart rate at rest (bpm)	86±14	81±12	89±15	87±14	0.2
Peak heart rate (bpm)	160±18	161±18	164±16	157±19	0.3
Systolic BP at rest (mmHg)	136±19	139±23	130±15	138±18	0.2
Peak systolic BP (mmHg)	199±28	204±31*	183±23* **	203±26**	0.01
Diastolic BP at rest (mmHg)	89±10	92±11*	84±9*	89±10	0.03
Peak diastolic BP (mmHg)	91±15	92±16	88±10	92±16	0.6
RER at peak exercise	1.15±0.08	1.15±0.09	1.16±0.09	1.14±0.08	0.7
Peak VO <sub>2</sub> (l/min)	2.76±0.80	2.69±0.83	2.76±0.70	2.78±0.85	0.9
Percent predicted peak VO <sub>2</sub>	110±27	115±26	112±23	106±29	0.4
Peak VO <sub>2</sub> BW (ml kg <sup>-1</sup> min <sup>-1</sup> )	30.9±9.5	31.9±10.3	32.1±7.9	30.0±9.9	0.6
VE/VCO <sub>2</sub> slope	23.5±2.8	24.0±2.5	23.6±3.5	23.2±2.5	0.6

The *p* values are given for the results of ANOVA and the Kruskal–Wallis test, respectively.

AHI Apnea–hypopnea index, BP blood pressure, peak VO<sub>2</sub> peak oxygen consumption, peak VO<sub>2</sub> BW peak VO<sub>2</sub> indexed for body weight, RER respiratory exchange ratio, VE/VCO<sub>2</sub> slope relationship between minute ventilation and carbon dioxide production

\**p*<0.05 for AHI 5–15 vs AHI 15–30 h<sup>-1</sup> (results of post hoc tests)

\*\**p*<0.05 for AHI 5–15 vs AHI >30 h<sup>-1</sup> (results of post hoc tests)

*p*=0.5], and NT-proBNP [25 (14–48) vs 22 (11–61); *p*=0.70]; thus, the echocardiography subgroup was representative of the entire study population.

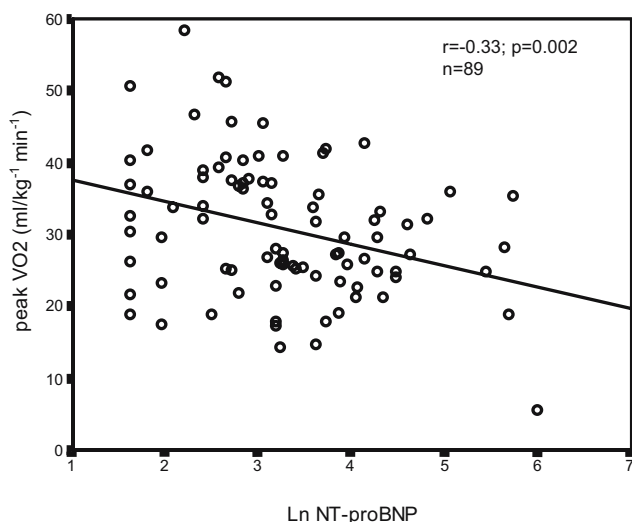
Echocardiography findings are presented in Table 3. Four (13%) patients had left ventricular hypertrophy. All patients had an LVEF ≥50%. There was a significant correlation between AHI and left ventricular posterior wall thickness. Otherwise, AHI was not related to any echocardiographic parameter. NT-proBNP was not significantly related to LVMI. If left ventricular mass was indexed as height to the power of 2.7 instead of body surface, NT-proBNP was similarly not related to LVMI. There was a

trend toward a correlation between NT-proBNP and LVEF (*p*=0.06).

## Discussion

The present study confirms previous findings in that, in OSAS patients, NT-proBNP levels were generally low and not related to disease severity as expressed by AHI. In addition, our findings suggest that this is not due to a significant influence of body composition on NT-proBNP levels. There was a statistically significant but comparatively weak independent relationship between NT-proBNP and functional capacity.

In previous studies, BNP or NT-proBNP levels measured before [20, 22, 43] or after [20–22, 44] sleep were not found to be elevated in patients with OSAS. Similarly, a recent analysis among 623 patients from the Framingham study did not find an association between AHI and BNP [19]. However, in the latter study, the median time between BNP measurement and polysomnography of 79 (27–280) days is an important limitation given that the half-life of BNP is approximately 20 min [23]. In the present examination, which to the best of our knowledge is the largest and most detailed study on NT-proBNP in OSAS, patients underwent phlebotomy in the morning after polysomnography, and the more stable NT-proBNP (half-life several hours) [24] instead of BNP was measured. Despite this, there was nevertheless no association between subjective measures of daytime sleepiness and objective measures of OSAS severity.



**Fig. 2** Scatter plot showing the relationship between NT-proBNP (ln-transformed values) and peak VO<sub>2</sub>

**Table 3** Left ventricular structure and function and relationship with AHI and NT-proBNP ( $n=32$ )

Echo parameter		Echo vs AHI		Echo vs NT-proBNP	
		<i>R</i>	<i>p</i>	<i>R</i>	<i>p</i>
Left ventricular end-diastolic diameter (mm/m <sup>2</sup> )	23.1±2.9	-0.15	0.4	0.005	1.0
Left ventricular end-systolic diameter (mm/m <sup>2</sup> )	15.3±2.8	-0.08	0.6	-0.05	0.8
Interventricular septal diameter (mm/m <sup>2</sup> )	5.8±0.9	-0.2	0.2	0.05	0.8
Left ventricular posterior wall diameter (mm/m <sup>2</sup> )	4.8±0.8	-0.47	0.007	0.25	0.2
Relative wall thickness	0.42±0.09	-0.26	0.2	0.18	0.3
Left ventricular mass (g)	173 (151–220)	0.002	1.0	0.18	0.3
Left ventricular mass index (g/m <sup>2</sup> )	85 (77–101)	-0.12	0.6	0.26	0.2
Left ventricular mass index (g/m <sup>2.7</sup> )	42.1 (33.1–50.7)	-0.09	0.6	0.17	0.3
Left ventricular ejection fraction (%)	63±5	-0.19	0.3	0.34	0.06
Left atrial size (mm/m <sup>2</sup> )	17.9±2.3	-0.12	0.5	0.14	0.4
Peak flow velocity in early diastole ( <i>E</i> ; m/s)	0.66 (0.57–0.76)	-0.3	0.1	0.05	0.8
Peak flow velocity at atrial contraction ( <i>A</i> ; m/s)	0.66 (0.54–0.78)	0.06	0.8	0.25	0.2
<i>E/A</i> ratio	0.91 (0.80–1.28)	-0.2	0.3	-0.17	0.4
Deceleration time (ms)	222 (193–259)	0.24	0.2	0.12	0.5

*R* Spearman's correlation coefficients between echocardiographic measures and AHI and NT-proBNP, respectively

In the Framingham population, the authors concluded that OSAS in their cross-sectional setting was not associated with persistent daytime left ventricular dysfunction as reflected in morning natriuretic peptide levels [19]. Although this is a possible explanation for the negative findings, one should also consider the alternative possibility that left ventricular dysfunction and other cardiovascular abnormalities were present, but were not reflected by BNP. Natriuretic peptide levels are influenced by many factors other than left ventricular wall stress, and it has not been determined whether BNP and NT-proBNP levels in OSAS patients actually reflect left ventricular wall stress and its echocardiographic surrogates. In patients with hypertension, an association between BNP and LVMI (left ventricular mass indexed to body weight) has been reported [13]. However, in the present study, the relationship between NT-proBNP and LVMI did not reach statistical significance, even when left ventricular mass was indexed to height to the power of 2.7 as suggested for obese subjects [45], nor was NT-proBNP related to measures of left ventricular diastolic dysfunction. The only association between NT-proBNP and echocardiographic measures was a trend toward a correlation with LVEF, although LVEF was preserved in all patients. Thus, NT-proBNP clearly did not accurately reflect left ventricular hypertrophy and dysfunction in our study subgroup, which was representative for the whole sample with respect to age, body mass index, AHI, and NT-proBNP.

There is evidence for a relationship between OSAS and congestive heart failure [9], and impaired exercise tolerance is a hallmark of this condition [16]. Peak VO<sub>2</sub> is closely related to cardiac output [46], which in turn depends on preload, left ventricular systolic and diastolic function, and

afterload, the latter two factors being abnormal in many OSAS patients according to previous studies [3, 4, 6, 8]. Interestingly, data on exercise capacity in OSAS patients are sparse and conflicting [25–27]. Whereas in the study by Oztürk et al. [25], peak VO<sub>2</sub> values were similar in OSAS patients and controls; Lin et al. [26] reported lower peak VO<sub>2</sub> in patients with OSAS as compared to controls. In a retrospective analysis, Guillermo et al. [27] found lower peak VO<sub>2</sub> in patients with AHI >20 h<sup>-1</sup> as compared to controls, whereas overall peak VO<sub>2</sub> did not differ among patients with OSAS and controls. In the present study among OSAS patients without obvious cardiac disease, peak VO<sub>2</sub> was overall normal without significant differences across the AHI categories. This indicates that OSAS per se—even if severe—is not necessarily associated with impaired exercise tolerance, and that any cardiovascular abnormalities—if present—must be regarded as subclinical. However, many patients had antihypertensive therapy, and blood pressure values were normal or only moderately elevated in most cases. Results might have been different if blood pressure would have been untreated. Values for the VE/VCO<sub>2</sub> slope were normal across the AHI groups, which well fits the fact that exercise capacity was normal.

Although untreated severe OSAS is associated with a higher risk of fatal and nonfatal cardiovascular events when compared to healthy people and patients with wild or moderate OSAS [47], and NT-proBNP is a predictor of major cardiovascular events and death [48], peak VO<sub>2</sub> and NT-proBNP values did not differ among the AHI subgroups, which is an unexpected finding.

In patients with heart failure, peak VO<sub>2</sub> has been found to be moderately related to BNP and NT-proBNP [17, 18], and it has even been proposed that BNP might be used to

predict low exercise capacity in these patients [17]. Interestingly, NT-proBNP was also associated with peak  $\text{VO}_2$  in the present study of OSAS patients without symptoms and signs of heart failure. However, similar to the relationship between peak  $\text{VO}_2$  and BNP in patients with mild-to-moderate chronic heart failure undergoing treadmill exercise ( $r=-0.31$ ;  $p<0.05$ ) [18], this correlation was only moderate ( $r=0.33$ ), and although interesting from a pathophysiological point of view, it might not be clinically useful.

Several recent studies revealed an inverse relationship between natriuretic peptides and body mass index [28, 49, 50], suggesting that cut-points for natriuretic peptides for the diagnosis of acute heart failure [51] and the prediction of prognosis in chronic heart failure [52] should be adjusted for body mass index. We, therefore, considered that low NT-proBNP levels in OSAS patients might be due to frequent coexisting obesity and altered body composition. However, in contrast to a previous publication [28], we did not find an association between NT-proBNP and body mass index and body composition, and thus, lack of a relationship between OSAS severity NT-proBNP levels is not due to a significant influence of body composition on NT-proBNP.

#### Limitations

Our study has several limitations. The sample size was small, and there was no control group of similarly obese patients without OSAS. A second limitation was the lack of a more systematic and detailed examination of left ventricular diastolic function. The  $E/A$  ratio and deceleration time are imperfect measures of left ventricular diastolic function due to their U-shaped relationship with the severity of left ventricular diastolic dysfunction. However, it has been previously observed that most OSAS patients without significant associated cardiac disease have a normal mitral filling pattern or impaired relaxation, and that more advanced left ventricular diastolic dysfunction (i.e., pseudonormal and restrictive patterns) is rare [6]. Given the inclusion criteria, mean deceleration time and atrial size values, this was also likely the case in our population. Accordingly, a lower  $E/A$  ratio and a longer deceleration time might have been acceptable although imperfect parameters for more impaired relaxation.

#### Conclusions

Circulating levels of NT-proBNP do not reflect OSAS severity as expressed by AHI, and this is not due to a significant influence of body composition on NT-proBNP levels. However, this does not necessarily mean that left ventricular hypertrophy and dysfunction are absent, as

indicated by the poor correlation between NT-proBNP and measures of left ventricular hypertrophy and diastolic dysfunction. A new observation is that a higher NT-proBNP level is an independent predictor of a lower peak  $\text{VO}_2$ , indicating that NT-proBNP is global marker of cardiopulmonary fitness. However, the association is too weak to be clinically useful.

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