

Sleep Apnoea in Patients With Nocturnal Hypertension – a Multicenter Study in the Czech Republic

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Summary

Sleep apnoea (SA) is common in patients with hypertension. Nowadays, limited data on the prevalence of SA in nocturnal hypertension (NH) exist. Therefore, we studied the occurrence of SA in Czech patients and its association with 24-h ambulatory blood pressure monitoring (ABPM), breathing disturbances in sleep, anthropometric data, Mallampati score and Epworth sleepiness scale (ESS) using the Apnea Link device. Undiagnosed SA was found in 72.9 % patients (29.3 % mild, 26.6 % moderate, 17.0 % severe) of 188 patients with NH measured by ABPM. The median of the apnoea-hypopnoea index (AHI) was 12.0 (25th-75th percentile 5.0-23.8). Moderate/severe SA (AHI \geq 15) was associated with BMI, waist circumference, mean night saturation (SpO₂), t90, oxygen desaturation index (ODI), ESS (daytime BP only) ($p\leq$ 0.032), but not ABPM parameters and Mallampati score ($p>$ 0.09). A likelihood of moderate/severe SA was enhanced by ODI $>$ 14.5 events/h (odds ratio=57.49, 95 % CI=22.79-145.01), t90 $>$ 6.5 % (8.07, 4.09-15.92), mean night SpO₂ $<$ 93.5 % (3.55, 1.92-6.59), BMI $>$ 29.05 kg/m² (6.22, 3.10-12.49), circum waist $>$ 105.5 cm (3.73, 1.57-8.83), but not by any ABPM parameter. In conclusion, a high incidence of SA (72.9 %) was observed in Czech patients with NH. SA severity was associated with body characteristics and oxygenation

parameters, but not with ABPM parameters and Mallampati score.

Key words

Sleep apnoea • Nocturnal hypertension • Ambulatory blood pressure monitoring • Mallampati score • Epworth sleepiness scale • BMI

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Introduction

Obstructive sleep apnoea (OSA) is one of the most common sleep-disordered breathing (SDB), characterized by repeated obstruction of the upper airways during sleep, leading to hypopnoea (reduced air flow to 20-70 % of previous steady breathing) or apnoea (complete cessation of airflow and decrease in flow through the respiratory tract to $<$ 20 % of previous stable breathing), lasting at least 10 s (Parati *et al.* 2012,

Qaseem *et al.* 2014). These events may occur more than five times per hour of sleep accompanied by awakening and/or arousal reactions. The incidence of OSA, according to major studies is between 3-7 % in adult men and 2-5 % in adult women (Lindberg 2010). The prevalence of OSA is higher in patients with hypertension (30-83 %), heart failure (12-53 %), ischemic heart disease (30-58 %) and stroke (43-91 %) (Bradley and Floras 2009). OSA is also found in 64-83 % of patients with resistant hypertension (Logan *et al.* 2001), of whom more than 55 % have moderate to severe forms (Gonçalves *et al.* 2007, Pedrosa *et al.* 2011).

Patients with OSA exhibit a high prevalence of nocturnal blood pressure (BP) with non-dipping or rising pattern, which is related to clinical and subclinical organ damage to heart and brain (Torres *et al.* 2015). The pathogenesis of OSA is multifactorial, involving airway obstructions resulting in hypoxia and hypercapnia increasing sympathetic neural tone, which in turn causes vasoconstriction and marked increases in BP (Wolf *et al.* 2010). Besides this, intermittent hypoxia associated with hyperaldosteronism, endothelial dysfunction, nocturnal fluid redistribution, sleep inefficiency, increased sympathetic tone, oxidative stress and inflammation are involved in the pathogenesis (Khan *et al.* 2013, Phillips *et al.* 2013, Konecny *et al.* 2014, Fernandez-Mendoza *et al.* 2012). However, the relationship of OSA to nocturnal hypertension is still unclear. Moreover, there is no data on OSA in Czech patients with nocturnal hypertension and on the incidence of sleep apnoea (SA), or other breathing disorders linked to sleep.

The aim of this multicenter study was: i) to assess the prevalence of undiagnosed SA in patients with nocturnal hypertension, assessed by 24-h ambulatory BP monitoring (ABPM) and determine the relationship of ABPM to the apnoea-hypopnoea index (AHI), other variables of oxygenation during sleep, and anthropometric characteristics; ii) to determine whether the Mallampati score, and Epworth sleepiness scale (ESS) questionnaire correlate with hypertension; iii) to determine whether, for those with nocturnal hypertension and daytime normotensive BP there is a higher incidence of SA than those with hypertension, day and night.

Methods

Patients

Study cohort consists of consecutive patients with nocturnal hypertension, who were referred by

a cardiologist or an internist for examination at a sleep center (Fig. 1). Nocturnal hypertension was defined as nighttime systolic and/or diastolic BP means $\geq 120/70$ mm Hg (Parati *et al.* 2014, Mancia *et al.* 2013). Four accredited sleep centers in the Czech Republic took part in this study. Enrolled patients were those treated for hypertension with no night drop in pressure (non-dippers), patients with isolated nocturnal hypertension and those with persistent high BP day and night despite treatment. Exclusion criteria were age below 18 years, sleep apnoea and other sleep disorders in the history, neuromuscular disease, stroke, severe pulmonary obstruction associated with bronchial asthma and chronic obstructive pulmonary disease, other secondary hypertension (endocrine disorders, renal artery stenosis, renal parenchymal disease, intracranial tumors), pulmonary fibrosis, clinical signs of heart failure, treatment with benzodiazepines and myorelaxants or lack of interest in participation.

All patients signed an informed consent, and the study was approved by local ethics committees.

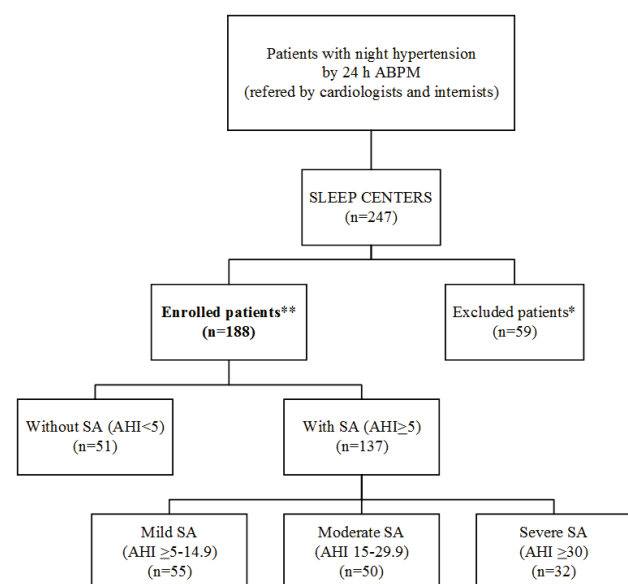


Fig. 1. Flow chart of patients who met inclusion/exclusion criteria for this study. ** Inclusion criteria: patients with night hypertension: i) non-dippers – those treated for hypertension with no night drop in pressure, ii) patients with isolated nocturnal hypertension and iii) those with persistent high BP day and night despite treatment. * Exclusion criteria: age below 18 years, sleep apnoea and other sleep disorders in the history, neuromuscular disease, stroke, severe pulmonary obstruction (bronchial asthma and chronic obstructive pulmonary disease), pulmonary fibrosis, other secondary hypertension (endocrine disorders, renal artery stenosis, renal parenchymal disease, intracranial tumors), clinical signs of heart failure, treatment with benzodiazepines and myorelaxants or lack of interest in participation.

Demographic and clinical data

Following demographic and medical history data were recorded in all enrolled patients: age, gender, snoring, apnoea occurrence, other concomitant diseases, especially coronary heart disease (CHD) and myocardial infarction, and hypertensive medication. We established the proportion of patients treated for hypertension. The percentage of patients with SA (mild, moderate, severe) and without SA was then determined. The investigation involved completing ESS questionnaire which captures daytime somnolence in eight different everyday situations for the last week. Excessive daytime sleepiness is considered a score of 10 or higher (Johns 1991).

Anthropometry

We measured body characteristics height, weight, body mass index (BMI), neck, waist, and hip circumference, the Mallampati class – classification of visibility of the oropharynx for intubation (Mallampati 1983). The Mallampati score is assessed by asking the patient (in a sitting posture) to open his/her mouth and protrude the tongue as far as possible. The anatomy of the oral cavity is visualized; specifically, whether the base of the uvula, faucial pillars (the arches in front of and behind the tonsils) and soft palate are visible. Following Mallampati classes were evaluated: class I (soft palate, uvula, fauces, pillars visible), class II (soft palate, uvula, fauces visible), class III (soft palate, base of uvula visible), and class IV (only hard palate visible).

Sleep respiration studies

The night screening for sleep apnoea was done in all enrolled patients on an outpatient basis using the Apnea Link device (ResMed Inc, Bella Vista, Australia). The Apnea Link device is a simple, easy-to-use device, and is highly sensitive and specific in calculating the AHI compared with the AHI from full polysomnography (Erman *et al.* 2007). Apnea Link device monitors the apnoea and hypopnoea from the respiratory flow (nasal cannula), snoring, oximetry and pulse rate from the sensor of the pulse oximeter, and it assesses Cheyne-Stokes respiration probability from the flow. The record lasted 6-8 h. A shorter recording than 6 h or non-valid records were repeated the following night. The record was visually evaluated for the following data: AHI (apnoea-hypopnoea index – the number of apnoeas and hypopnoeas per hour of registration), ODI (oxygen desaturation index – the number of drops in desaturation by 4 % per hour of registration), average night saturation

in % (mean SpO₂) and t90 (time in saturation below 90 % oxygen saturation (SaO₂), expressed in %) and the presence or absence of Cheyne-Stokes respiration (proportion of probable 0.5 % Cheyne-Stokes epochs). SA was assessed according to the AHI as mild for AHI=5-14.9, moderate for AHI=15-29.9 and AHI≥30 as severe (Flemons *et al.* 1999).

Ambulatory blood pressure monitoring

Measurement of 24-h ABPM started each morning at 07-08 a.m. The average 24-h BP was calculated along with average daytime and nighttime BP (systolic and diastolic) from which the percentage of non-dippers (a BP drop <10 %, both systolic and diastolic) was estimated. Normal average BP values on ABPM were daytime <135/85 mm Hg, night time <120/70 mm Hg and average over 24-h <130/80 mm Hg (Mancia *et al.* 2013). The incidence of SA was compared in patients with nocturnal hypertension and daytime normotension and those with day and night hypertension.

Statistical methods

The statistical analyses (nonparametric Mann-Whitney U-test, Kruskal-Wallis test, Receiver-Operator Characteristic (ROC) curves, chi-squared test) were performed using the software IBM SPSS Statistics 22 (US) and R statistical software (<https://www.r-project.org/>). The normality of the data was tested using the Shapiro-Wilk test. The data are shown as medians (25th-75th percentile). A logistic regression model was used to estimate Odds Ratio with a 95 % confidence interval (CI) for categorical variables. Spearman correlation coefficient was used for assessment of correlations between studied parameters. A *p*-value<0.05 was considered significant.

Results

Patient characteristics

We examined 188 patients (male/female 123/65; median age 59.0 years) with nocturnal hypertension. Descriptive characteristics of patients and ABPM data are shown in Table 1. On ABPM, 89 % were non-dippers for systolic BP and 71 % non-dippers for diastolic BP. 97.6 % patients were on medication for hypertension. From ABPM, only 27.1 % of patients had systolic BP within the norm in the daytime, and only 3.2 % at the night interval. Diastolic BP was more often within the norm (daytime 59.0 %, nighttime 18.1 %).

Table 1. Demographic and clinical characteristics of enrolled subjects including the ambulatory BP monitoring data and subjective evaluation of daytime sleepiness and night registered breathing data. Data are shown as median, 25th-75th percentiles in parenthesis.

	Whole sample set n=188	Male n=123	Female n=65
<i>Age (years)</i>	59.0 (53.0-65.0)	58.0 (50.0-64.0)	62.0 (58.0-67.0)
<i>Medical history of snoring (%)</i>	71.5 %	76.2 %	62.5 %
<i>Medical history of apnoea (%)</i>	41.8 %	46.3 %	33.3 %
<i>ESS</i>	6.0 (3.0-9.0)	6.0 (3.0-9.0)	5.0 (2.0-9.0)
<i>Anthropometry</i>			
<i>BMI (kg/m²)</i>	30.9 (27.4-35.1)	30.5 (27.3-34.5)	31.2 (28.0-36.0)
<i>Neck circumference (cm)</i>	42.0 (39.0-44.0)	43.0 (41.0-45.0)	39.0 (36.5-40.0)
<i>Waist circumference (cm)</i>	108.0 (98.0-115.0)	109.0 (100.0-117.5)	103.0 (95.0-114.0)
<i>Hip circumference (cm)</i>	108.0 (103.8-115.2)	107.0 (102.5-114.0)	110.0 (105.0-117.0)
<i>ABPM</i>			
<i>24-h systolic (mm Hg)</i>	139.0 (133.0-149.0)	139.9 (134.0-151.0)	138.0 (133.0-143.5)
<i>24-h diastolic (mm Hg)</i>	80.0 (76.0-87.0)	81.0 (77.0-89.0)	78.0 (69.0-83.0)
<i>Daytime systolic (mm Hg)</i>	140.0 (134.0-149.0)	142.0 (134.0-152.0)	137.0 (131.8-145.0)
<i>Daytime diastolic (mm Hg)</i>	83.0 (76.0-90.0)	84.0 (78.0-92.0)	79.0 (72.0-85.0)
<i>Nighttime systolic (mm Hg)</i>	139.0 (131.0-149.0)	139.0 (130.0-150.0)	140.0 (131.0-148.0)
<i>Nighttime diastolic (mm Hg)</i>	78.0 (73.0-85.0)	80.0 (75.0-87.0)	75.0 (66.2-85.0)
<i>Respiration parameters</i>			
<i>AHI (events/h)</i>	12.0 (5.0-23.8)	14.0 (6.0-28.5)	10.0 (5.0-21.0)
<i>ODI (events/h)</i>	10.5 (5.0-22.8)	13.0 (6.0-26.0)	8.0 (5.0-16.0)
<i>Mean SpO₂ (%)</i>	93.0 (92.0-95.0)	93.0 (92.0-95.0)	93.0 (92.0-95.0)
<i>t90 (%)</i>	8.0 (1.0-25.8)	9.0 (1.0-25.0)	6.0 (2.0-27.0)

ABPM – 24-h ambulatory BP monitoring, ESS – Epworth sleepiness scale, AHI – apnoea-hypopnoea index, ODI – oxygen desaturation index, Mean SpO₂ – mean night saturation (%), t90 % – time in saturation below 90 % SaO₂.

Of enrolled patients, 27.1 % had no SA (AHI<5) and in 72.9 % patients SA (AHI≥5) was detected. Of those with SA, 29.3 % had mild SA, 26.6 % moderate SA

and 17.0 % severe SA.

Results for ESS and night registered breathing are presented in Table 1. Cheyne-Stokes breathing

probability was demonstrated in 4.8 % patients (4.3 % of men, 0.5 % women). Numbers of apnoea with Cheyne-Stokes respiration are included in the AHI.

Mallampati score

In the whole sample set, the Mallampati class I was observed in 32 patients (17.0 %), class II in 68 patients (36.2 %), class III in 62 patients (33.0 %), and class IV in 26 patients (13.8 %).

Comparison of patient data in subgroups according to the AHI

When comparing patients without SA ($AHI < 5$) with those with SA ($AHI \geq 5$), we observed higher occurrence of snoring ($p=0.007$) and apnoea ($p < 0.001$) in the medical history, $BMI > 30$ ($p=0.009$), medical history of coronary artery disease ($p=0.015$), Mallampati class IV ($p < 0.001$) in patients with SA. Patients without SA and with SA did not differ in the pathological $ESS \geq 10$ ($p=0.222$), drug treatment for hypertension ($p=0.580$), and history of myocardial infarction ($p=0.236$).

Comparison of body characteristics and oxygenation parameters in patients without SA ($AHI < 5$) with SA subgroups according to the AHI (mild, moderate and severe SA) is shown in Figure 2. The Kruskal-Wallis test revealed the differences in weight ($p < 0.001$), BMI ($p=0.003$), neck circumference ($p < 0.001$), waist circumference ($p < 0.001$), hip circumference ($p < 0.001$) as well as in the parameters: night saturation SpO_2 ($p < 0.001$), higher $t90$ ($p < 0.001$) and ODI ($p < 0.001$) between studied subgroups.

Comparison of ABPM parameters between patient's subgroups with no SA and mild SA ($AHI=5-14.9$) and moderate and severe AHI ($AHI \geq 15$) is shown in Figure 3. Only patients with $AHI \geq 15$ were treated with continuous positive airway pressure (CPAP). No differences were observed between subgroups in 24-h systolic ($p=0.906$), 24-h diastolic ($p=0.959$), daytime systolic ($p=0.923$), daytime diastolic ($p=0.893$), nighttime systolic ($p=0.397$), nighttime diastolic BP ($p=0.234$).

When comparing patients according to the severity of SA, we observed higher occurrence of $BMI > 30$ ($p < 0.001$), waist circumference ($p=0.001$), and trend for higher neck circumference ($p=0.066$) in moderate/severe SA comparing with mild SA. We also detected higher occurrence of lower mean night saturation SpO_2 ($p < 0.001$), higher $t90$ ($p < 0.001$) and

higher ODI ($p=0.032$) in moderate/severe cases comparing to mild SA cases. Regarding ABPM parameters, we did not observe any significant association with the studied parameters: 24-h systolic ($p=0.095$), 24-h diastolic ($p=0.816$), daytime systolic ($p=0.996$), daytime diastolic ($p=0.451$), nighttime systolic ($p=0.272$), nighttime diastolic ($p=0.895$). Combination of $BMI > 30$ with high $t90$ or high ODI further increase the significance ($p < 0.001$) between studied subgroups.

In order to establish the sensitivity and specificity of investigated parameters as well as to determine the threshold for the best separation of patients without SA and mild SA and those with moderate and severe SA, we constructed the ROC curves. The highest sensitivity 81.5 % and specificity 93.4 % (for threshold 14.5, area under curve (AUC) 0.921) was observed for ODI, followed by $t90$ (threshold 6.5, sensitivity 82.5 %, specificity 65.1 %, AUC 0.790), mean night SpO_2 (93.5, sensitivity 71.6 %, specificity 52.5 %, AUC 0.719), BMI (29.05 kg/m^2 , sensitivity 84.0 %, specificity 55.1 %, AUC 0.698) and age (63.5 years, sensitivity 43.2 %, specificity 75.7 %, AUC 0.594) (Fig. 4). For neck circumference the ROC revealed (40.5 cm, sensitivity 74.1 %, specificity 52.3 %, AUC 0.668), for waist circumference (105.5 cm, sensitivity 75.3 %, specificity 62.6 %, AUC 0.737) and hip circumference (111.5 cm, sensitivity 58.0 %, specificity 79.4 %, AUC 0.718) for compared groups. The ROC curve analysis showed that the AUC of AMBP 24-h systolic, 24-h diastolic, daytime systolic, daytime diastolic, nighttime systolic, nighttime diastolic was 0.50, 0.51, 0.49, 0.51, 0.52, 0.54, respectively.

Correlation analysis

Correlations of the ABPM parameters with the results of other nocturnal breathing registration (ODI, mean SpO_2 , $t90$), anthropometric parameters, ESS and Mallampati score in subgroups of patients divided according to the AHI ($AHI=0-14.9$ vs. $AHI \geq 15$) are shown in Figure 5. The analysis showed no correlation of ABPM parameters with severity of SA, nor with AHI and other studied parameters (Fig. 5). In both studied subgroups according to the AHI, a strong correlation between respiratory parameters (ODI, average night saturation and $t90$) as well as body characteristics (height, weight, BMI, neck, waist and hip circumference) was observed (Fig. 5).

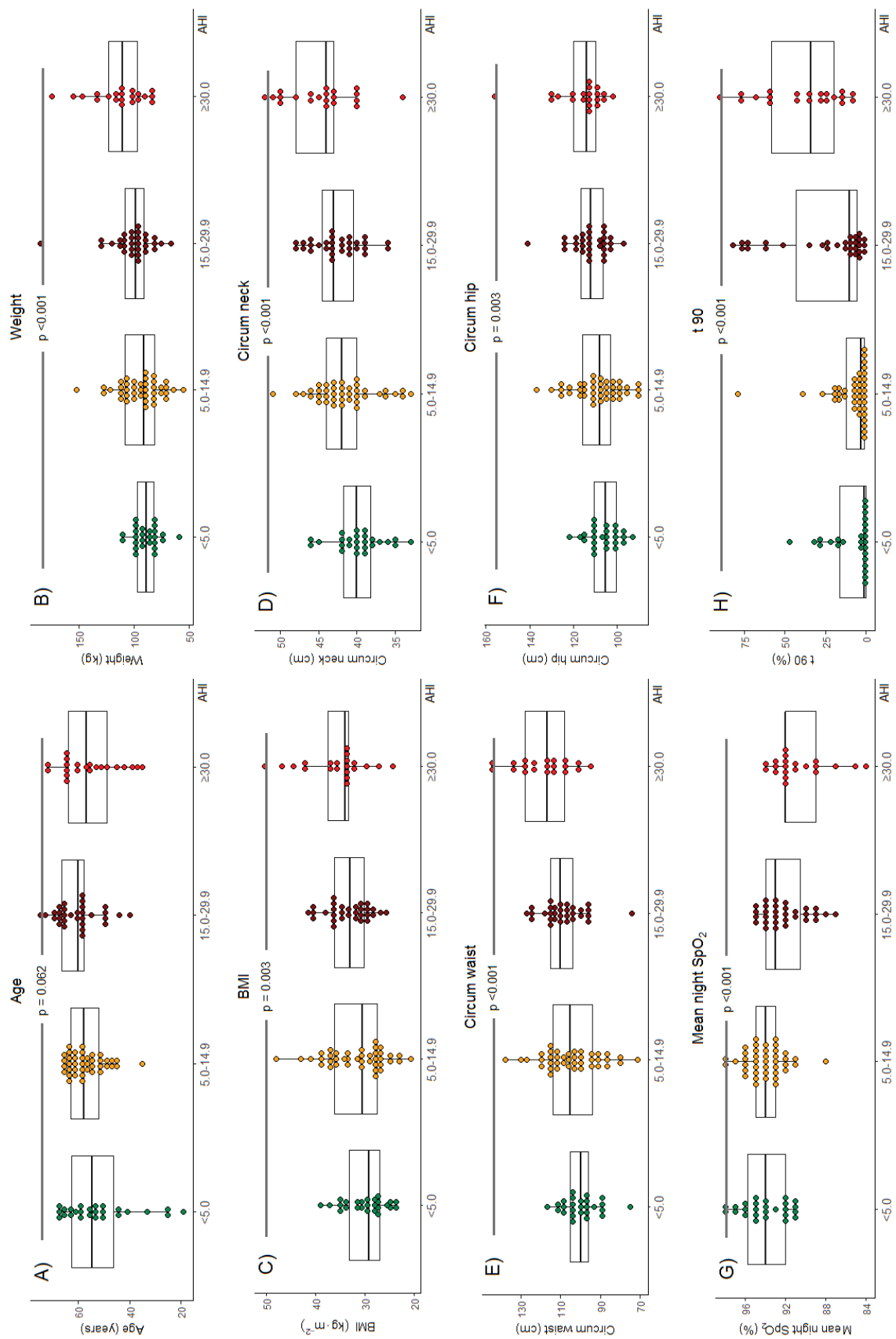


Fig. 2. Comparison of subgroups of patients with non-SA, mild, moderate and severe SA in following parameters: **A)** age, **B)** weight, **C)** BMI, **D)** neck circumference, **E)** waist circumference, **F)** hip circumference, **G)** mean SpO_2 , **H)** t90. The median is represented by a vertical bar in the center of the box, the ends of the box show the 25 % percentile and 75 % percentile. Whiskers showed the maximum and minimum of the data distribution for each studied parameter. The Kruskal-Wallis test was used to determine the differences between studied patient subgroups (p<0.05 significant).

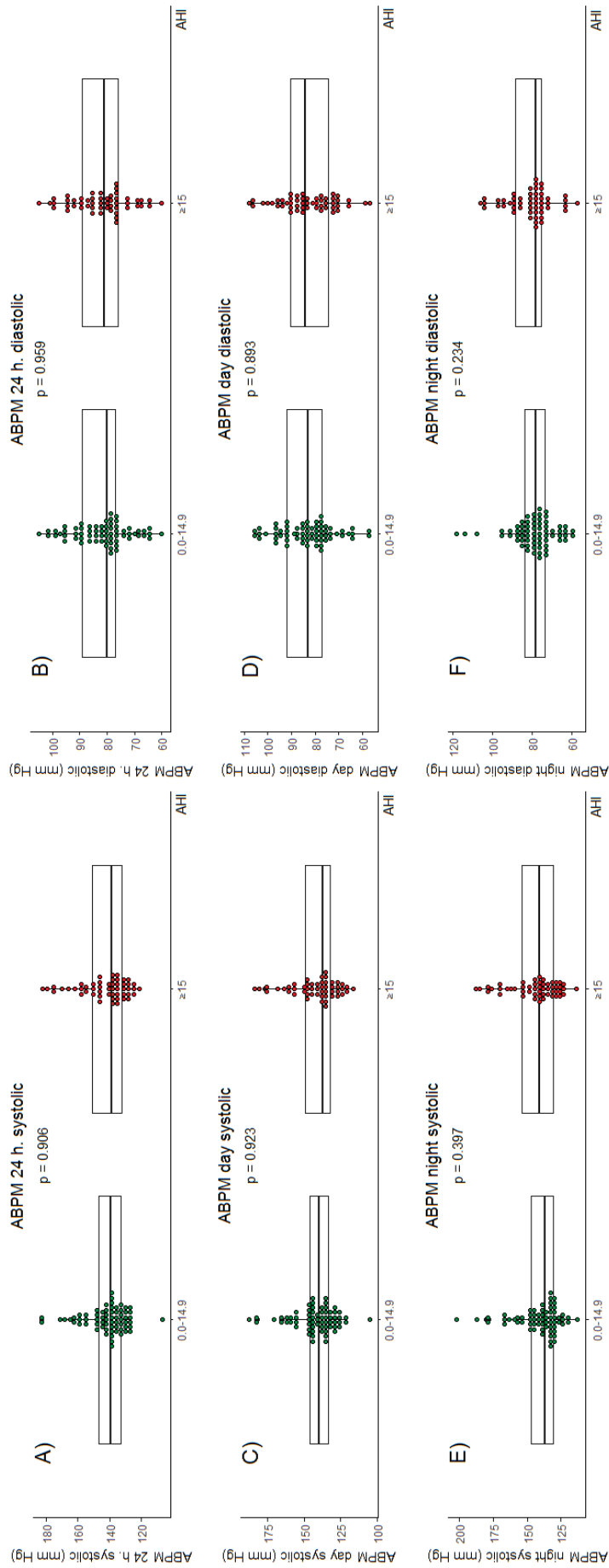


Fig. 3. Comparison of subgroups of patients with AHI=0-14.9 (non-SA, mild SA) vs. AHI≥15 (moderate and severe SA) in ABPM parameters: **A)** mean 24-h time systolic BP, **B)** mean 24-h time diastolic BP, **C)** mean daytime systolic BP, **D)** mean daytime diastolic BP, **E)** mean nighttime systolic BP, **F)** mean nighttime diastolic BP. The median is represented by a vertical bar in the center of the box, the ends of the box show the 25 % percentile and 75 % percentile. Whiskers showed the maximum and minimum of the data distribution for each studied parameter. BP – blood pressure, AHI – apnoea-hypopnoea index.

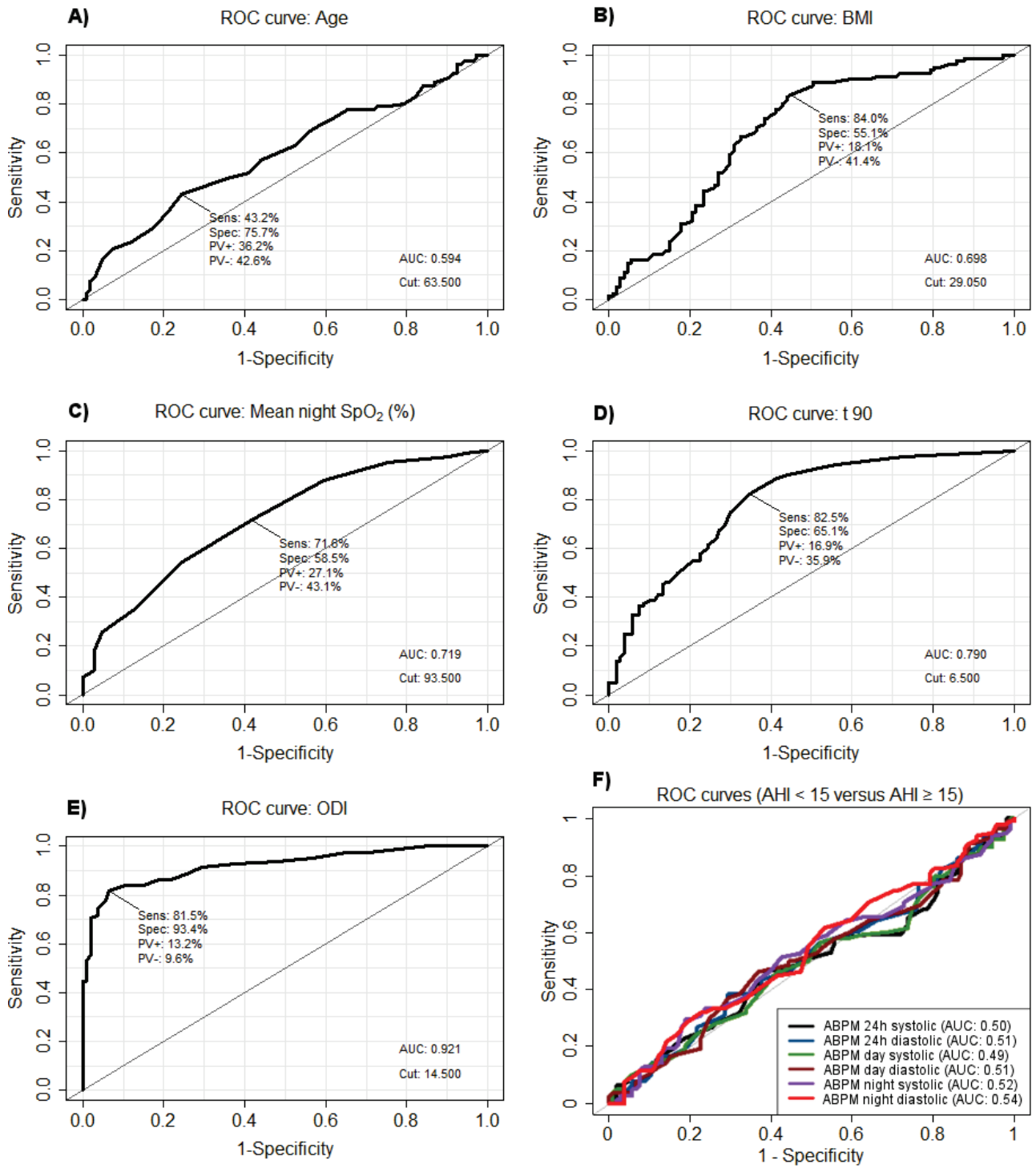


Fig. 4. ROC curves with AUC values for subgroups of patients with AHI=0-14.9 (non-SA, mild SA) and AHI≥15 (moderate and severe SA) in patient subgroups according to the **A)** age, **B)** BMI, **C)** mean night SpO₂, **D)** t90, **E)** ODI, **G)** ABPM parameters.

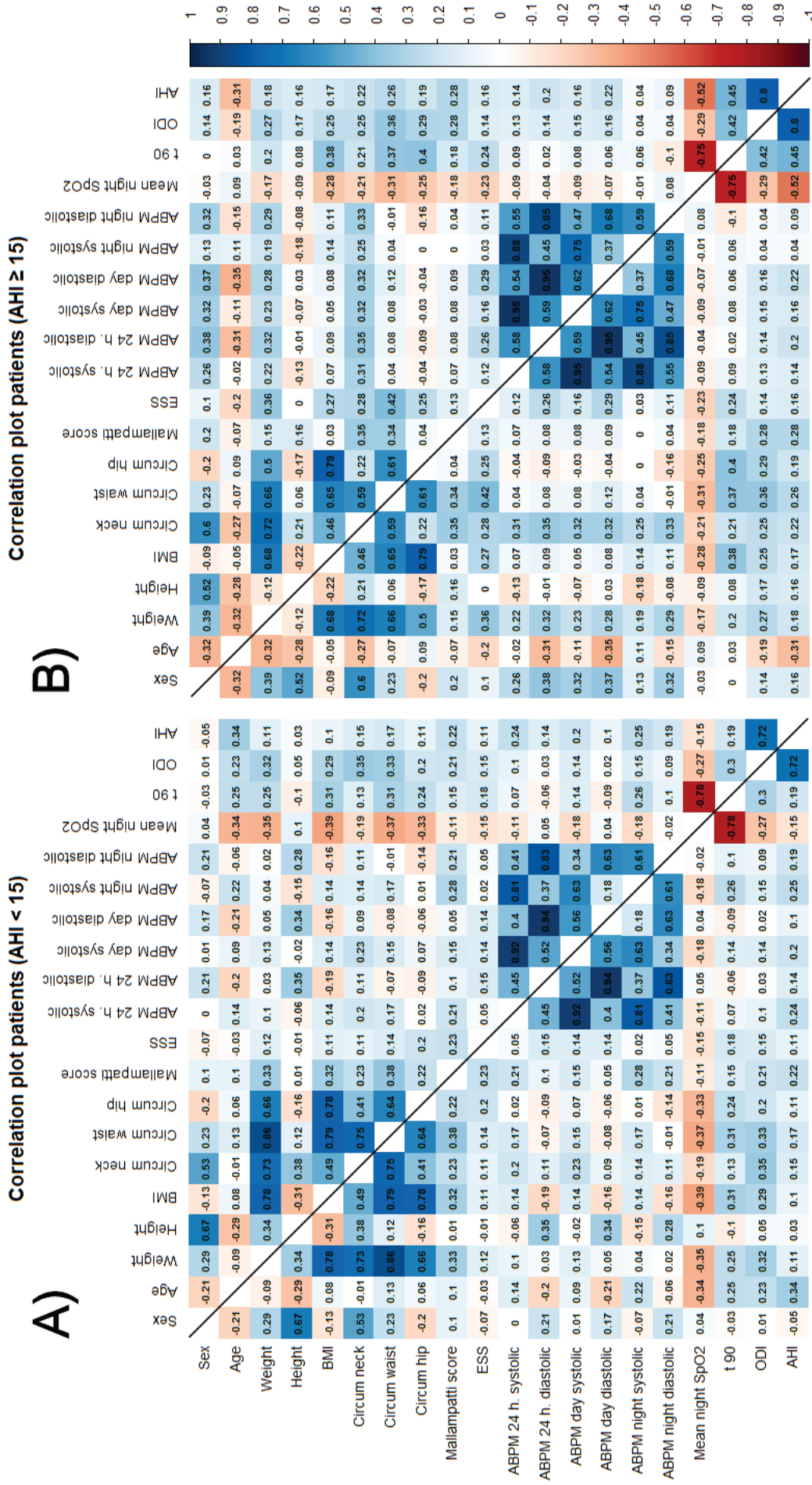


Fig. 5. Correlation analysis of nocturnal registered breathing (AHI, ODI, mean SpO₂, t90) and body characteristics, ESS and Mallampatti score with BP on ABPM in patients with **A)** AHI=0-14.9 (non-SA, mild SA) and **B)** AHI≥15 (moderate and severe SA).

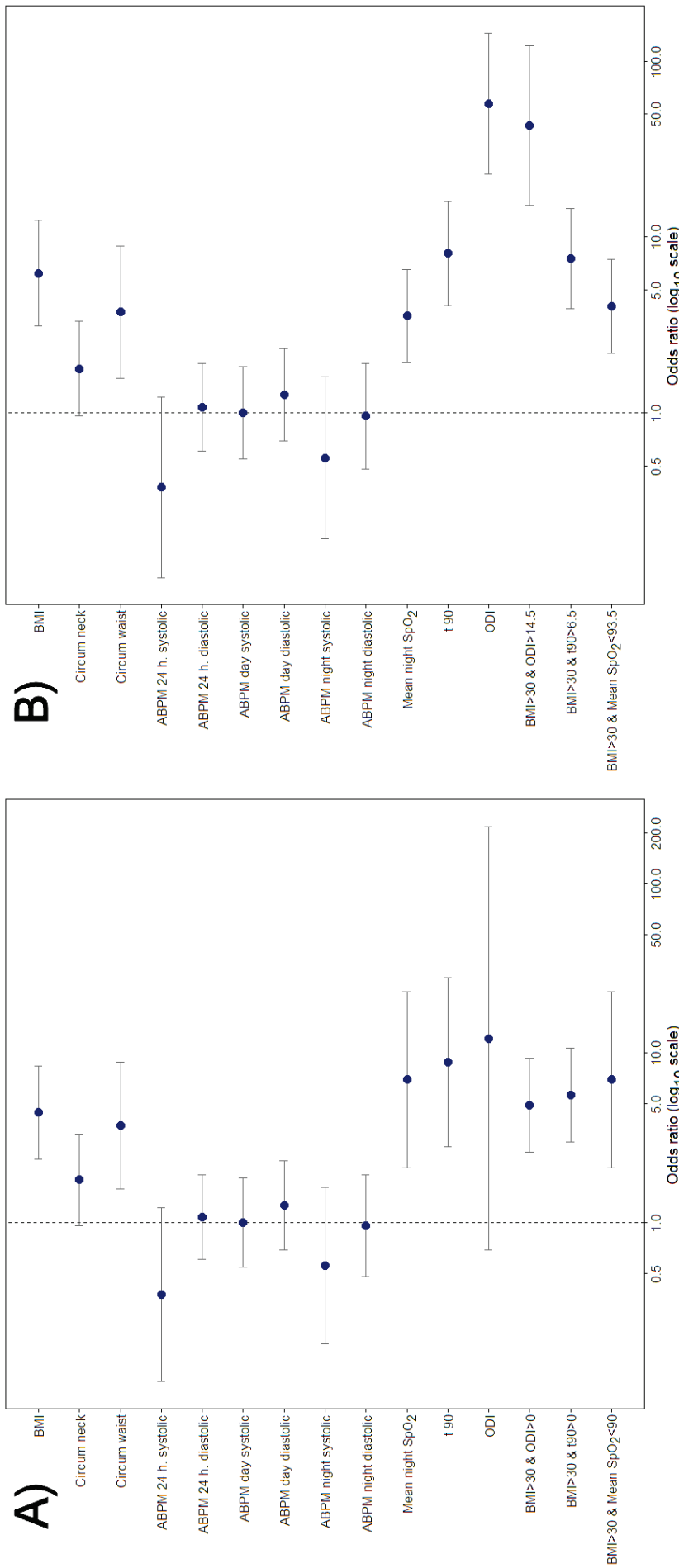


Fig. 6. Odds ratio for patient subgroups with AHI=0-14.9 (non-SA, mild SA) and AHI≥15 (moderate and severe SA) for **A** the normal levels for studied parameters based on the literature, and **B** for levels for studied parameters based on the ROC analysis. For each parameter or combinations of parameters, the odds ratio and the confidence interval (95 % CI) are given. If the confidence interval crosses 1, this implies there is no difference between the studied subgroups.

Comparison of parameters associated with moderate and severe SA

The odds ratios were used to determine whether studied parameters are associated with moderate or severe SA as assessed by AHI, and to compare the magnitude of various risk factors for that outcome (AHI=0-14.9 vs. AHI \geq 15).

Figure 6 shows the results of a logistic regression model used to explore the relationship between clinical and laboratory data and the occurrence of moderate and severe SA, defined as AHI \geq 15. Sleep respiration characteristics such as t90 (odds ratio=8.82, 95 % CI=2.80 to 27.87), mean night SpO₂ (6.96, 2.10-23.10), and ODI (12.16, 0.68-216.17) were associated with having an increased likelihood of moderate/severe SA (Fig. 6A). Additional characteristics associated with an increased likelihood of moderate/severe SA were BMI (4.44, 2.37-8.36), neck circumference (1.78, 0.96-3.31) and waist circumference (3.73, 1.57-8.83). No correlations of AHI were observed for any of ABPM parameters: 24-h systolic (0.37, 0.12-1.22), 24-h diastolic (1.07, 0.60-1.90), daytime (1.00, 0.54-1.82), daytime diastolic (1.26, 0.69-2.31), nighttime systolic (0.55, 0.19-1.60), nighttime diastolic (0.95, 0.47-1.90). The confidence interval crosses 1 for all APBM parameters. This implies there is no association between the studied APBM parameters and AHI.

When the analysis was performed for cut-off values revealed from ROC curves, ODI higher 14.5 markedly increased the likelihood of moderate/severe SA (57.49, 22.79-145.01) (Fig. 6B). The increased likelihood of moderate/severe SA was associated with higher t90 (cut-off 8.07, 4.09-15.92), mean night SpO₂ (3.55, 1.92-6.59), BMI (6.22, 3.10-12.49), neck circumference (1.78, 0.96-3.31), waist circumference (3.73, 1.57-8.83), but not with any of the ABPM parameters (Fig. 6B).

Moreover, we did not reveal an additional significant effect on likelihood of moderate/severe SA when we combined any respiratory parameter (t90, ODI, mean night SpO₂) with BMI (Fig. 6).

Comparison of patients with isolated nocturnal hypertension vs. both daytime-nighttime hypertensions

In order to determine whether patients with nocturnal hypertension and daytime normotensive BP have a higher incidence of SA than those with daytime and nighttime hypertensions, we compared respiratory parameters, anthropometric and anamnestic data between these patient subgroups. There was no statistically

significant difference in respiratory parameters for the group with nocturnal hypertension and daily normotension (n=44) compared with daytime and nighttime hypertensives (n=144): AHI (p=0.297), ODI (p=0.914), mean night saturation (p=0.104), t90 (p=0.081), ESS (p=0.089). We observed higher body weight (p=0.048) and larger neck circumference (p=0.031) in the subgroup of patients with nighttime hypertension and normotension in the day. There was no difference either in age (p=0.141), waist (p=0.519), and hip (p=0.374) between the subgroups of patients with isolated nocturnal hypertension and normotension in the day.

Discussion

This prospective multicenter study showed a high prevalence of SA (72.9 %) in patients with nocturnal hypertension diagnosed by ABPM.

Our results from the Czech patient cohort indicate that SA does not bother patients with nocturnal hypertension, even though 20.2 % reported increased daytime sleepiness (ESS \geq 10). Previous studies indicate that 30 % of hypertensive patients have OSA and conversely 50 % of patients with OSA have hypertension (Peppard *et al.* 2000). Our results on nocturnal hypertension are consistent with studies of resistant hypertension (Logan *et al.* 2001, Gonçalves *et al.* 2007, Pedrosa *et al.* 2011). Hypertension in patients with OSA often presents during the night and has the form of a non-dipper type (Baquet *et al.* 2009). There was a high percentage of non-dippers in our group. This non-dipping pattern can be explained by the increased adrenergic activity during the night in SA as a result of apnoic pause and intermittent hypoxia. There may be also other factors involved as shown e.g. for melatonin reducing BP in rats due inhibition of sympathetic nerve activity (Klimentova *et al.* 2016). Even a mild OSA may prevent nocturnal physiological decrease in BP and can even increase it (Wolf *et al.* 2010). Sekizuka *et al.* (2010) showed that OSA causes nocturnal BP rise even in OSA patients without hypertension. Treating OSA with CPAP leads to a significant decrease in BP (Montesi *et al.* 2012).

Several studies showed that ABPM correlates more closely with organ damage and morbid or fatal events than office BP (Mancia *et al.* 2013). According to the American Heart Association, SA is considered one of the most common identifiable causes of hypertension (Calhoun *et al.* 2008). Previously published studies found

a linear relationship between ABPM and AHI (Young *et al.* 1997) and correlation of BP during sleep with AHI (Lavie *et al.* 1993). Recent epidemiological studies have yielded conflicting data on whether patients with OSA are at increased risk of developing hypertension or whether the frequent development of hypertension is due to other associated factors, such as age, BMI, neck circumference, alcohol and smoking (Cano-Pumarega *et al.* 2011, Marin *et al.* 2012). In our study, there was no correlation of AHI with ABPM in any measurement. Similarly Lévy *et al.* (2011) found no correlation between AHI and nocturnal hypertension. Here, the question is whether OSA is not only a confounding factor in hypertension caused by metabolic parameters, which could support previous epidemiologic studies (Cano-Pumarega *et al.* 2011, Marin *et al.* 2012). In our patients with nighttime hypertension and normotension during the day, we observed association with higher body weight and larger neck circumference.

Despite no association of AHI with ABPM in any measurement, we observed strong association of moderate and severe SA with body characteristics, particularly with BMI and waist circumference, and oxygenation parameters. A likelihood of moderate and severe SA was markedly enhanced by $ODI > 14.5\%$, $t90 > 6.5\%$ and mean night $SpO_2 < 93.5\%$, followed by body characteristics such as $BMI > 29.05 \text{ kg/cm}^2$ and waist circumference $> 105.5 \text{ cm}$. Nevertheless, the decrease of oxygenation parameter may be not only a sign of SA, but of nocturnal hypoventilation in obesity patients thus further supporting the key role of anthropometric parameters in these patients. Importantly, we did not observe any association of severity of SA with any of ABPM parameters. A multivariate analysis did not confirm that combination of BMI or their body characteristics with any oxygenation parameters enhance the likelihood of moderate and severe SA.

In ABPM there were more patients with normal diastolic pressure. In elderly patients this was lower due to frequent isolated systolic hypertension. A number of patients in our sample met the criteria for a diagnosis of resistant hypertension (i.e. patients taking at least three medications, one of which was a diuretic) (Mancia *et al.* 2013). Our data are in line with the literature on the high incidence of OSA in drug resistant hypertension (Logan *et al.* 2001, Gonçalves *et al.* 2007, Pedrosa *et al.* 2011). OSA is currently recognized as an independent risk factor for cardiovascular diseases (CHD, hypertension, cardiac arrhythmias and stroke) (McNicholas and Bonsignore

2007, Bradley and Floras 2009, Pedrosa *et al.* 2011, Jaffe *et al.* 2013). In our group of patients with proven SA, the medical records revealed a fourfold higher incidence of CHD, and more than twice as frequent myocardial infarction than in patients without SA.

Despite high prevalence of SA (72.9 %) in patients with nocturnal hypertension, subgroups with nocturnal hypertension had no higher incidence of SA compared to those who had night and day hypertension. In this exploratory study, we did not analyze other phenotypes and subgroups according to comorbidity, thus future investigation in larger sample cohorts are needed.

To evaluate symptoms of OSA, we used the ESS (subjective daytime sleepiness). The ESS did not prove to be a good screening test: in the whole group, the mean ESS was within the norm (6.3), and even though in patients with confirmed SA there was a higher proportion with $ESS \geq 10$, the difference between groups was not statistically significant. Our results are consistent with similar recent work showing that the ESS is not an adequate screening tool for OSA in patients with night or resistant hypertension (Abrishami *et al.* 2010, Parati *et al.* 2013).

Suspected SA in routine clinical examination can often be demonstrated by Mallampati class. In line with the literature (Nuckton *et al.* 2006), our patients with SA often demonstrated impaired visibility pharyngeal area due to the decline of soft palate and pharyngeal narrowing. There are also other published data (Hukins 2010), where Mallampati class was associated with AHI but did not modify likelihood of severe SA or absence of SA. Our study showed a significant difference in incidence of the most reduced visibility of oropharynx, Mallampati class IV, between groups with and without evidence of SA. However, no Mallampati class relationship to BP on ABPM was proven. According to our knowledge, this is the first report on Mallampati class in hypertensive patients.

This study has several limitations. The patients were recruited from routine examinations from local cardiologists and internists, and there is no information regarding the number of patients who were screened for the presence of nocturnal hypertension and the percentage of patients who had nocturnal hypertension. Moreover, we do not know the primary reason for the investigation of patients by the cardiologists and internists.

Conclusions

Our data demonstrated that SA is frequently

associated with nocturnal and pharmacoresistant hypertension and is underdiagnosed in patients with nocturnal hypertension. SA severity was associated with body characteristics and oxygenation parameters, but not with ABMP parameters and Mallampati score. Thus, especially obese patients with nocturnal hypertension and a non-dipping night BP pattern, breathing during sleep should be investigated for presence of SA.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

ABPM – ambulatory blood pressure monitoring, AHI – apnoea-hypopnoea index, AUC – area under curve, BMI – body mass index, BP – blood pressure, CHD – coronary heart disease, CPAP – continuous positive airway pressure, ESS – Epworth sleepiness scale, Mean SpO₂ – mean night saturation (%), NH – nocturnal hypertension, ODI – oxygen desaturation index, OSA – obstructive sleep apnoea, ROC – Receiver-Operator Characteristic curves, SA – sleep apnoea, SaO₂ – oxygen saturation, SDB – sleep-disordered breathing, t90 – time in saturation below 90 % SaO₂, expressed in %.

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