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Sleep apnoea in patients with nocturnal hypertension – a multicentre study in the Czech Republic.

Short title: Sleep apnoea in nocturnal hypertension

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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. We, therefore, studied the occurrence of SA in Czech patients and its association with 24-hour 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≥15) was associated with BMI, waist circumference, mean night saturation $Sp0_2$, 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 SpO_2<93.5% (3.55, 1.92-6.59), BMI>29.05kg/m^2 (6.22, 3.10-12.49), circum waist>105.5cm (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 ABMP parameters and Mallampati score.

Key words: sleep apnoea, nocturnal hypertension, ambulatory blood pressure monitoring, Mallampati score, Epworth sleepiness scale, BMI

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 seconds (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). 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 multicentre study was: i) to assess the prevalence of undiagnosed SA in patients with nocturnal hypertension, assessed by 24-hour 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 centre (Figure 1). Nocturnal hypertension was defined as nighttime systolic and/or diastolic BP means≥120/70 mm Hg (Parati *et al.* 2014, Mancia *et al.* 2013). Four accredited sleep centres 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, neuroneuromuscular 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 tumours), 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.

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 hips 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 Ltd. 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 hours. A shorter recording than 6 hours 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 SpO_2) and t90 (time in saturation below 90% SaO_2, 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-hour ABPM started each morning at 07-08 a.m. The average 24-hour 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-hours<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 (125 men; median age 59.0 years) with nocturnal hypertension (Table 1). 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%).

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 registrated 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≥5), we observed higher occurence of snorring (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≥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 $Sp0_2$ (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≥15) is shown in Figure 3. Only patients with AHI≥15 were treated with continuous positive airway pressure (CPAP). No differences were observed between subgroups in 24-hour systolic (p=0.906), 24-hour 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 $Sp0_2$ (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-hour systolic (p=0.095), 24-hour 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/m2, sensitivity 84.0%, specificity 55.1%, AUC 0.698) and age (63.5 yrs, sensitivity 43.2%, specificity 75.7%, AUC 0.594) (Figure 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-hour systolic, 24-hour 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 *versus* AHI≥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 (Figure 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 hips circumference was observed (Figure 5).

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 *versus* AHI≥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≥15. Sleep respiration characteristics such as t90 (odds ratio=8.82, 95% CI=2.80 to 27.87), mean night SpO_2 (6.96, 2.10-23.10), and ODI (12.16, 0.68-216.17) were associated with having a increased likelihood of moderate/severe SA (Figure 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-hour systolic (0.37, 0.12-1.22), 24-hour 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) (Figure 6B). The increased likelihood of moderate/severe SA was associated with higher t90 (cut-off 8.07, 4.09-15.92), mean night SpO_2 (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 (Figure 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 SpO_2) with BMI (Figure 6).

Comparison of patients with isolated nocturnal hypertension versus 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 multicentre 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 in patients with nocturnal hypertension are bothered by it little, even though 20.2% reported increased daytime sleepiness (ESS≥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.* showed that OSA causes nocturnal BP rise even in OSA patients without hypertension (Sekizuka *et al.* 2010). 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 Levy et al. (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 likehood 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>29.05kg/cm^2 and waist circumference>105.5cm. 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 Bonsigore 2007, Bradley *et al.* 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 analyse 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≥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 oropharyngx, Mallampati class IV, between groups with and without evidence of SA. No

Mallampati class relationship to BP on ABPM, however, 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.

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Conflict of interest

Authors declare no conflict of interest.

References

ABRISHAMI A, KHAJEHDEHI A, CHUNG F: A systematic review of screening questionnaires for obstructive sleep apnea. *Can J Anaesth* **57**: 423-438, 2010.

BAQUET JP, BARONE-ROCHETTE G, PÉPIN JL: Hypertension and obstructive sleep apnoea syndrome: current perspectives. *J Hum Hypertension* **23**: 431-443, 2009.

BRADLEY, TG, FLORAS JS: Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* **373**: 82-93, 2009.

CALHOUN DA, JONES D, TEXTOR S, GOFF DC, MURPHY TP, TOTO RD, WHITE A, CUSHMAN WC, WHITE W, SICA D, FERDINAND K, GILES TD, FALKNER B, CAREY RM: American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension* **51**: 1403-1419, 2008.

CANO-PUMAREGA I, DURÁN-CANTOLLA J, AIZPURU F, MIRANDA-SERRANO E, RUBIO R, MARTÍNEZ-NULL C, DE MIGUEL J, EGEA C, CANCELO L, ALVAREZ A, FERNÁNDEZ-BOLAÑOS M, BARBÉ F: Obstructive sleep apnea and systemic hypertension: longitudinal study in the general population: the Vitoria Sleep Cohort. *Am J Respir Crit Care Med* **184**: 1299-1304, 2011.

ERMAN MK, STEWART D, EINHORN D, GORDON N, CASAL E: Validation of the ApneaLink for the screening of sleep apnea: a novel and simple single-channel recording device. *J Clin Sleep Med* **3**: 387-392, 2007.

FERNANDEZ-MENDOZA J, VGONTZAS AN, LIAO D, SHAFFER ML, VELA-BUENO A, BASTA M, BIXLER EO: Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension* **60**: 929-935, 2012.

FLEMONS WW, BUYSSE D, REDLINE S, PACK A, STROHL K, WHEATLEY J, YOUNG T, DOUGLAS N, LEVY P, MCNICHOLAS W, FLEETHAM J, WHITE D, SCHMIDT.NOWARRA W, CARLEY D, ROMANIUK J: Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* **22**: 667-689, 1992.

GONÇALVES SC, MARTINEZ D, GUS M, DE ABREU-SILVA EO, BERTOLUCI C, DUTRA I, BRANCHI T, MOREIRA LB, FUCHS SC, DE OLIVEIRA AC, FUCHS FD: Obstructive sleep apnea and resistant hypertension: a case-control study. *Chest* **132:** 1858-1862, 2007.

HUKINS C: Mallampati class is not useful in the clinical assessment of sleep clinic patients. J Clin Sleep Med **6**: 545-549, 2010.

JAFFE LM, KJEKSHUS J, GOTTLIEB SS: Importance and management of chronic sleep apnoea in cardiology. *Eur Heart J* **34**: 809-815, 2013.

JOHNS MW: A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep* **14**: 540-545, 1991.

KHAN A, PATEL NK, O'HEARN DJ, KHAN S. Resistant hypertension and obstructive sleep apnea. *Int J Hypertens* 2013: 193010, 2013.

KLIMENTOVA J, CEBOVA M, BARTA A, MATUSKOVA Z, VRANKOVA S, REHAKOVA R, KOVACSOVA M, PECHANOVA O: Effect of melatonin on blood pressure and nitric oxide generation in rats with metabolic syndrome: *Physiol Res* **65** (Suppl. 3): S373-S380, 2016.

KONECNY T, KARA T, SOMERS VK: Obstructive sleep apnea and hypertension: an update. *Hypertension* **63**: 203-209, 2014.

LAVIE P, YOFFE N, BERGER I, PELED R: The relationship between the severity of sleep apnea syndrome and 24-h blood pressure values in patients with obstructive sleep apnea. *Chest* **103**: 717–7721, 1993.

LÉVY P, TAMISIER R, MINVILLE C, LAUNOIS S, PÉPIN JL: Sleep apnoea syndrome in 2011: current concepts and future directions. *Eur Respir Rev* **20**: 134-146, 2011.

LINDBERG E: Epidemiology of OSA. In: *European Respiratory Society Monograph, vol 50.*

LOGAN AG, PERLIKOWSKI SM, MENTE A, TISLER A, TKACOVA R, NIROUMAND M, LEUNG RS, BRADLEY TD: High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens* **19**: 2271-2277, 2001.

MALLAMPATI SR: Clinical sign to predict diffucult tracheal intubation (hypothesis). *Can Anaesth Soc J* **30**: 316-317, 1983.

MANCIA G, FAGARD R, NARKIEWICZ K, REDON J, ZANCHETTI A, BÖHM M, CHRISTIAENS T, CIFKOVA R, DE BACKER G, DOMINICZAK A, GALDERISI M, GROBBEE DE, JAARSMA T, KIRCHHOF P, KJELDSEN SE, LAURENT S, MANOLIS AJ, NILSSON PM, RUILOPE LM, SCHMIEDER RE, SIRNES PA, SLEIGHT P, VIIGIMAA M, WAEBER B, ZANNAD F: 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *J Hypertens* **31**: 1281-1357, 2013.

MARIN JM, AGUSTI A, VILLAR I, FORNER M, NIETO D, CARRIZO SJ, BARBÉ F, VICENTE E, WEI Y, NIETO FJ, JELIC S: Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA* **307**: 2169-2176, 2012.

MCNICHOLAS WT, BONSIGORE MR: Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J* **29**: 156-178, 2007.

MONTESI SB, EDWARDS BA, MALHOTRA A, BAKKER JP: The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med* **8**: 587-596, 2012.

NUCKTON TJ, GLIDDEN DV, BROWNER WS, CLAMAN DM: Physical examination: Mallampati score as an independent predictor of obstructive sleep apnea. *Sleep* **29**: 903-908, 2006.

PARATI G, LOMBARDI C, HEDNER J, BONSIGNORE MR, GROTE L, TKACOVA R, LEVY P, RIHA R, BASSETTI C, NARKIEWICZ K, MANCIA G, MCNICHOLAS WT: Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (Cooperation in Scientific and Technological research) ACTION B26 on obstructive sleep apnea. *J Hypertens* **30**: 633-646, 2012.

PARATI G, LOMBARDI C, HEDNER J, BONSIGNORE MR, GROTE L, TKACOVA R, LÉVY P, RIHA R, BASSETTI C, NARKIEWICZ K, MANCIA G, MCNICHOLAS WT: Recommendations for the management of patients with obstructive sleep apnoea and hypertension. *Eur Respir J* **41**: 523-538, 2013.

PARATI G, STERGIOU G, O'BRIEN E, ASMAR R, BEILIN L, BILO G, CLEMENT D, DE LA SIERRA A, DE LEEUW P, DOLAN E, FAGARD R, GRAVES J, HEAD GA, IMAI Y, KARIO K, LURBE E, MALLION JM, MANCIA G, MENGDEN T, MYERS M, OGEDEGBE G, OHKUBO T, OMBONI S, PALATINI P, REDON J, RUILOPE LM, SHENNAN A, STAESSEN JA, VANMONTFRANS G, VERDECCHIA P, WAEBER B, WANG J, ZANCHETTI A, ZHANG: European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *Journal of Hypertension* **32**: 1359-1366, 2014.

PEDROSA RP, DRAGER LF, GONZAGA CC, SOUSA MG, DE PAULA LKG, AMARO AC, AMODEO C, BORTOLOTTO LA, KRIEGER EM, BRADLEY TD, LORENZI-FILHO G: Obstructive sleep apnea: The most common secondary cause of hypertension associated with resistant hypertension. *Hypertension* **58**: 811-817, 2011.

PEPPARD PE, YOUNG T, PALTA M, SKATRUD J: Prospective study of the association between sleep- disordered breathing and hypertension. *N Engl J Med* **342**: 1378-1384, 2000.

PHILLIPS CL, O´DRISCOLL DM: Hypertension and obstructive sleep apnea. *Nat Sci Sleep* **5**: 43-52, 2013.

QASEEM A, DALLAS P, OWENS DK, STARKEY M, HOLTY JE, SHEKELLE P: Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* **161**: 210-220, 2014.

SEKIZUKA H, KIDA K, AKASHI YJ, YONEYAMA K, OSADA N, OMIYA K, MIYAKE F: Relationship between sleep apnea syndrome and sleep blood pressure in patients without hypertension. *J Cardiol* **55**: 92-98, 2010.

TORRES G, SÁNCHEZ-DE-LA-TORRE M, BARBÉ F: Relationship between OSA and hypertension. *Chest* **148**: 824-832, 2015.

WOLF J, HERING D, NARKIEWICZ K: Non-dipping pattern of hypertension and obstructive sleep apnea syndrome. *Hypertens Res* **33:** 867-871, 2010.

YOUNG T, PEPPARD P, PALTA M, HLA KM, FINN L, MORGAN B, SKATRUD J: Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med* **157**: 1746-1752, 1997.

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

	Whole sample set n=188	**Male n=123**	**Female n=65**
age (years)	59.0 (53.0-65.0)	58.0 (50.0-64.0)	62.0 (58.0-67.0)
Male/female	123(65.4%)/65 (34.6%)	123/0	0/65
Medical history of snoring (%)	71.5%	76.2%	62.5%
Medical history of apnoea (%)	41.8%	46.3%	33.3%
ESS	6.0 (3.0-9.0)	6.0 (3.0-9.0)	5.0 (2.0-9.0)
Anthropometry			
BMI (kg/m^2)	30.9 (27.4-35.1)	30.5 (27.3-34.5)	31.2 (28.0-36.0)
neck circumference (cm)	42.0 (39.0-44.0)	43.0 (41.0-45.0)	39.0 (36.5-40.0)
waist circumference (cm)	108.0 (98.0-115.0)	109.0 (100.0-117.5)	103.0 (95.0-114.0)
hip circumference (cm)	108.0 (103.8-115.2)	107.0 (102.5-114.0)	110.0 (105.0-117.0)
ABPM			
24-hour systolic (mm Hg)	139.0 (133.0-149.0)	139.9 (134.0-151.0)	138.0 (133.0-143.5)
24-hour diastolic (mm Hg)	80.0 (76.0-87.0)	81.0 (77.0-89.0)	78.0 (69.0-83.0)
daytime systolic (mm Hg)	140.0 (134.0-149.0)	142.0 (134.0-152.0)	137.0 (131.8-145.0)
daytime diastolic (mm Hg)	83.0 (76.0-90.0)	84.0 (78.0-92.0)	79.0 (72.0-85.0)
nighttime systolic (mm Hg)	139.0 (131.0-149.0)	139.0 (130.0-150.0)	140.0 (131.0-148.0)
nighttime systolic (mm Hg)	78.0 (73.0-85.0)	80.0 (75.0-87.0)	75.0 (66.2-85.0)
Respiration Parameters			
AHI (events/h)	12.0 (5.0-23.8)	14.0 (6.0-28.5)	10.0 (5.0-21.0)
ODI (events/h)	10.5 (5.0-22.8)	13.0 (6.0-26.0)	8.0 (5.0-16.0)
Mean SpO_2 (%)	93.0 (92.0-95.0)	93.0 (92.0-95.0)	93.0 (92.0-95.0)
t90 (%)	8.0 (1.0-25.8)	9.0 (1.0-25.0)	6.0 (2.0-27.0)

Legend: ABPM - 24-hour ambulatory BP monitoring, ESS - Epworth sleepiness scale, AHI - apnoea-hypopnoea index, ODI - oxygen desaturation index, Mean SpO_2 - mean night saturation (%), t90% - time in saturation below 90% SaO_2

Figure Legends

Figure 1 Flow chart of patients who met inclusion/exclusion criteria for this study.
Legend: ****Inclusion criteria:** patients with nigth 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, neuroneuromuscular 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 tumours), clinical signs of heart failure, treatment with benzodiazepines and myorelaxans or lack of interest in participation.

Figure 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 centre 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).

Figure 3. Comparison of subgroups of patients with AHI=0-14.9 (non-SA, mild SA) *versus* AHI≥15 (moderate and severe SA) in ABPM parameters:
A) mean 24-hour time systolic BP, **B)** mean 24-hour 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 centre 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.
Legend: BP - blood pressure, AHI - apnoea-hypopnoea index

Figure 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 SpO_2, **D)** t90, **E)** ODI, **G)** ABPM parameters

Figure 5. Correlation analysis of nocturnal registered breathing (AHI, ODI, mean SpO_2, t90) and body characteristics, ESS and Mallampati 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)

Figure 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.

Figure 1

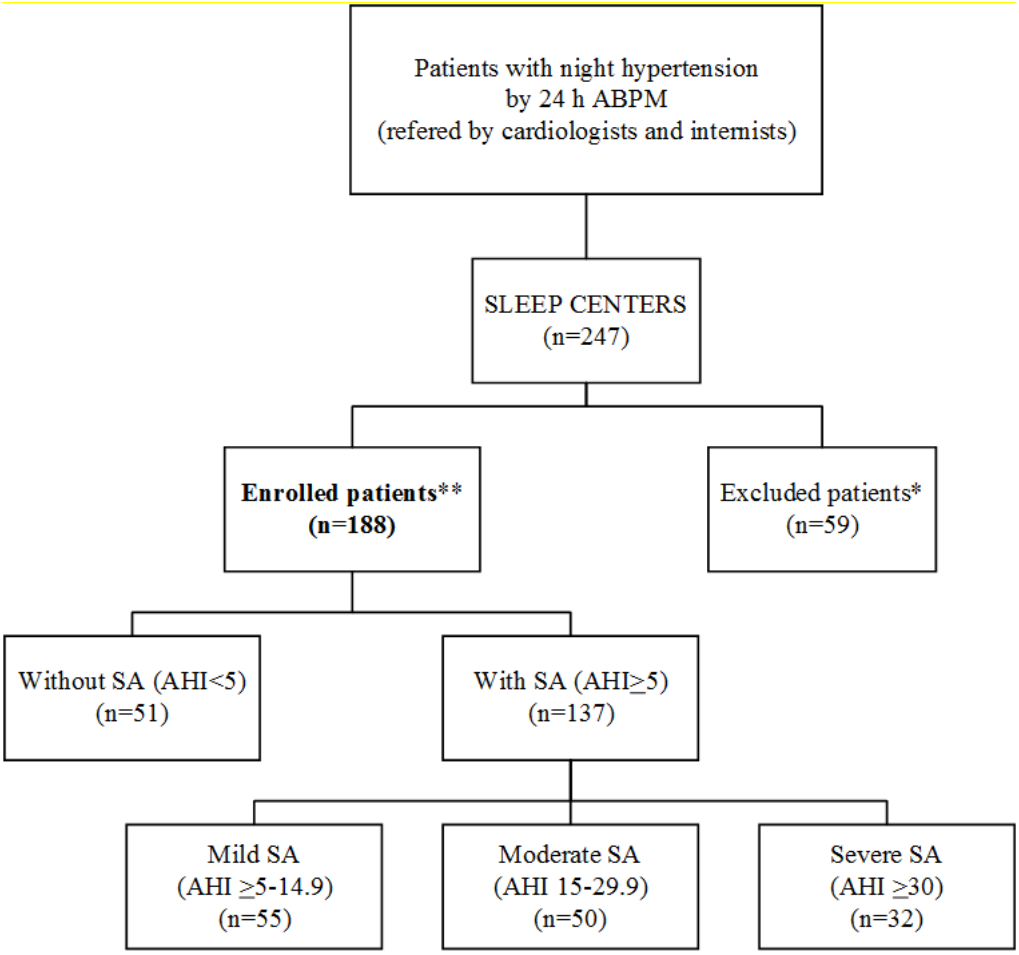

Patients with night hypertension
by 24 h ABPM
(refered by cardiologists and internists)
SLEEP CENTERS
(n=247)
Enrolled patients**
(n=188)
Excluded patients*
(n=59)
Without SA (AHI<5)
(n=51)
With SA (AHI≥5)
(n=137)
Mild SA
(AHI ≥5-14.9)
(n=55)
Moderate SA
(AHI 15-29.9)
(n=50)
Severe SA
(AHI ≥30)
(n=32)

Figure 2

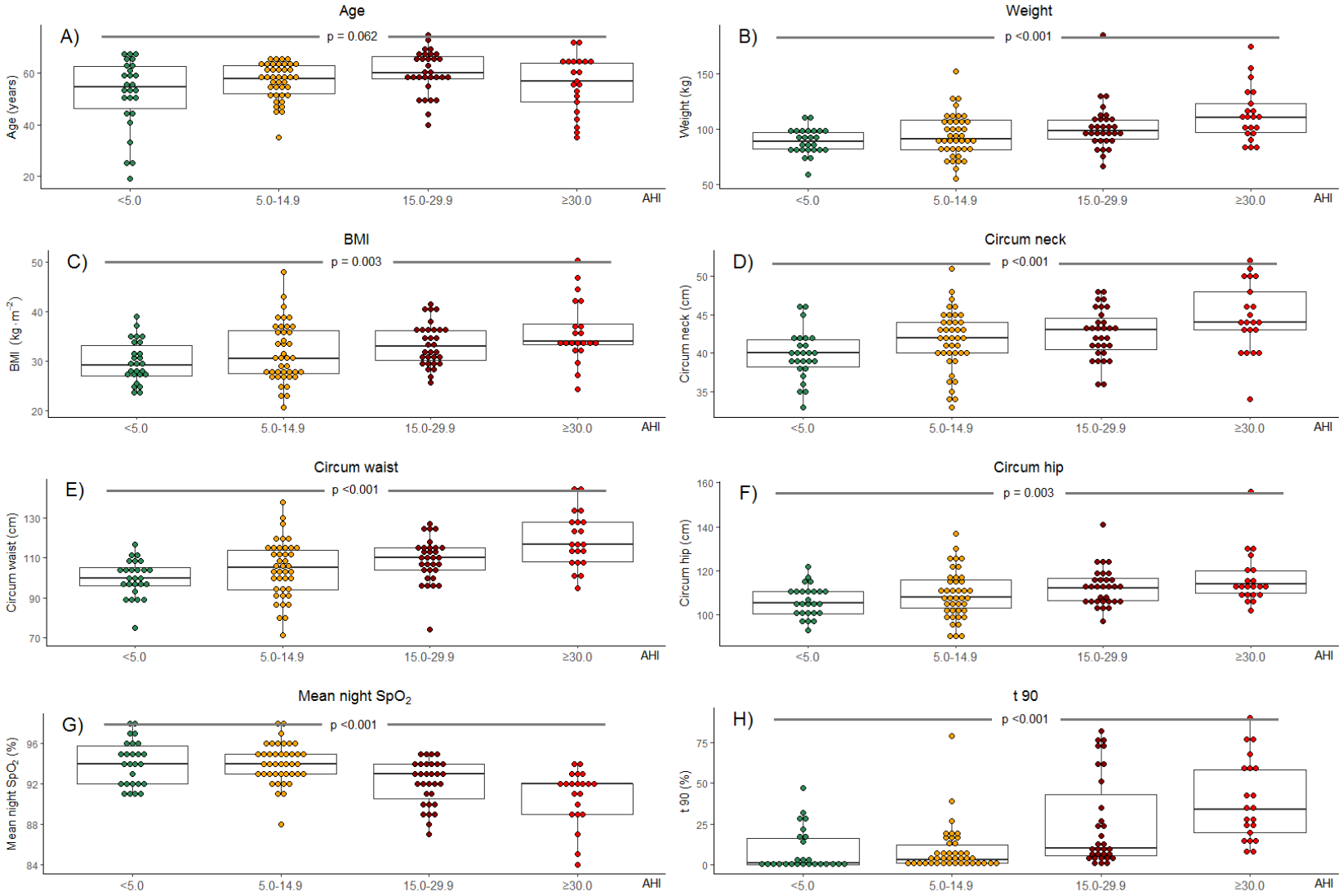

Age
A)
p = 0.062
Age (years)
Weight
B)
p <0.001
Weight (kg)
BMI
C)
p = 0.003
BMI (kg·m-2)
Circum neck
D)
p <0.001
Circum neck (cm)
Circum waist
E)
p <0.001
Circum waist (cm)
Circum hip
F)
p = 0.003
Circum hip (cm)
Mean night SpO2
G)
p <0.001
Mean night SpO2 (%)
t 90
H)
p <0.001
t 90 (%)
<5.0
5.0-14.9
15.0-29.9
≥30.0
AHI

Figure 3

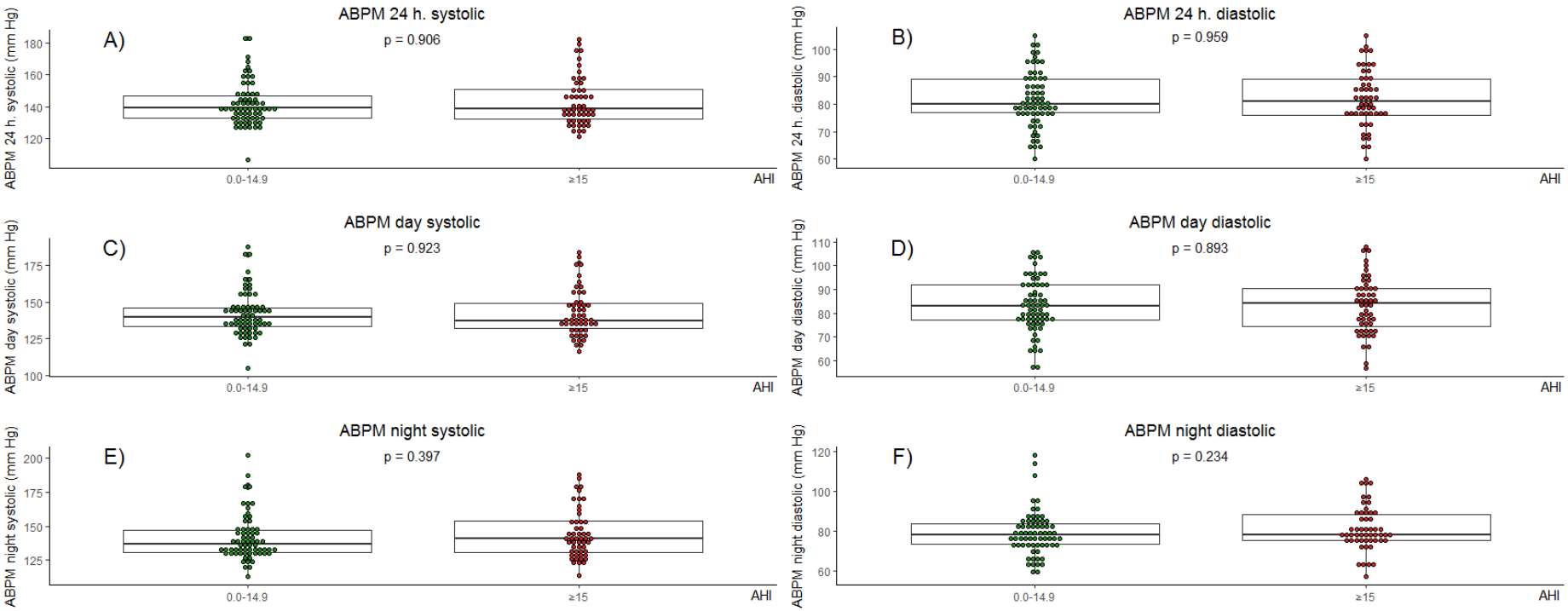

ABPM 24 h. systolic
A)
p = 0.906
ABPM 24 h. systolic (mm Hg)
180
160
140
120
0.0-14.9
≥15
AHI
ABPM 24 h. diastolic
B)
p = 0.959
ABPM 24 h. diastolic (mm Hg)
100
90
80
70
60
0.0-14.9
≥15
AHI
ABPM day systolic
C)
p = 0.923
ABPM day systolic (mm Hg)
175
150
125
100
0.0-14.9
≥15
AHI
ABPM day diastolic
D)
p = 0.893
ABPM day diastolic (mm Hg)
110
100
90
80
70
60
0.0-14.9
≥15
AHI
ABPM night systolic
E)
p = 0.397
ABPM night systolic (mm Hg)
200
175
150
125
0.0-14.9
≥15
AHI
ABPM night diastolic
F)
p = 0.234
ABPM night diastolic (mm Hg)
120
100
80
60
0.0-14.9
≥15
AHI

Figure 4

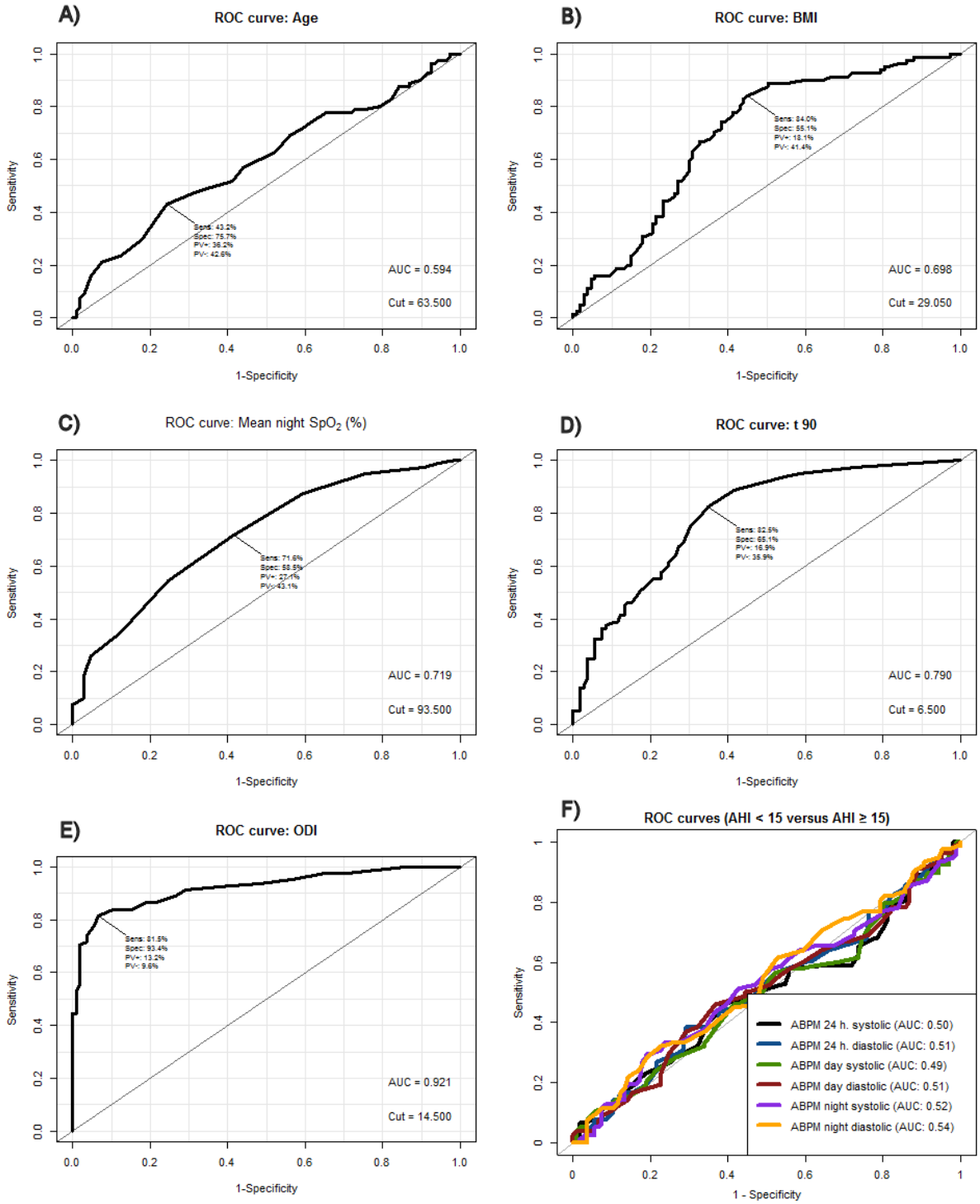

A)
ROC curve: Age
Sens: 43.2%
Spec: 75.7%
PV+: 36.2%
PV-: 42.6%
AUC = 0.594
Cut = 63.500
B)
ROC curve: BMI
Sens: 84.0%
Spec: 55.1%
PV+: 18.1%
PV-: 41.4%
AUC = 0.698
Cut = 29.050
C)
ROC curve: Mean night SpO2 (%)
Sens: 71.6%
Spec: 68.5%
PV+: 27.1%
PV-: 43.1%
AUC = 0.719
Cut = 93.500
D)
ROC curve: t 90
Sens: 82.5%
Spec: 66.1%
PV+: 16.9%
PV-: 35.9%
AUC = 0.790
Cut = 6.500
E)
ROC curve: ODI
Sens: 81.5%
Spec: 93.4%
PV+: 13.2%
PV-: 9.6%
AUC = 0.921
Cut = 14.500
F)
ROC curves (AHI < 15 versus AHI ≥ 15)
ABPM 24 h. systolic (AUC: 0.50)
ABPM 24 h. diastolic (AUC: 0.51)
ABPM day systolic (AUC: 0.49)
ABPM day diastolic (AUC: 0.51)
ABPM night systolic (AUC: 0.52)
ABPM night diastolic (AUC: 0.54)
Sensitivity
1-Specificity
1 - Specificity

Figure 5

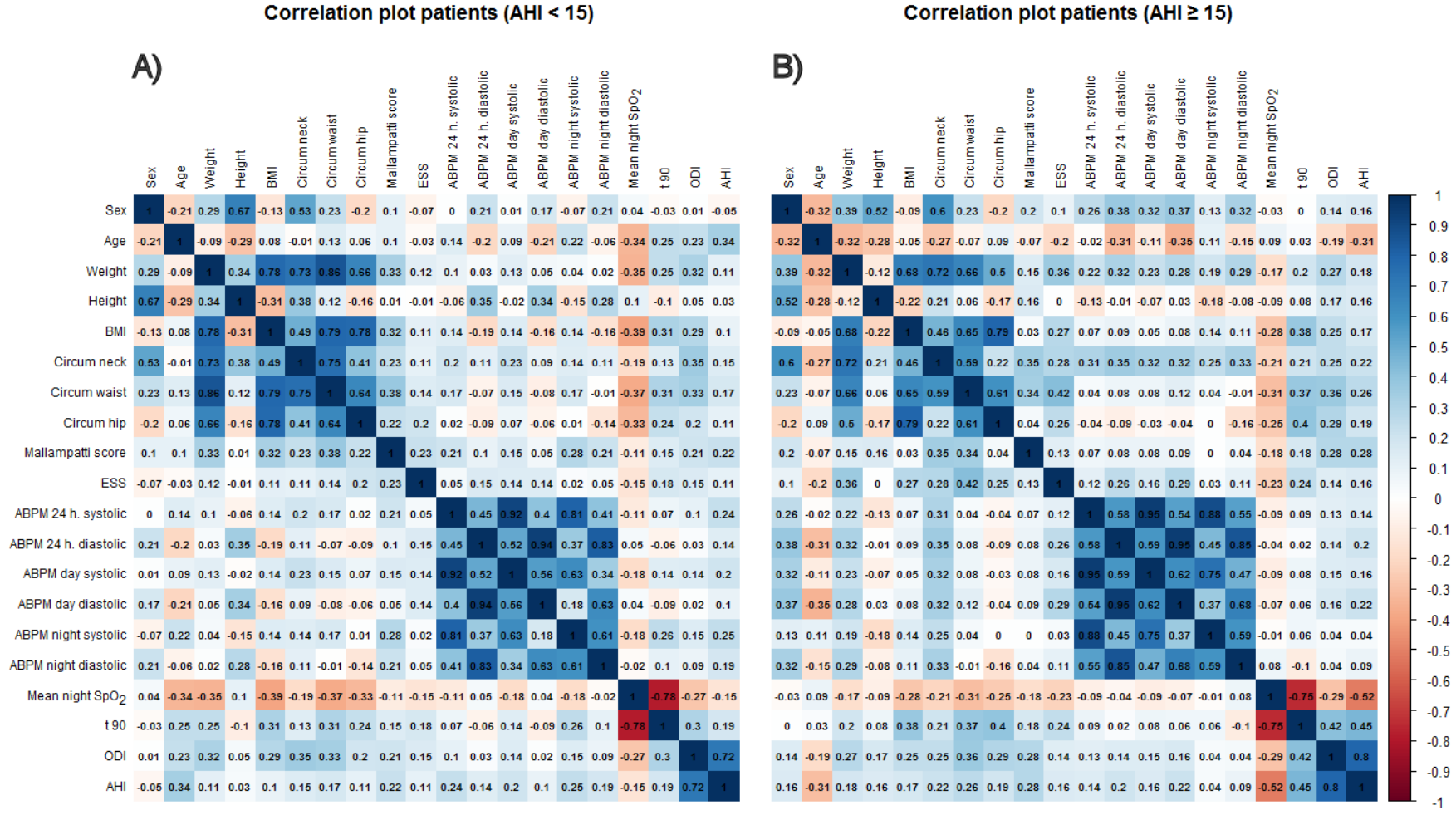
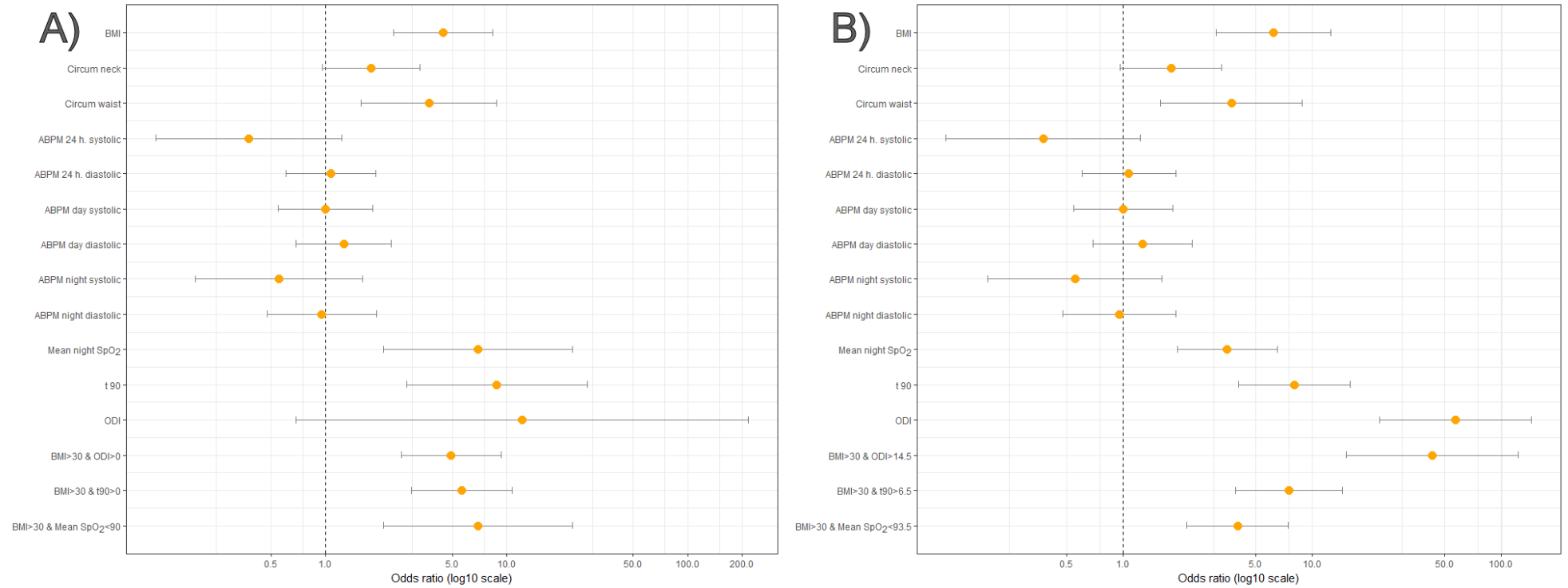

Correlation plot patients (AHI < 15)
A)
Correlation plot patients (AHI ≥ 15)
B)
Sex
Age
Weight
Height
BMI
Circum neck
Circum waist
Circum hip
Mallampatti score
ESS
ABPM 24 h. systolic
ABPM 24 h. diastolic
ABPM day systolic
ABPM day diastolic
ABPM night systolic
ABPM night diastolic
Mean night SpO2
t 90
ODI
AHI
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9
-1

Figure 6


A)
BMI
Circum neck
Circum waist
ABPM 24 h. systolic
ABPM 24 h. diastolic
ABPM day systolic
ABPM day diastolic
ABPM night systolic
ABPM night diastolic
Mean night SpO2
t 90
ODI
BMI>30 & ODI>0
BMI>30 & t90>0
BMI>30 & Mean SpO2<90
0.5
1.0
5.0
10.0
50.0
100.0
200.0
Odds ratio (log10 scale)
B)
BMI
Circum neck
Circum waist
ABPM 24 h. systolic
ABPM 24 h. diastolic
ABPM day systolic
ABPM day diastolic
ABPM night systolic
ABPM night diastolic
Mean night SpO2
t 90
ODI
BMI>30 & ODI>14.5
BMI>30 & t90>6.5
BMI>30 & Mean SpO2<93.5
0.5
1.0
5.0
10.0
50.0
100.0
Odds ratio (log10 scale)