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NT-proBNP is not elevated in patients with obstructive sleep apnoea

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Summary
Background: N-terminal pro-brain natriuretic peptide (NT-ProBNP) has emerged as an important marker of cardiac stress and may reflect the severity of underlying cardiac dysfunction, which is thought to be associated with obstructive sleep apnoea syndrome (OSAS).
Methods: This study evaluated the plasma concentration of NT-ProBNP in 60 consecutive patients (median age 55.7 years, median body mass index (BMI) 31.8) who were referred to a sleep laboratory with a suspicion of OSAS. Each subject underwent measurement of morning NT-ProBNP plasma levels, polysomnography and echocardiography. Patients were treated with nasal continuous or bilevel positive airway pressure ventilation (nCPAP/BIPAP) or without mechanical respiratory support, depending on clinical symptoms and results of polysomnography. Three months after treatment of OSAS 28 of the patients were reassessed for re-evaluation of NT-ProBNP and polysomnography.
Results: Low or high levels of NT-proBNP were not associated with AHI and other sleep related indices ($p > 0.3$). There was no correlation between NT-proBNP and AHI or other sleep related indices. In multiple regression analysis, NT-proBNP was significantly correlated with left ventricular ejection fraction, creatinine clearance and the presence of systemic arterial hypertension but not with AHI.

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Conclusions: Our results show by a robust multiple regression analysis, that NT-pro BNP is not associated with OSAS and NT-pro BNP cannot be used as a sensitive marker for underlying cardiovascular abnormalities in patients with OSAS.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common disorder with an estimated prevalence of at least 2–4% among middle aged adults.[1] There has been a growing interest in potential relationships between OSAS and brain natriuretic peptide (BNP) regulation.[2–6]

BNP is a hormone which is synthesized predominantly by myocytes of the left ventricle in response to wall distension.[7] It is synthesized as a prohormone (ProBNP) that upon secretion is cleaved into a biologically active peptide BNP and an N-terminal proBNP fragment (NT-proBNP). NT-ProBNP is preferred as a more sensitive diagnostic measure of BNP secretion, because it has a relatively long half-life and is stable in whole blood samples.[8–10]

BNP has been extensively studied in patients with cardiac disease and elevated levels have been associated with diminished left ventricular functional capacity and a poor prognosis among such patients.[11–15] OSAS is associated with coronary heart diseases, heart failure and cardiac arrhythmias. It has been suggested that OSAS causes an increased ventricular load and therefore ventricular distension during periods of apnoea.[16,17] Therefore it is tempting to propose that BNP could serve as a prognostic and risk marker in patients with OSAS.

In previous studies the role of natriuretic peptides in OSAS has been controversial.[2–6] Conclusions are difficult to make because patient groups have been too small or subclass differences were not well considered. It is known that BNP is strongly influenced by confounders like gender, creatinine clearance, age, adiposity, left ventricular function and other coexisting diseases.[18–21] According to this, we elucidated the value of NT-ProBNP in patients with OSAS considering potentially confounding variables.

Methods

Patients and study design

Patients who were referred to our sleep laboratory with excessive snoring, a suspicion of OSAS or excessive daytime somnolence were consecutively included in this study. Males or females were eligible for the study if they were >21 years old. Exclusion criteria included refusal to participate in the study, shift workers, a preceding diagnosis of OSAS, psychiatric causes of sleep disorder, central sleep apnoea or Cheyne-Stokes respiration on polysomnography (>20% events) and the use of sedatives and muscle relaxants. Altogether 60 patients with a median age of 55.7 years (inter quartile range: 43–62) and a body mass index (BMI) of 31.8 kg/m^2 (28–38) were included.

All patients referred to the sleep laboratory had current pulmonary function tests and electrocardiogram. Lung function parameters included forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). Each parameter was calculated as percent of predicted.

Each patient received a standard echocardiograph in our clinic. Echocardiographic images were obtained in the long axis, short axis, apical two-chamber, four-chamber, and subcostal views. All measurements were made under standardized resting conditions with the subjects in the supine position after a minimum rest period of 5 min in a quiet, darkened examination room. The left ventricular internal end-diastolic dimension (LVDd), left ventricular internal systolic dimension (LVDs), left ventricular posterior wall thickness (LVPWT) and interventricular septal thickness (IVST) were measured manually. End-diastole was defined by the onset of the QRS complex. Left ventricular mass (LVmass) was estimated according to the method of DEVEREUX and REICHEK[22] and LVmass was corrected for body surface area (LVmass index) in order to adjust for differences in cardiac size due to variations in body size. Left ventricular ejection fraction (LVEF) was calculated from LVDd and LVDs. The sonographer was blinded to the results of the polysomnography and NT-ProBNP levels.

Chest X-ray was performed when the patient was over 45 years old and the last chest X-ray was imaged greater than one year ago. Previously clinical variables were collected from case notes and questionnaires completed during assessments. These comprised pretreatment demographic variables (age, sex, BMI, current cigarette smoking status, history of preexisting diseases and current drug usage). Daytime systemic blood pressure was measured in the right upper arm using an automatic oscillometric device after at least 10 min periods of rest with the subjects in the seated position and the mean blood pressure was used for subsequent analyses. The epworth sleepiness scale (ESS) was used to investigate changes in subjective daytime sleepiness.[23] Blood samples for evaluation of serum NT-ProBNP and creatinine levels were taken directly after polysomnography between 6.00 a.m. and 6.30 a.m. None of the subjects reported significant strenuous physical activity within a period of 72 h before testing. All blood samples were taken following of a rest period for at least 20 min and in the supine position. The creatinine clearance was calculated using the formula derived by COCKCROFT and GAULT.[24]

All patients underwent an overnight standard polysomnography in the sleep laboratory. A second polysomnography was subsequently performed to determine the appropriate continuous or bilevel positive airway pressure (nCPAP or BIPAP) in those patients who were deemed eligible for treatment depending on clinical symptoms and result of diagnostic polysomnography. For nCPAP treatment either SOMNOcomfort (Weinmann, Hamburg, Germany) or Mini MAX (MAP, Martinsried, Germany) were used, while for BIPAP therapy only SOMNOvent S (Weinmann) was used. Thirty-six patients were treated with nCPAP, seven patients were

treated with BIPAP and one patient was offered a mandibular advancement device. Twenty-nine of these patients were readmitted after 3–4 months of treatment to our sleep laboratory for re-evaluation with polysomnography and measurement of NT-ProBNP level. Seventeen of the 44 patients had removed or discontinued nCPAP therapy due to discomfort. Compliance with prescribed nCPAP/BIPAP therapy was based on the actual hours of usage as registered by an integrated hour meter.

The study was approved by the ethics committee of the Schleswig-Holstein University, Campus Kiel. Informed consent was obtained from all patients.

Polysomnography

All patients underwent overnight polysomnography in the sleep laboratory. All variables were recorded on a commercially available computer system (CNS SleepLab, Jaeger and Toennies, Hoechburg, Germany) and included (1) electroencephalography (C4/A1, C3/A2 of the international 10–20 system), (2) bilateral electrooculography, (3) submental electromyography, (4) thoracic and abdominal movements measured by uncalibrated inductive plethysmography, (5) saturation of oxyhaemoglobin (SaO_2) using a finger oxymeter, (6) air flow through the nose and mouth recorded by thermistors, (7) electrocardiography, (8) snoring microphone and (9) video monitoring using an infrared video camera. The entire recording was supervised by a technician.

Polysomnography records were scored in 30 s periods for sleep, breathing and oxygenation. According to the commonly used clinical criteria[25]: obstructive apnoeas were defined as a complete cessation of oronasal airflow for $\geqslant$10 s in the presence of chest-wall motion, hypopnoeas were defined as a reduction in respiratory airflow of $\geqslant$50% of the airflow or a clear reduction in airflow associated with more than 3% arterial oxygen desaturation or an arousal, both events lasting $\geqslant$10 s. The average number of apnoeas and hypopnoeas per hour of sleep were calculated as the apnea hypopnea index (AHI). OSAS was diagnosed when AHI was $\geqslant$5/h. Sleep was staged manually using the methods of RECHTSCHAFFEN and KALES as described.[26]

Serum NT-ProBNP measurements

Blood samples (EDTA plasma) for NT-ProBNP measurements were immediately centrifuged at 1800 $\times$ *g* for 20 min at 0 °C. Plasma concentrations of NT-proBNP were measured by a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany) as previously described.[27] The analytical range extended from 5 to 35,000 pg/ml and the total coefficient of variation was below 0.061 in pooled human plasma samples. The NT-proBNP levels were measured by a technician who was blinded to the results of the polysomnography. We defined a normal NT-proBNP level for men $<$85 pg/ml, and for woman $<$155 pg/ml according to previously described criteria.[28]

Statistical analysis

Data of patients were sorted into two groups above and below the medians of primary endpoints NT-ProBNP and AHI. Basic characteristics of patients were compared using χ^2 test for categorical characteristics and Wilcoxon for all other tests. For correlation analysis Spearman test was performed. To identify independent predictors of NT-ProBNP, a multiple linear regression model was used. NT-ProBNP was set as the continuous dependent variable and AHI and significant or trend towards significant ($p<0.09$) characteristics from univariate analyses (age, sex, LVEF, LVmass index, creatinine clearance and systemic arterial hypertension, Table 1) were entered as independent variables. In a second multiple linear regression model AHI was set as dependent variable and NT-proBNP and significant or trend towards significant ($p<0.09$) characteristics from univariate analyses (BMI, minimal SaO_2, mean SaO_2 and ESS, Table 2) were selected as independent variables. The results of the linear regression analysis are represented after backward selection (likelihood-ratio criteria). The regression coefficients were calculated according to Wald test. One observation was assumed to be an outlier and was excluded from correlations analysis and multiple linear regression models because these analyses are sensitive against particular isolated realizations. For all tests, the level of significance was set to 5%. Group values are presented by median values with 25th and 75th percentile for continuous variables, and proportions with 95% confidence interval for binary response. Statistical analysis was performed by Matlab, The MathWorks, Inc., Version 5.3.

Results

Patients characteristics and NT-ProBNP values

Patients were subdivided into two groups above and below the median of NT-ProBNP or AHI. The plasma levels of NT-proBNP ranged from 5 pg/ml (the lowest detectable value) to 665 pg/ml with a median of 42.1 pg/ml and AHI ranged from 0 to 107/h with a median of 22.4/h from all patients at first presentation. Baseline characteristics for NT-ProBNP and AHI groups are shown in Tables 1 and 2. Increased levels of NT-proBNP were found more frequently in female ($p<0.01$), older age groups ($p<0.01$) and in patients with impaired LVEF ($p<0.001$), higher LVmass index ($p<0.001$), impaired creatinine clearance ($p<0.001$) and known systemic arterial hypertension ($p<0.05$). Low or high levels of NT-proBNP were not associated with AHI and other sleep related indices (ESS, minimal SaO_2, mean SaO_2, Table 1). High baseline AHI levels were significantly associated with BMI ($p<0.01$), minimal SaO_2 ($p<0.001$), mean SaO_2 ($p<0.01$) with a trend towards higher ESS ($p=0.07$). Low or high levels of AHI were not associated with NT-proBNP (Table 2). One female 41-year-old patient (M.F.) presented an extraordinary high level of NT-ProBNP level (665 pg/ml) that was outlying from all other observations. This obese patient (BMI 37.6 g/m^2) had a known history of systemic arterial hypertension, echocardiography revealed a ventricular hypertrophy without an impairment of function and polysomnography showed a severe obstructive sleep apnoea syndrome (RDI 107/h). This patient was excluded from correlation analysis and multiple linear regression models

Table 1 Baseline patients characteristics according to baseline NT-proBNP level.

	Below median NT-ProBNP group ($n = 30$)	Above median NT-ProBNP group ($n = 30$)	p-Value
NT-Pro BNP (pg/ml)*	22 (10–29)	86 (53–160)	$<0.001^{\dagger}$
AHI (events/h)*	29 (6–55)	20 (7–48)	n.s.†
Female no (%)‡	7 (23)	18 (60,0)	$<0.01^{\S}$
Age (year)*	52 (39–58)	60 (48–64)	$<0.01^{\S}$
Body mass index (kg/m^2)*	32 (28–38)	31 (27–37)	n.s.†
ESS (points)*	12 (6–15)	10 (5–12)	n.s.†
Minimal SaO_2 (%)*	87 (86–89)	87 (84–89)	n.s.†
Mean SaO_2 (%)*	93 (91–94)	93 (91–95)	n.s.†
Mean systolic blood pressure (mm Hg)*	97 (93–103)	100 (93–109)	n.s.†
LVEF (%)*	59 (58–62)	53 (51–57)	$<0.001^{\dagger}$
LVmass index (g/m^2)*	109 (96–127)	143 (107–164)	$<0.01^{\dagger}$
FEV_1 (%)*	97 (88–103)	90 (74–102)	n.s.†
FVC (%)*	95 (85–99)	90 (75–103)	n.s.†
Creatinine clearance (ml/min)*	150 (132–198)	105 (95–136)	$<0.001^{\dagger}$
Smoking n (%)‡	11 (37)	11 (37)	n.s.§
Diabetes mellitus n (%)‡	3 (10)	3 (10)	n.s.§
Coronary diseases n (%)‡	5 (17)	2 (7)	n.s.§
Systemic arterial hypertension n (%)‡	13 (43)	23 (77)	$<0.05^{\S}$

*Results expressed as median (25–75th percentile).
†Wilcoxon test.
‡Results expressed as number (percentage).
§Chi-square test. NT-proBNP, N-terminal pro-brain natriuretic peptide; AHI, apnea hypopnea index; ESS, Epworth sleepiness scale; LVEF, left ventricular ejection fraction; LV, mass index left ventricular mass corrected for body surface area; FEV_1, forced expiratory volume in 1 s; FVC, forced expiratory vital capacity. n.s. not significant.

Table 2 Baseline patients characteristics according to baseline AHI.

	Below median AHI group ($n = 30$)	Above median AHI group ($n = 30$)	p-Value
AHI (events/h)*	7 (2–18)	48 (34–72)	$<0.001^{\dagger}$
NT-ProBNP (pg/ml)*	46 (24–90)	32 (20–86)	n.s.†
Female no (%)‡	15 (50)	10 (33)	n.s.§
Age (year)*	58 (43–63)	55 (42–62)	n.s.†
Body mass index (kg/m^2)*	29 (27–32)	35 (30–40)	$<0.01^{\dagger}$
ESS (points)*	9 (4–13)	12 (9–15)	$0.07^{\dagger}$
Minimal SaO_2 (%)*	89 (88–91)	86 (83–87)	$<0.001^{\dagger}$
Mean SaO_2 (%)*	94 (93–95)	92 (87–94)	$<0.01^{\dagger}$
Mean systolic blood pressure (mm Hg)*	98 (93–105)	98 (93–107)	n.s.†
LVEF (%)*	57 (52–61)	57 (52–60)	n.s.†
LVmass index (g/m^2)*	114 (101–149)	120 (98–157)	n.s.†
FEV_1 (%)*	92 (80–106)	94 (84–101)	n.s.†
FVC (%)*	95 (77–105)	92 (83–100)	n.s.†
Creatinine clearance (ml/min)*	108 (96–167)	145 (108–176)	n.s.†
Smoking n (%)‡	13 (43)	9 (30)	n.s.§
Diabetes mellitus n (%)‡	3 (10)	3 (10)	n.s.§
Coronary diseases n (%)‡	3 (10)	4 (13)	n.s.§
Systemic arterial hypertension n (%)‡	15 (50)	21 (70)	n.s.§

*Results expressed as median (25–75th percentile).
†Wilcoxon test.
‡Results expressed as number (percentage).
§Chi-square test. NT-proBNP, N-terminal pro-brain natriuretic peptide; AHI, apnea hypopnea index; ESS, Epworth sleepiness scale; LVEF, left ventricular ejection fraction; LV, mass index left ventricular mass corrected for body surface area; FEV_1, forced expiratory volume in 1 s; FVC, forced expiratory vital capacity. n.s. not significant.

because these analyses are sensitive against particular isolated realizations.

Correlations of NT-proBNP

No significant correlation was identified between NT-proBNP and AHI ($r = -0.03$, Figure 1A), ESS ($r = -0.10$, Figure 1B), minimal SaO_2 ($r = -0.09$, Figure 1C) and mean SaO_2 ($r = -0.03$, Figure 1D). There was a significant correlation between NT-proBNP and creatinine clearance ($r = -0.5$, $p < 0.001$, Figure 1E), age ($r = 0.4$, $p < 0.001$, Figure 1F), LVmass index ($r = 0.4$, $p < 0.01$, Figure 1G), and LVEF ($r = -0.4$, $p < 0.01$, Figure 1(H).

Multiple regression models of NT-proBNP and AHI

To determine whether NT-proBNP or AHI was influenced by confounders, a stepwise multiple regression model was used with either NT-proBNP or AHI as the dependent variable. For NT-proBNP-model, AHI and significant determinants (Table 1) such as age, sex, LVEF, LVmass index, creatinine clearance and systemic arterial hypertension were used as independent variables. Analogously, for AHI model, NT-proBNP and significant determinants (Table 3) such as BMI, minimal SaO_2, mean SaO_2 and ESS were selected as independent variables.

The NT-proBNP-model model ($R^2 = 0.46$) identified LVEF ($\beta = -0.38$, $p < 0.001$), creatinine clearance ($\beta = -0.48$, $p < 0.001$), and systemic arterial hypertension ($\beta = 0.21$, $p < 0.05$) as significantly correlated with NT-proBNP levels (Table 2). The AHI model regression model ($R^2 = 0.277$) identified BMI ($\beta = 0.28$, $p < 0.01$) and minimal SaO_2 ($\beta = -0.39$, $p < 0.01$) as the only significant independent predictors of AHI (Table 4). In both models there was no association between AHI and NT-proBNP levels.

Effect of nCPAP therapy

Twenty-nine patients, who were treated with nCPAP or BIPAP therapy were re-examined after a follow-up of 106 (92–136) days. The integrated hour meter showed a regular use of nCPAP/BIPAP therapy for all patients. One patient was diagnosed with acute pulmonary embolism 4 weeks before reassessment and was subsequently excluded from further analysis. With regard to the other 28 subjects there were no changes in health status or medications during the period of treatment. Treatment with nCPAP significantly decreased AHI ($p < 0.001$, Figure 2A) and ESS (11 (6–15) to 5 (3–8), $p < 0.001$, data not shown) and increased the mean SaO_2 (91.4% (89–93) to 94.1% (93–95); $p < 0.001$, data not shown). nCPAP therapy did not significantly alter NT-proBNP levels (Figure 2B) during the follow-up period. At initial examination seven of those 28 patients presented pathologically elevated NT-proBNP levels and sex of this subgroup demonstrated a reduction in NT-proBNP levels following nCPAP treatment.

Discussion

Our results show that NT-proBNP is not associated with obstructive sleep apnoea syndrome by four major findings: (1) low or high levels of NT-proBNP were not associated with AHI and other sleep related indices, (2) AHI did not correlate with NT-proBNP, (3) NT-proBNP was only related to LV-function, systemic arterial hypertension and creatinine clearance and not to AHI and other sleep related indices and (4) treatment with nCPAP did not change NT-proBNP levels significantly.

In several studies it has already been shown that OSAS and cardiovascular diseases are strongly associated suggesting OSAS as a probable independent risk factor for systemic arterial hypertension and other cardiovascular diseases.[16,17,29,30] Obstructive apnoeas are accompanied by hypoxemia, CO_2 retention and arousals which activate the sympathetic nervous system and cause repetitive surges in heart rate and blood pressure.[31] Moreover, permanent exaggerated negative intrathoracic pressure against an occluded upper airway markedly increases LV afterload during sleep, and all these together may stimulate myocyte growth and promote cardiac hypertrophy.[32] Accordingly, a large population based study identified OSAS as an independent risk factor for heart failure.[33] Although it was not a primary goal of our study, we found high incidences of systemic arterial hypertension and ventricular hypertrophy in patients with obstructive sleep apnoea. However, these results need careful interpretation because patients in this study may have more co-morbidity than the general population and therefore not reflect a representative sample, albeit patients were randomly selected and included in this study consecutively as they presented to the clinic.

BNP is a cardiac neurohormone which is secreted predominantly by ventricular myocytes under the influence of ventricular volume expansion, pressure overload and myocardial hypoxemia.[8,34] Several studies have shown that BNP or NH2-terminal portion proBNP (NT-proBNP) is increased in different cardiac diseases such as heart failure, different stages of coronary heart disease and cardiac hypertrophy.[18–20,35] BNP has been utilized for diagnostic purposes to distinguish patients with cardiac diseases from those who present with dyspnea from some other causes.[36] There were also findings that BNP is a valuable prognostic marker in cardiac patients, since it has been suggested that elevated levels of this hormone were associated with higher rates of hospital admissions, overall mortality and sudden death.[37] These observations are in agreement with our study. We found baseline NT-proBNP levels significantly increased in patients with impaired LVEF, higher LVmass according to body surface area and known systemic arterial hypertension in medical history. After robust statistical analysis with a multiple regression model, a significant correlation between NT-proBNP and both LVEF and systemic arterial hypertension was identified. Interestingly, LVmass index did not correlate significantly with NT-proBNP, which suggests a weaker association than between LVEF and systemic arterial hypertension with NT-proBNP. In contrast, NT-proBNP was not significantly associated with coronary heart disease, which may be due to the low numbers of patients in this study or to undetected preclinical coronary heart disease in some patients.

There are some studies addressing circulating BNP levels in patients with OSAS.[2–6] However, conclusions about the role of NT-proBNP are difficult to make, because (1) most of these studies did not sufficiently consider confounding factors such

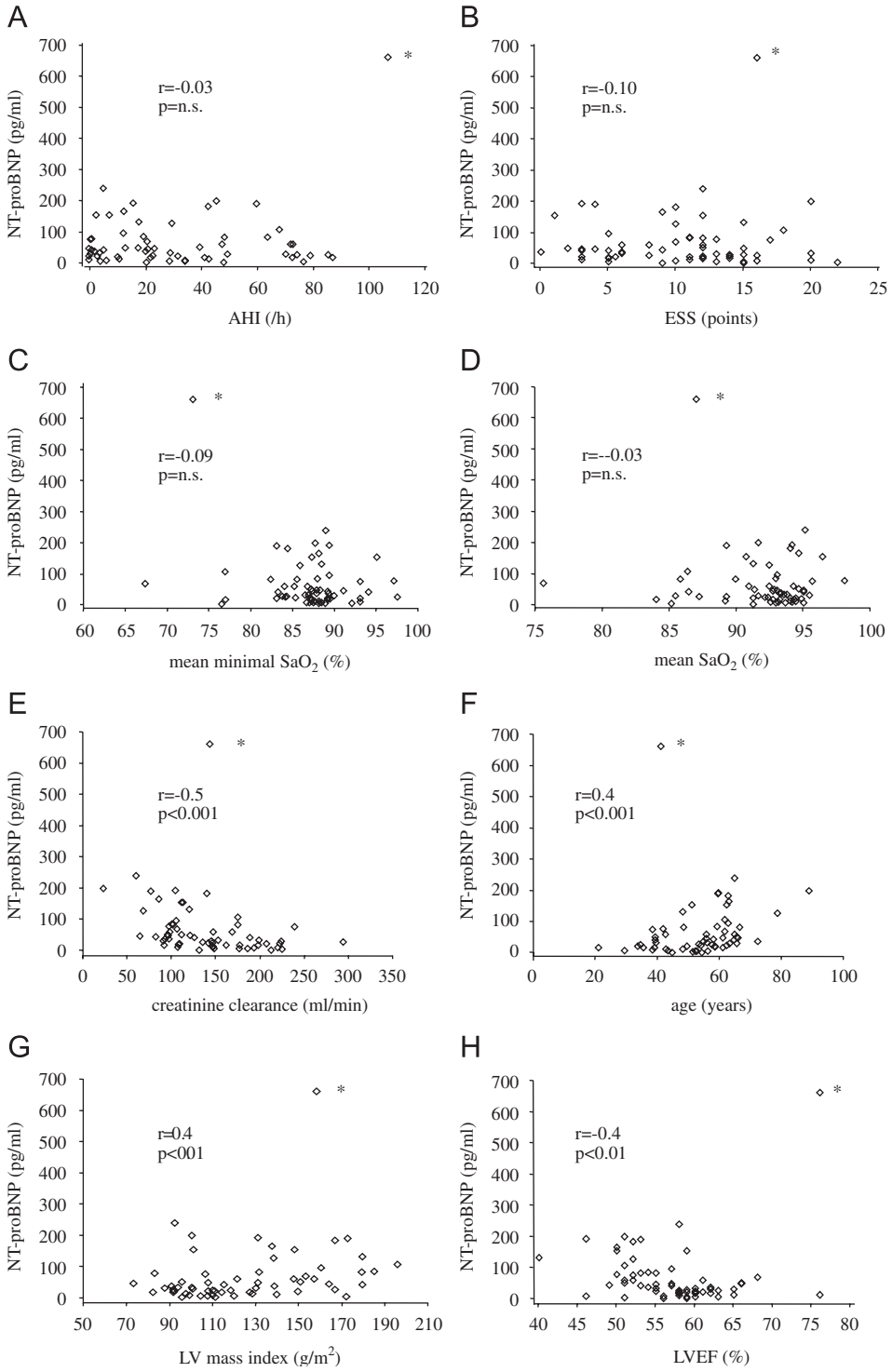

Figure 1 Correlation of N-terminal pro-brain natriuretic peptide (NT-proBNP) in 60 consecutive patients with a suspicion of OSAS. (A) Correlation between NT-proBNP and apnoe-hypnoe index (AHI); $r = -0.03$, $p =$ not significant (n.s.). (B) Correlation between NT-proBNP and Epworth sleepiness scale (ESS); $r = -0.10$, $p =$ n.s. (C) Correlation between NT-proBNP and minimal saturation of oxyhaemoglobin (SaO_2); $r = -0.09$, $p =$ n.s. (D) Correlation between NT-proBNP and mean SaO_2; $r = -0.03$, $p =$ n.s. (E) Correlation between NT-proBNP and creatinine clearance; $r = -0.5$, $p < 0.001$. (F) Correlation between NT-proBNP and age; $r = 0.4$, $p < 0.001$. (G) Correlation between NT-proBNP and left ventricular mass corrected for body surface area (LVmass index); $r = 0.4$, $p < 0.01$. (H) Correlation between NT-proBNP and left ventricular ejection fraction (LVEF); $r = 0.4$, $p < 0.01$. * Excluded from analysis.

as obesity, age, creatine clearance, sex or cardiovascular disease, all of which influence NT-proBNP and OSAS, (2) study groups were small or (3) only a selected study subgroup were included. For example, Kita and coworkers[3] found BNP levels elevated in patients with severe OSAS during sleep, however cardiovascular disease was not considered and the study group

Table 3 Stepwise multiple regression models for N-terminal pro-brain natriuretic peptide.

R^2	Independent variables*	β	95% Confidence interval	p-Value
0.460	LVEF	−0.381	−5.67/−1.56	<0.001
	Creatinine clearance	−0.476	−0.75/−0.31	<0.001
	Systemic arterial hypertension	0.214	1.59/49.27	<0.05

95% Confidence interval expressed in (minimum)/(maximum).
*Initial independent variables: apnoea-hypopnoea index, age, sex, left ventricular ejection fraction (LVEF), left ventricular mass index, creatinine clearance, systemic arterial hypertension.

Table 4 Stepwise multiple regression models for apnoe-hypopnoe index.

R^2	Independent variables*	β	95% Confidence interval	p-Value
0.277	Body mass index	0.217	−0.13/1.57	0.09
	Minimal SaO_2	−0.390	−4.65/−0.97	<0.01

95% Confidence interval expressed in (minimum)/(maximum).
*Initial independent variables: N-terminal pro-brain natriuretic peptide, body mass index, minimal saturation of oxyhemoglobin (SaO_2), mean saturation of oxyhemoglobin, Epworth sleepiness scale.

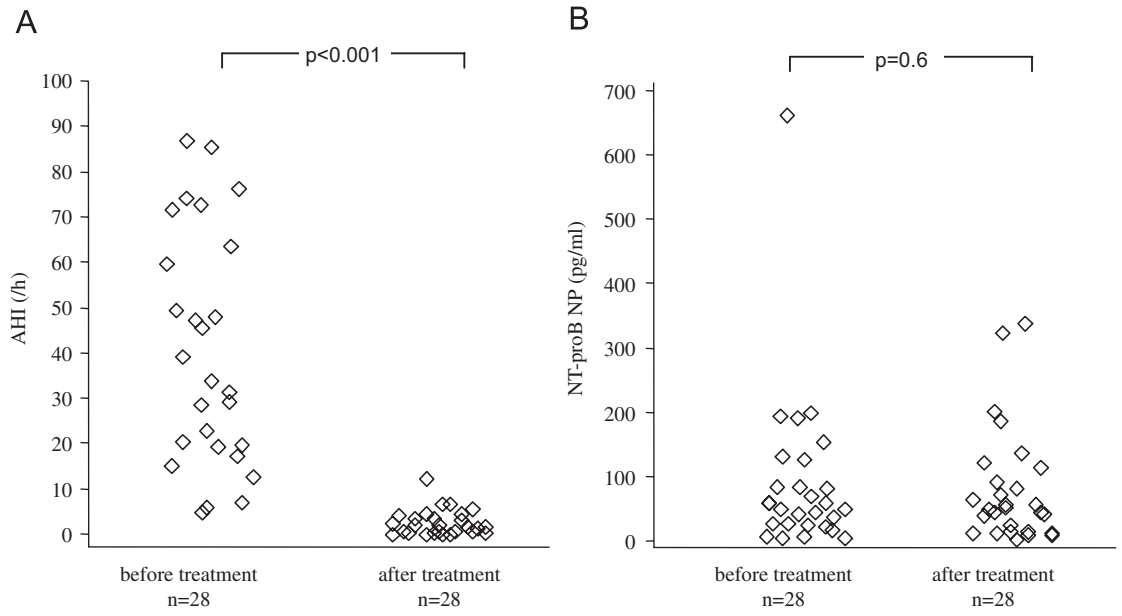

Figure 2 Comparison of patients with obstructive sleep apnoea syndrome before and after treatment. Twenty-eight patients were reassessed 3 months after treatment of OSAS for re-evaluation of N-terminal pro-brain natriuretic peptide (NT-proBNP) and polysomnography. (A) Apnoe-hypopnoe index (AHI). (B) NT-ProBNP.

was small ($n = 14$). Moller and coworkers[4] who reported BNP levels in patients with OSAS mildly but not significantly elevated, had excluded diseases of the heart, lungs, kidneys and endocrine organs but had not considered other confounding factors such as age, obesity or sex. Recently, Svatikova and coworkers,[2] Tasci and coworkers[5] and Vartany and coworkers[6] suggested, in agreement with our data, that BNP levels are not elevated in patients with OSAS compared to a healthy control group, but here control groups were either not matched to age and sex or confounders like obesity were not considered.

To our knowledge we were the first to perform a robust statistical multivariate analysis to adjust for most confounding factors. After regarding most contributing confounding factors in our study (*for AHI*: BMI, mean and minimal SaO_2, ESS; *for BMI*: age, sex, LVEF, LVmass index, creatinine clearance, systemic arterial hypertension), we showed that NT-pro BNP levels in blood were not associated with OSAS. The strong independent association between NT-proBNP with higher age, female sex and impaired renal function assessed by creatinine clearance are in agreement with previously reported results.[18,19] It was suggested that

association of female gender and BNP may be related to hormonal status because BNP levels were found to be higher in woman using hormone replacement therapy.[38] The strong association between BNP and age independent of cardiovascular or renal disease has been demonstrated in other studies.[19,39] Although data is limited, it is assumed that alterations in BNP production, secretion or degradation occurs with age.[39] The association with impaired renal function is already well known and probably caused by impaired clearance of natriuretic peptides in these patients.[40] It has recently been shown in a large population-based cohort that obesity, as indexed by elevated BMI, has an inverse relationship with BNP concentration, whereby it is unknown whether obesity either suppresses synthesis or release from cardiomyocytes or increases clearance of natriuretic peptides.[41] Interestingly, we did not observe any relationship between NT-proBNP and BMI in our patients. However, conclusions are difficult to draw because of the strong confounder between OSAS and obesity.

Our results suggest that NT-proBNP is not sensitive to detect myocardial stress caused by OSAS. In agreement to this observation, we did not see a change of NT-proBNP in the total patient population, which is partly in agreement with other studies.[2,5] We observed an interesting longterm lowering effect of NT-proBNP levels by nCPAP therapy in six patients with pathological elevated levels before treatment suggesting an improvement of cardiovascular function due to nCPAP therapy. However, this observation was not statistically significant probably due to the small subset group. This is in agreement with findings that effective OSAS treatment by CPAP in patients with coexisting heart failure improved LV-function and reduced systolic blood pressure.[16] However the effect of nCPAP treatment with regard to natriuretic peptides remains controversial and needs careful interpretation due to the possible role of other confounding variables.

In conclusion, the study shows by a robust multiple regression analysis, that NT-pro BNP is not associated with OSAS and NT-pro BNP cannot be used as a sensitive marker for underlying preclinical cardiovascular changes in patients with OSAS.

Conflict of interest

Ralf H. Huebner, Nour Eddine El Mokhtari, Sandra Freitag, Robert Goeder, Andreas Tiroke, Markus Lins, Rüdiger Simon and Bukhard Bewig have no conflicts to disclose.

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