

N-TERMINAL B-TYPE NATRIURETIC PEPTIDE (NT-PROBNP) IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

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SUMMARY

The aim of the present study is to evaluate the plasma N-terminal pro BNP in patients with obstructive sleep apnea syndrome (OSAS). A prospective study of 40 patients was carried out. Thirteen of them were accepted for diagnostic evaluation of a suspected sleep apnea which was proved with polysomnography (PSG), 26 were with documented congestive heart failure (CHF). The values of NTpro-BNP are not different between the patients with OSAS without concomitant diseases. There is a significant difference in the NT pro-BNP in OSAS patients with and without arterial hypertension, as well as in patients with CHF. There is no association between the values of the natriuretic peptide and the variables assessing the severity of OSAS. In conclusion: the undiagnosed OSAS is not related with severe impairment of the left ventricular function. The analysis of the NT-pro-BNP in patients with possible OSAS may be used as a fast, easily accessible, and reliable diagnostic marker as well as suitable improving the treatment and control of the concomitant cardiovascular morbidity and mortality.

Key words: obstructive sleep apnea syndrome, NT-proBNP, sleep disordered breathing

INTRODUCTION

The obstructive sleep apnea syndrome is characterized with repetitive collapse of the pharynx and oxygen desaturation during sleep which leads to sleep fragmentation and excessive sleepiness during daytime. OSAS is a frequent condition; its prevalence is up to 4% of the middle-aged males and 2% in females (20). The intermittent night hypoxemia and the continuous sympathetic nervous system activation are considered as stress factors for the cardiovascular system in untreated patients with OSAS (8). Through this pathway OSAS is associated with arterial hypertension (AH) (3,9,14,16), cardiac arrhythmias (12), coronary artery disease (12,16,17), pulmonary arterial hypertension and cerebrovascular incidents (4). In the Sleep Heart Health Study was established that OSAS is an independent risk factor for hypertension and CHF (16). There is an increasing evidence that the effective treatment of OSAS with continuous positive air pressure (CPAP) lowers blood pressure and improves the LV function (2,7). Aminoterminal pro-brain natriuretic peptide (NT pro-BNP) is a cardiac neurohormone secreted predominantly by the ventricular myocytes in response to increased volume overload and the increasing intraventricular pressure. The level of BNP rises quickly in response to various stimuli. Recent studies found that NT-pro-BNP is an important prognostic factor in patients with hypertension and LV hypertrophy, especially in those without evident signs of a cardiovascular disease (18,19). Uncertain data exist whether OSAS affects BNP and whether the application of ventilation with constant positive pressure influences the BNP excretion in patients with OSAS. New reports are controversial about the levels of BNP in patients with OSAS and the effects of the treatment with CPAP on the BNP values.

The aim of the present study is the evaluation of the plasma concentration of NT-pro-BNP in patients with obstructive sleep apnea.

PATIENTS AND METHODS

This is a prospective study of NT-pro-BNP in patients with OSAS and patients with documented CHF in order to assess the effect of OSAS on BNP. Overall, 40 patients were included. Thirteen of them were accepted for diagnostic evaluation in the centre for sleep medicine in the Pulmonary Clinic of MHAT "St. Marina" - Varna with the suspicion of sleep apnea. The inclusion criterion was clinical doubt for OSAS. Demographic data: 10 males (76.9%) and 3 females (23.1%) at a mean age 49.6±9.2 years and a mean BMI 38.2±9.9

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kg/m^2 were included in the study. Their results were compared to those of 27 patients with documented CHF, 18 males (66.7%) and 9 females (33.3%), comparable for age and BMI. All patients had a history of daily sleepiness, life style, the presence of concomitant diseases, the medication for basic treatment and were physically examined. The sleep analysis included overnight PSG which document the sleep disturbances and the severity of the OSAS according standard criteria (1). The investigation was performed on a monitoring system MEPAL (MAP, Medizin-Technologie, Martinsried, Germany). The minimal time of investigation was 6 hours according to the known diagnostic criteria. The sleep was documented by standard 16-18 channel polysomnography including electroencephalogram (EEG: C3-A2, C4-A1, O1-A2, O2-A1), electroocculograms (EOG) electromyograms - Chin EMG, extremities EMG left/right, EKG, heart rate, nasal and oral air flow, thoracic and abdominal movements, snoring registration, body position, SaO_2, monitoring of pulse oxymetry, video surveillance associated with the PSG. The sleep phases and arousals were analyzed in conformity with Rechtschaffen's and Kales' criteria (15). Apneas and hypopneas were evaluated in accordance with the accepted international criteria (1). Apnea index (AI) was defined as the number of apneas per hour sleep while hypopnea index (HI) - the number of hypopneas per 1 hour sleep. Apnea- hypopnea index (AHI) combined the number of apneas and hypopneas per 1 hour sleep. The severity of the seep apnea was graded as: mild, with AHI 5-15 episodes/hour sleep; moderate, with 16-30 episodes/hour sleep; severe, with more than 30 episodes/hour sleep. Blood pressure was measured three times in sitting position after 10 min rest in standard conditions. The patients with hypertension during the study continued their prescribed medication. The subjects in the group with documented CHF had history data, clinical signs and echocardiographic findings to prove the diagnosis of CHF without OSAS. In all patients routine blood samples were drawn including the analysis of NT-pro-BNP. The quantitative analysis of NT-pro-BNP was done using heparinised plasma. The methodology was adapted for automated immunoanalyser IMMULITE 2000 /Siemens Healthcare Group/. The expected values of NT-pro-BNP using this method in patients below 75 years were ≤ 110 pg/ml.

Statistical analysis

The data analysis was performed on a commercial statistical package (SPSS 11 for Windows). The relationship between NT-pro-BNP and the variables from the polysomnographic study and other laboratory tests were evaluated by the means of Pearson's correlation analysis, variability analysis for continuous variables - Student's t-test. Statistical significance was accepted if $p<0.05$.

RESULTS

All patients with suspected sleep disturbances measured by PSG study had severe OSAS (AHI=65.9±15.3/h). The main variables characterizing sleep disturbance in the studied subjects are presented on Fig. 1.

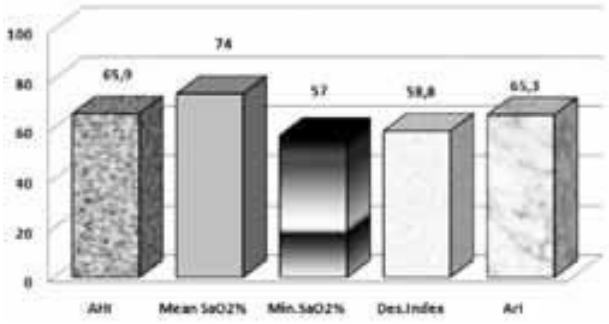

Fig. 1. Variables characteristic of sleep and breathing

It is prominent that females are fewer which reflects the disease profile and the smaller relative share of women with sleep breathing disturbances. From the 13 patients with OSAS, 4 (30.8%) have a history of arterial hypertension. One (7.8%) of the patients with OSAS has a history of coronary artery disease. All hypertensive patients with OSAS had basic antihypertensive treatment. Two patients (50%) received β-blockers and the other half - ACE/ATII inhibitors with a diuretic. All patients with OSAS became normotensive. Fig. 2 demonstrates the NT-pro-BNP values in patients with OSAS.

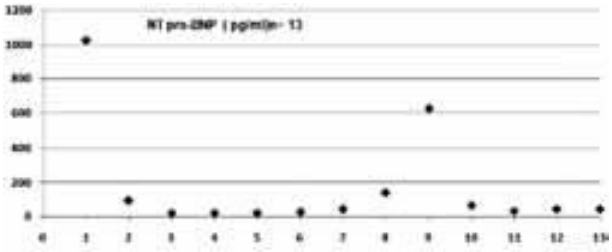

Fig. 2. NT-pro-BNP values in patients with OSAS.

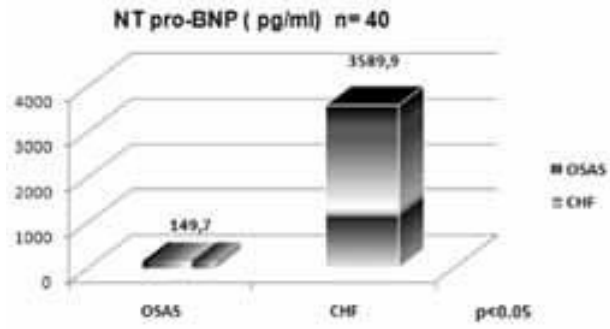

Fig. 3. NT-pro-BNP in patients with OSAS and with CHF

The results show that in 11 (84.6%) of the studied patients with OSAS the NT-pro-BNP values are within normal

range. In only 2 patients (15.4%) which have arterial hypertension the NT-pro-BNP are pathologically elevated. There are no patients with NT-pro-BNP which may classify them as having heart failure. The mean values of NT-pro-BNP in patients with OSAS and with CHF are presented on Fig. 3. Our data show that the OSAS patients have significantly lower levels of NT-pro-BNP ($p<0.05$) compared to the control group of patients with CHF.

The results for NT-pro-BNP in hypertensive OSAS patients (patients 2 and 9) are significantly higher from those in normotensive. The correlation analysis revealed lack of statistically important correlation between NT-pro-BNP and age, AHI, mean SaO_2, minimal SaO_2, desaturation index and AH. Significant correlation was found between NT-pro-BNP, BMI, and Arousal index (Table 1).

Table 1. Correlation between BNP and different variables for OSAS (n=13).

	age	ÂÌ ²	ÀH²	Mean SaO_2	Min. SaO_2	Desat. index	ArI	AP
Pearson's Correlation (r)	0.36	0.65	0.05	-0.45	-0.54	0.37	0.44	0.32
p	0.23	0.02	0.88	0.12	0.06	0.22	0.03	0.28

DISCUSSION

It is well known that there is a linear relationship between the severity of OSAS and the cardiovascular morbidity and mortality (1). It I s suggested that the major factors affecting the cardiovascular system in OSAS depend on sympathetic nervous system and its over activity, on the variation in thoracic pressures and the intermittent hypoxia, as well as on the changes in the inflammatory pathogenic pathway due to intermittent disorders in the reoxigenation, the reperfusion injury and, thus, the increased oxidative stress (7,8). This pathologic mechanism induces arrhythmias, LV systolic and diastolic dysfunction, and CHF which leads to polyorgan impairment (5). There are only a few data which pertain to prognosis whether OSAS is related to cardiac impairment before the objective occurrence of clinical and echocardiographic signs. Maeder et al. determined that the high level of NT-pro-BNP is a useful marker to detect cardiovascular injury in patients with OSAS (11). Another study of the effect of snoring in children finds out that in patients with definite apnoic pauses during sleep there are higher serum levels of BNP compared to those with ordinary snoring (6). The study of Lavie et al. shows reduction in serum pro-BNP levels in patients with CHF and OSAS after introducing treatment with CPAP (9). As a result from our study we may draw the following main conclusions: in normotensive patients with AH and OSAS there is no significant increase in NT-pro-BNP. NT-pro-BNP is significantly elevated in patients with OSAS and other co-morbidities. Although there is a trend for higher NT-pro-BNP values, in patients with OSAS we did not find elevated levels of NT-pro-BNP unlike these with CHF. In the study by Kita et al. the BNP values increased during sleep between 2 and 6 o'clock a.m. in patients with OSAS and decrease significantly after effective treatment with CPAP (7). The mean NT-pro-BNP in our group with OSAS is 149.7 (range 22-1024 pg/ml). All studied patients are with severe OSAS, AHI 65.9/h sleep, the NT-pro-BNP are not significantly different between the various patients with the exception of those with arterial hypertension ($p<0.005$). Our results show no significant correlation with age ($r=0.36$, $p=0.23$); AHI ($r=0.05$, $p=0.28$); the mean SaO2 ($r=-0.45$, $p=0.012$); minimal SaO2 ($r=-0.54$, $p=0.06$); desaturation index ($r=0.37$, $p=0.22$); arterial hypertension ($r=0.32$; $p=0.28$). NT-pro-BNP do not differby gender in patients with OSAS. NT-pro-BNP showed a positive correlation with BMI ($r=0.65$, $p=0.02$) and the Arousal index (ArI) ($r=0.44$, $p=0.03$). They are in accordance with Nil?fer et al.(13) who did not find a correlation between serum pro-BNP levels and the severity of OSAS, AHI, and the variables of the oxygen saturation. Data from the Framingham Sudy (10) in 623 patients also did not find an association between AHI and BNP. Several recent studies showed a negative relationship between natriuretic peptides and the BMI (Das, et al., Wang et al., Olsen et al.) which suggest that the natriuretic peptide as an endpoint in acute heart failure and as apredictor in CHF should be corrected for BMI. We consider that the low level of NT-pro-BNP in patients with OSAS may be due to obesity and the altered body stature in patients with OSAS. The present correlation between NT-pro-BNP, ArI, and the BMI and the missing relation between age, severity of OSAS and the variables of the saturation can be explained with the impact of the body stature on NT-pro-BNP. In our sample, the patients with OSAS and hypertensionin patients with showed a trend of higher NT-pro-BNP compared to non-hypertensive. The application of CPAP treatment in patients with AH and OSAS results in greater drop of NT-pro-BNP as in the normotensive patients with OSAS. The effective application of CPAP in OSAS patients leads to normalization of the intrathoracic pressure which goes down by 50 mm Hg during the apnea episodes (Moller's manouvre) . This can be explained with the fact that the treatment with CPAP at a high baseline NT-pro-BNP generates normalization of the elevated systolic and transmural pressures and LV afterload which results in lowering the BNP. Whether this effect is due to interruption of the apnea and hypopnea episodes or is a direct result of the treatment with CPAP it is not well known. The results of our study emphasize the need of additional investigation to evaluate the effect of CPAP treatment on mortality in patients with cardiovascular diseases and SDB.

CONCLUSION

The present study adds more evidence that OSAS is not related to substantial expression of the B-natriuretic peptide. Undiagnosed OSAS is not connected with severe LF dysfunction. The test for NT-pro-BNP in patients with proba-

ble OSAS may be used as fast, easily accessible, and reliable diagnostic marker in the presence of dyspnea and heart failure and also for the treatment improvement and control of the cardiovascular co-morbidity and mortality in patients with OSAS. The ability of CPAP to have a long-term effect on NT-pro-BNP levels and to be an endpoint of the treatment of patients with OSAS and cardiovascular diseases has to be confirmed in additional studies.

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