VERSITA

Cent. Eur. J. Med. • 4(2) • 2009 • 222-232
DOI: 10.2478/s11536-009-0011-z

Central European Journal of **Medicine**

Blood pressure increase detected by ambulatory monitoring correlates with hypoxemia reflecting sleep apnea severity

Research Article

Soňa Grešová[1], Zoltán Tomori[1], Martin Kurpas[2], Alexander Marossy[1], Adela Vrbenská[3], Martin Kundrík[1], Viliam Donič[1].

[1] *Department of Physiology, Medical Faculty, Safarik University, 040 66 Kosice, Slovak Republic*

[2] *Department of Pathological Physiology, Medical Faculty, Safarik University, 040 66 Kosice, Slovak Republic*

[3] *Department of Pathology, Medical Faculty, Safarik University, 040 66 Kosice, Slovak Republic*

Received 17 April 2008; Accepted 27 August 2008

Abstract: Ambulatory blood pressure monitoring and parallel polysomnographic study were performed in 116 adult males divided into 6 groups. Thirty blood-pressure (BP) and polysomnographic variables were measured to test their usefulness for screening for both arterial hypertension and sleep apnea–hypopnea syndrome (SAHS). The development of severe breathing disorders and hypoxemia during sleep was attributed to SAHS, when compared with measurements in healthy controls and in patients with arterial hypertension. Such disorders manifested as an increased apnea–hypopnea index, apnea index, duration of arterial oxygen saturation of less than 85%, and decrease of average arterial oxygen saturation that correlated with nocturnal average diastolic BP ($p=0.0049$, $p=0.0027$, $p=0.049$ and $p=0.0457$, respectively). These respiratory disorders resulted in various nocturnal, rather than diurnal, and diastolic and systolic BP variables. The acute antihypertensive effect of continuous positive airway pressure therapy for SAHS significantly reduced the episodes of apnea and hypopnea and the secondary component of hypertension caused by excessive sympathetic stimulation. For the SAHS-induced, dose-dependent component of hypertension that responded to continuous positive airway pressure, the following variables, in decreasing significance, were useful: nocturnal average systolic and diastolic BP and 24-hour average systolic and diastolic BP, as well as percent time elevation and mean blood pressure load. The monitoring of these variables could contribute to early diagnostic and prognostic stratification of complications and adequate therapy of the secondary component of hypertension caused by SAHS.

Keywords: *Blood pressure monitoring • Hypertension • Hypoxemia • Sleep apnea • Screening*

1. Introduction

Sleep-disordered breathing and its clinically very important and treatable component, the sleep apnea–hypopnea syndrome (SAHS), is characterized by more than 5 apnea– hypopnea episodes per 1 hour of sleep, as defined by the apnea–hypopnea index (AHI). Sleep-disordered breathing has been found to occur in 24% of men and 9% of women in the general population [1,2]. Frequent apnea–hypopnea episodes in patients with SAHS trigger various hemodynamic effects that are in direct contrast to the relaxation effects of physiological sleep; these include arterial hypertension (AH) resulting from hypoxia, hypercapnia, arousal, and sympathetic stimulation [3-7]. Several studies have established that patients with SAHS have a higher prevalence of AH than the general population, even after adjusting for such confounding variables as body mass index, age, and sex [5,8-12]. Previously unrecognized AH has also been found by clinical BP measurement in 39% of patients with newly diagnosed SAHS and by ambulatory blood pressure monitoring (ABPM) in as many as 62%

* *E-mail: gresovas@lf.upjs.sk*

[13,14]. SAHS is also an independent risk factor for AH and various cardiovascular diseases, such as coronary artery disease, myocardial infarction, stroke, and atherosclerosis [2,4,10,15-21].

In AH, different pathogenetic mechanisms determine variable symptomatology, therapy, and prevention. In addition to the most prevalent form, essential hypertension, characterized by chronic sympatho-adrenal activation, about 15% of hypertensive patients older than 60 years have an isolated systolic hypertension due to lower sympathetic reactivity [12,16]. Several studies have shown that, without consideration of other secondary presentations of AH, more than 10% of established hypertensive patients are refractory to treatment by three or more drugs, despite good compliance [5,18,22-24].

Noninvasive 24-hour ABPM could be useful for screening for both unrecognized AH and SAHS, for detection of the hypertensive effect of SAHS, and for assessing the treatment of SAHS with continuous positive airway pressure (CPAP) therapy [10,21-23]. Previous studies have used other methods to assess ABPM [25,26]. Several recent studies have demonstrated primary increases in nocturnal and diastolic BP in patients with SAHS [12,14,27]. However, only a tendency for a parallel increase in diastolic pressure and in nocturnal and diurnal systolic BP has been observed in a few studies [18,24,28]; this finding could be due to either a low number of patients or an inability to correlate BP changes with ventilatory and respiratory variables determined mostly on non-parallel ABPM and polysomnographic (PSG) examination [17,21,28], especially when the measurements were unattended [24].

The current study compared the circadian variation of BP as detected by continuous 24-hour noninvasive ABPM with variables reflecting the severity of SAHS as assessed by parallel whole-night PSG examination. We sought to determine which of the 30 BP and PSG parameters and indices could be useful for screening for both AH and SAHS for possible use in the diagnosis, prognostic stratification of complications, and adequate therapy of these two disorders. In particular, we focused on both the secondary hypertensive effect of SAHS and the acute antihypertensive efficacy of CPAP therapy, which has been examined in only a few studies with only a limited number of BP variables or with a primary interest in the long-term effects of CPAP in refractory hypertension [5,18,27,28].

2. Material and Methods

2.1. Subjects and protocol

The study included 116 adult males selected from more than 600 subjects examined between 2004 and 2007 in our sleep laboratory because of symptoms of sleep-disordered breathing. General and anthropometric data were collected for all subjects to determine fulfillment of inclusion and exclusion criteria, which were analyzed in more detail in our previous study [20]. These data included medical history, especially concerning symptoms of suspected SAHS and AH (e.g., habitual snoring, witnessed apneas, other disorders during sleep, and frequent interruption of sleep with subsequent daytime sleepiness as quantified by the Epworth Sleepiness Scale), as well as cardiorespiratory disorders (e.g., cardiac arrhythmias, older myocardial infarction, stroke or hypertension, and use of antihypertensive medication or any other drugs capable of interfering with BP values). Antihypertensive or other therapy was not modified during the ABPM (Table 1) for ethical reasons. The definition for AH was occasional BP greater than or equal to 140/90 mm Hg according to the World Health Organization (WHO) guidelines [29].

Patients with failure of vital organs were excluded from the trial on the basis of an appropriate clinical examination, including an electrocardiogram, echocardiogram with ejection fraction less than 50%, biochemical examination of blood, and acid-base balance focused mainly on evaluation of various risk factors. Additional exclusion criteria were heart failure; asthma, or other severe pulmonary disease; hepatic insufficiency; chronic renal failure, as indicated by more than 200 μmol/l serum creatinine; complicated atherosclerosis of the brain, cardiac, or renal or limb arteries; malignant diseases; and diabetes mellitus with chronic complications or insulin therapy.

Six groups of subjects were examined in the study: (1) healthy controls, (2) patients with AH alone, (3, 4, 5) those with mild, moderate and severe SAHS, and (6) those with SAHS treated by CPAP. The study was designed to determine the secondary hypertensive effect of SAHS and the BP-lowering effect of CPAP therapy by comparisons of approximately 30 variables obtained during parallel ABPM and whole-night polysomnography, with the informed consent of all subjects. The study was approved by the Ethics Committee of the Medical Faculty, P. J. Safarik University, Kosice, Slovakia.

Table 1. Distribution of 116 subjects into 6 groups with basic anthropometric data and presence or absence of antihypertensive medication.

Variable \ Group	Healthy control	AH	mild SAHS (5<AHI≤20/h)	moderate SAHS (20<AHI ≤40/h)	severe SAHS (AHI>40/h)	SAHS with CPAP
n-number of subjects	15	16	25	23	26	11
Age (years)	48.1±18.3	56.2±13.3	53.3±10.6	52.5±10.7	50.5±9.6	47.1±4.8
		.	..	...	... +	..+
BMI	26.5±3.2	30.0±5.3	29.9±3.8	33.3±6.9	35.2±6.4	36.2±7.7
Without antihypertensive therapy (%)	100	25	44	43.5	50	27.3
Without declared number of drugs (%)	0	18.75	20	8.7	23.2	45.4
ACE inhibitors (%)	0	6.25	0	0	7.7	0
ACE inhibitors+ Diuretics (%)	0	0	8	0	0	0
β blockers (%)	0	6.25	12	4.35	3.8	0
β blockers +Diuretics (%)	0	0	4	0	3.8	0
K- antagonists (%)	0	0	8	4.35	0	0
Combination of two antihypertensives (%)	0	31.25	4	17.4	7.7	27.3
Combination of three antihypertensives (%)	0	12.5	0	21.7	3.8	0

Means ± SD of measured parameters: Age (years), BMI – Body Mass Index (BMI=(weight-kg) / (height-cm)^2). The results indicate also the significant differences of each selected group compared to other 5 groups by various symbols: • - vs. healthy control, + - vs. AH, x- vs. mild SAHS, Δ - vs. moderate SAHS, and # - vs. severe SAHS. The level of significance is indicated by a number of the pertinent symbols (1: $p<0.05$, 2: $p<0.01$, 3: $p<0.001$).

2.2. Sleep study

An overnight recording of more than 20 electrophysiological and cardiorespiratory variables was performed with a polysomnograph (ALICE 3, Respironics), which provided automatic evaluation of the results indicated in Table 2. Occurrence of more than 5 apnea–hypopnea events during 1 hour of sleep served as the main diagnostic criterion for SAHS. The apnea–hypopnea index (AHI), apnea index (AI) and hypopnea index (HI), indicating the number of pertinent events per hour of sleep, were used for assessment of SAHS severity and subdivided into three degrees. Four electroencephalographic leads, 2 electrooculograms, and 2 electromyograms indicating activation of the nervous system were used mainly to determine sleep stages and various degrees of arousal reaction. Continuous pulse oxymetric recording of oxygen saturation on a finger of the right hand allowed detection of average value ($AvgSatO_2$), and duration of both oxygen saturations less than 85% and less than 90% ($SatO_2$ <85% and $SatO_2$ <90%) in minutes, reflecting both the intensity and duration of hypoxemia. These values were calculated automatically by the polysomnograph and validated manually, according to standard criteria indicated in a previous publication [20].

2.3. The 24-hour ABPM

ABPM and continuous recording of the electrocardiogram from a precordial lead were performed with a portable device (Cardiotens, Meditech, Budapest) with an appropriately sized cuff fixed on the left arm [17]. BP was measured automatically at 15-minute intervals during the day and at 30-minute intervals at night, or following an occasional cardiac arrhythmia. Eighteen BP variables, including the maximum and minimum values of the systolic, diastolic, and mean BPs, were measured as an average for the nocturnal, diurnal, and 24-hour periods. Some additional indices, such as percent time elevation of BP (PTE %), mean pressure load (mm Hg), heart rate, and other selected values, were calculated as in our previous study [17]. After complex analysis, the mean values plus or minus the standard deviation (SD) of selected BP and PSG variables were compared among the 6 groups of subjects as indicated in Table 2.

2.4. Patient groups and statistical analysis

Complex clinical and laboratory examinations, including repeated occasional BP measurements with limits for AH (140/90 mm Hg and higher) [29], were performed in all 116 adult male subjects. According to the presence or absence of AH and SAHS with three different degrees of severity as reflected by AHI and CPAP, the subjects were divided into six groups. Statistical evaluation of results was performed with Tukey-Kramer multiple comparisons of the six groups. The p value <0.05 was considered statistically significant. In addition, BP values were correlated with polysomnographic parameters by correlation and linear regression analysis.

Table 2. Selected blood pressure and polysomnographic variables and indices in 6 groups of 116 subjects.

Group / Variable	Healthy control	AH	mild SAHS (5<AHI≤20/h)	moderate SAHS (20<AHI ≤40/h)	severe SAHS (AHI>40/h)	SAHS with CPAP (AHI=41.2±16.4)
n-number of subjects	15	16	25	23	26	11
		...	...	...	... xx	...
nocturnal AvgSBP	110.1±7.9	134±10.7	127.7±12	135.2±17.4	140.9±13.9	133.5±10.5
			.	..	... + x	..
nocturnal AvgDBP	66.5±8.9	74.2±7.5	75.8±9.3	77.6±9.6	84.2±10.8	79.8±4.5
		...	..	..	...	..
diurnal AvgSBP	122.2±10.1	145.8±20.2	137.6±10.4	138.4±8.3	145.3±12.9	139.8±9.3
			.		...	
diurnal AvgDBP	76.5±10	85±12	85.7±7.6	84.9±5.9	89.7±9.8	83.2±4.0
		...	...	...	... x	...
24-h AvgSBP	118.1±8.6	140±13.7	133.8±10	137.1±10	143.2±12	136±7.8
			..	..	...	
24-h AvgDBP	73.2±9.1	80.9±7.8	81.9±7.2	82.2±6.4	87.4±8.9	81±4.1
		.		..	.. x	.. x
PTE (%)	17.5±24.1	49.3±23.5	29.3±16.6	52.8±27.3	62.3±22.5	59.4±25.8
				x		x
MPL (mmHg/h)	35.6±66	201.2±157.8	84.1±55.3	198.9±212.8	247±221.7	171.7±104.1
		.				
morning 2-h SBP	117.1±14.6	148.6±28.3	124±13.7	136.9±18.7	139.4±20.7	137.6±10.1
morning 2-h DBP	68.9±15	80.9±9.7	73.4±11.1	82.8±13.6	81±12.1	83.3±5.0
HR	69.0±9.4	70.5±10.4	71.8±8.6	74.4±12.5	76.6±9.9	74.4±16.1
				... +++ xxx	... +++ xxx ΔΔΔ	.. ++ ΔΔΔ ###
AHI (/h)	2.3±1.8	2.6±1.5	9.5±3.1	29.8±5.3	60.2±16.1	16.1±14.1
					... +++ xxx ΔΔΔ	###
AI (/h)	3.6±4.8	3.2±2.9	14.3±11.5	49.7±53.3	228±184.5	42.9±59.3
					... +++ xxx Δ	###
HI (/h)	6.0±6.1	7.6±6.6	31.5±21.4	59.1±49.5	148±144.2	33.2±38.2
					.	
AvgSatO$_2$ (%)	93.2±2.9	91.3±5.0	91.5±4.7	89.2±6.8	86.4±6.4	88.5±7.0
					.. ++ x	#
SatO$_2$ <90% (min)	19.3±54.5	17.6±27.0	36.4±55.5	72.1±108.1	132.5±129.8	38.4±50.1
					. ++ xx	##
SatO$_2$ <85% (min)	3.6±12.9	0.6±1.5	5.9±11.9	36.4±89.7	88.2±108.1	5.5±14

Means ± SD of measured parameters: BP in mmHg, PTE - Percent Time Elevation in %, MPL - Mean Pressure Load in mmHg/h, average SatO$_2$ in %, duration of SatO$_2$<90% and SatO$_2$<85% in minutes. The results indicate also the significant differences of each selected group compared to other 5 groups by various symbols: • - vs. healthy control, + - vs. AH, x- vs. mild SAHS, Δ - vs. moderate SAHS, and # - vs. severe SAHS. The level of significance is indicated by a number of the pertinent symbols (1: $p<0.05$, 2: $p<0.01$, 3: $p<0.001$).

3. Results

Table 1 shows the distribution of the subjects in six groups with basic anthropometric data and the patients' use of antihypertensive medication. The data were calculated according to the answers provided by the subjects on a written questionnaire and during a subsequent clinical interview with applicants for PSG examination, focusing on inclusion and exclusion criteria indicated in the section on Materials and Methods. Only adult males were included in the present study, and their age was comparable among the separate groups. The body mass index in patients with SAHS, compared with healthy controls and patients with AH alone, gradually increased with the severity of the disease. The levels of significant differences are indicated by symbols in Table 1. The use of antihypertensive medication was very similar in five groups of patients, contrary to that

in controls, suggesting a relatively high prevalence of hypertension not only in patients with AH alone but also in the four groups of patients with SAHS (Table 1).

The results of in-laboratory PSG examination with a cutoff AHI of 5 after 1 hour of sleep differentiated the subjects without SAHS from those with SAHS. Together with the increased value of AHI and the presence of AH, the results allowed for the distribution of subjects into six groups as follows: 1) clinically healthy controls (without SAHS and AH) investigated in the sleep laboratory to exclude suspected SAHS; 2) patients with AH, but without SAHS; 3) those with mild SAHS (AHI<5≤20/h); 4) those with moderate SAHS (AHI<20≤40/h); 5) those with severe SAHS (AHI>40/h); and 6) patients with SAHS treated overnight by CPAP with a titration pressure 7-14 cm H_2O, as needed for elimination of apnea episodes during at least 80 % of whole-night PSG examination. Mean values ± SD of selected BP and PSG parameters and indices are listed in Table 2, with the indication of significant differences among the separate groups.

The results of complex evaluation and comparison of data from 116 subjects divided into 6 groups allowed analysis of the following three main features: 1) changes in BP parameters and indices caused or supported by the presence of SAHS, 2) dependence of BP parameters on changes of PSG indices and their correlation, and 3) acute BP-lowering effect of CPAP therapy in patients with SAHS.

3.1. Changes in BP parameters and indices caused or supported by the presence of SAHS

Compared with healthy subjects, the nocturnal average systolic and diastolic blood pressure (AvgSBP and AvgDBP) increased gradually in patients with SAHS in accordance with the severity of their disease: mild SAHS (p=0.0009, p=0.0273, respectively), moderate (p< 0.0001, p= 0.0057), and severe (both p<0.0001). Also, the diurnal AvgSBP and the diurnal AvgDBP were increased in patients who had any of the three degrees of SAHS: mild (p=0.0039, p=0.0221, respectively), moderate (p=0.0026, p=0.0515), or severe (p<0.0001, p=0.0002). The 24-hour AvgSBP and the 24-hour AvgDBP were increased in patients with SAHS with increasing severity of the disease: mild (p=0.0003, p=0.009, respectively), moderate (p<0.0001, p=0.0065) and severe (both p<0.0001).

The percent time elevation of blood pressure was increased not only in patients with AH alone (p=0.0374), but even more in patients with moderate SAHS (p=0.0072) and in those with severe SAHS (p=0.0014). Severe SAHS resulted in a stronger increase in PTE than mild SAHS (p=0.0152). The nocturnal AvgSBP and the nocturnal AvgDBP were significantly higher in patients with severe SAHS than in those with mild SAHS (p=0.0062, p=0.0178, respectively), and the nocturnal AvgDBP was even higher than it was in the group who had AH alone (p=0.0108), indicating a marked additional hypertensive effect of severe SAHS. Severe SAHS also resulted in a stronger additive hypertensive effect on 24-hour AvgSBP than did mild disease (p=0.0299). Mean pressure load in mmHg was higher in patients with severe SAHS than in healthy controls (p=0.0417).

Compared with healthy controls, the presence of AH alone in patients manifested with an increase in both the 24-hour and the diurnal AvgSBP (both p<0.0001). The 2-hour early morning and maximum SBP were increased in patients with AH alone (p=0.0212, p=0.0042, respectively), suggesting strong sympatho-adrenal stimulation in essential hypertension, but not in those with SAHS, which contributes to the development of secondary hypertension.

Table 2 summarizes the values of main BP and PSG parameters and indices from all 116 subjects in the 6 groups. The results clearly demonstrate that severe and even moderate SAHS causes marked ventilatory disorder and hypoxemia, reflected by significant increases in AHI, AI, HI, a duration of $SatO_2$ less than 85% in minutes, and a decrease in $AvgSatO_2$. In addition to the SAHS-induced, dose-dependent hypertensive effect mediated by ventilatory disorder and subsequent hypoxemia, the acute antihypertensive effects of CPAP mediated by substantial reduction of apnea–hypopnea episodes are clearly demonstrated in Table 2, where the significant differences are indicated by symbols.

3.2. Dependence of BP parameters on changes of PSG indices and their correlation

Both the AHI and AI were much higher in patients with severe SAHS than in healthy subjects and patients with either AH alone or mild SAHS (all p<0.0001). The duration of the resulting hypoxemia reflected by $SatO_2$ less than 90% and less than 85% in minutes was higher in patients with severe SAHS than in control subjects (p=0.003, p=0.011, respectively), patients with AH alone (p=0.0061, p=0.005), or mild SAHS (p=0.0168, p=0.0041). The $AvgSatO_2$ was lower in patients with severe SAHS than in control subjects (p=0.0322) (Table 2).

In 74 patients with SAHS of 3 different degrees of severity the nocturnal AvgDBP very significantly correlated both with the AHI (p=0.0049, Figure 1A) and AI (p=0.0027, Figure 1B); it correlated positively with the resulting hypoxemia represented by the duration of

Figure 1. Correlation of nocturnal average diastolic blood pressure (AvgDBP) with apnea–hypopnea index (AHI, A) and with the number of apnea episodes (AI, B) in 74 patients with SAHS.

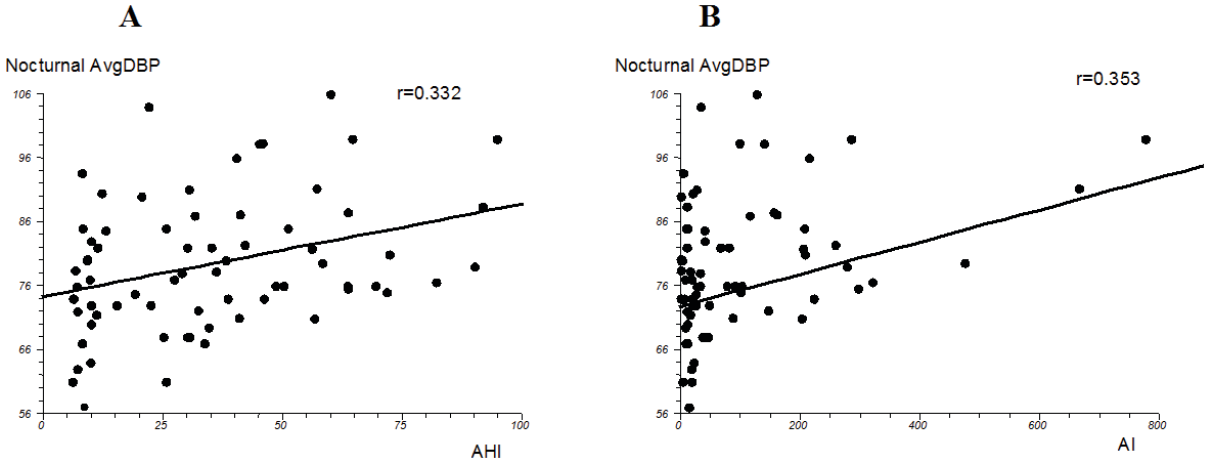


Figure 2. Correlation of nocturnal average diastolic blood pressure (AvgDBP) with duration of oxygen saturation ($SatO_2$) <85% in minutes (A) and with average $SatO_2$% (B) in 74 patients with SAHS.

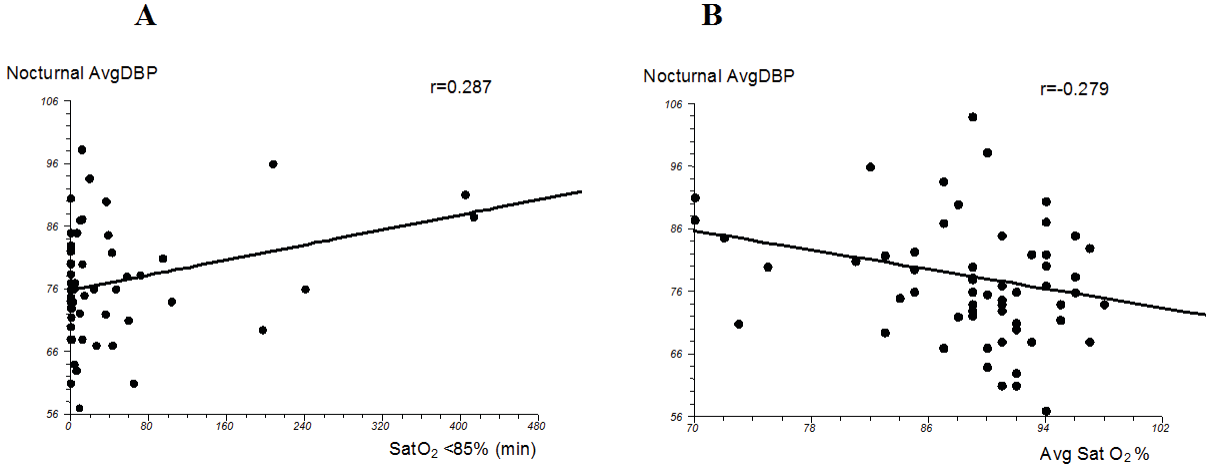
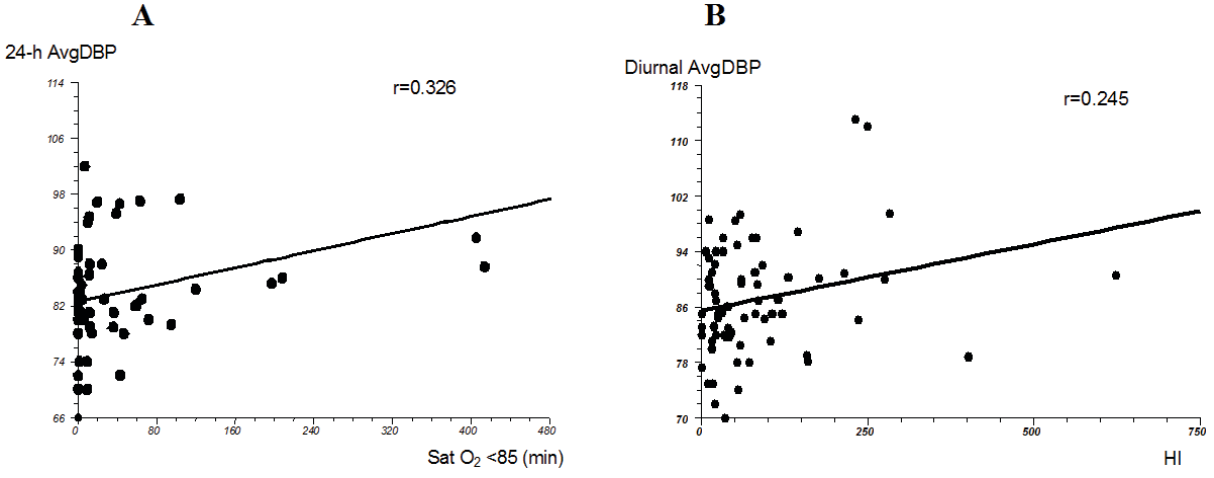


Figure 3. Correlation of 24-hour average diastolic blood pressure (AvgDBP) with duration of oxygen saturation ($SatO_2$) <85% in minutes (A) and of the diurnal AvgDBP with the number of hypopnea episodes (HI, B) in 74 patients with SAHS.



$SatO_2$ less than 85% in minutes during sleep (p=0.049, Figure 2A) and negatively with $AvgSatO_2$ (p=0.0457, Figure 2B).

Also, the 24-hour AvgDBP correlated with hypoxemia represented by $SatO_2$ less than 85% in minutes (p=0.0104, Figure 3A) and the diurnal AvgDBP with the number of episodes of hypopnea per 1 hour of sleep (p=0.0391, Figure 3B). These data clearly demonstrate that occurrence of frequent apnea–hypopnea episodes causing both intensification and prolongation of hypoxemia result primarily in nocturnal and diastolic hypertension (Figure 1, 2).

3.3. Acute BP-lowering effect of CPAP therapy in patients with SAHS

Overnight use of CPAP therapy in patients with moderate to severe SAHS decreased the initially high AHI from 41.2±16.4 to 16.1±14.1 per 1 hour of sleep. This 61% decrease represents a significant reduction in severity of SAHS compared with untreated patients with both severe SAHS (p<0.0001) and moderate SAHS (p=0.0024) and with the level of patients with mild SAHS (p=0.3732). However, despite CPAP therapy, the AHI remained higher in patients with SAHS than in healthy controls (p=0.0041) and in patients with AH alone (p=0.0057), indicating that not all apnea–hypopnea episodes were eliminated because of insufficient intensity and time of CPAP application. Substantial reduction of apnea–hypopnea episodes by overnight use of CPAP improved the $AvgSatO_2$ to 88.5±7.0%, which was no different from values in healthy controls and in patients with AH alone. Also, the duration of $SatO_2$ less than 90% and less than 85%, reflecting the severity of hypoxemia, was significantly lower than it was in patients with severe SAHS and did not differ from the values in healthy controls and in hypertensive patients without SAHS (Table 2).

The improvement in ventilation and oxygen saturation induced by overnight use of CPAP resulted in a decrease of diurnal AvgDBP below the values in patients with severe SAHS and to a level not significantly different from the data for healthy controls and for hypertensive patients without SAHS (Table 2). Use of CPAP decreased the 24-hour AvgDBP to values not differing significantly from the data for healthy controls (p=0.1099), but the 24-hour AvgSBP and the diurnal AvgSBP remained higher than were found in healthy controls (p=0.0008, p=0.0077, respectively) (Figure 3).

4. Discussion

The main results of this study provide three new findings. First, SAHS itself has a separate secondary hypertensive effect resulting in blood-pressure increases in nocturnal, rather than diurnal, parameters and in diastolic as well as systolic parameters. A secondary hypertensive effect occurs because a physiologic nocturnal decrease of BP during sleep (“dipping”) is prevented (“nondipping”) in patients with SAHS. This effect has been analyzed in several papers [21,24,30] and has been shown to cause a significant increase primarily in nocturnal DBP [26], particularly in patients with severe SAHS, and a somewhat selective increase in, or at least a tendency to, “nondipping” of diastolic, rather than systolic, BP. On the contrary, in healthy controls, as well as in hypertensive patients without SAHS, there is mostly “dipping” of nocturnal BP values during sleep. According to the percentage of nocturnal BP reduction, four groups of patients can be differentiated: extreme dippers (>20%), dippers (10% - 20%), nondippers (0% - 10%), and risers (< 0%), indicating that the reductions of nocturnal BP decreased adequately to result in an increase in AHI. Groups of patients with SAHS with AHI greater than 15 per 1 hour included significantly more nondippers than the groups of control subjects and patients with mild SAHS [21].

Second, the marked breathing disorders accompanied by hypoxemia, reflected by high values of PSG parameters (AHI, AI, HI, $SatO_2$<85%), that gradually increased with the severity of SAHS evoke appropriate dose–dependent changes in various BP parameters and indices. They correlate mostly with the frequency of apnea–hypopnea episodes and the intensity and duration of the subsequent hypoxemia in minutes, indicated by $SatO_2$ less than 85%. The degree of severity in SAHS at baseline examination was observed to predict the risk of hypertension 4 years later [2]. Similarly, the cardiovascular risk in essential hypertension could be stratified by ABPM during a mean period of 3.2 years [30]. Sleep-disordered breathing increased the mortality rates indirectly, probably because it is a risk factor for hypertension [15] and for stroke and death from any cause independent of other risk factors, including hypertension [19]. Nevertheless, its precise mechanism is still unclear.

Third, CPAP treatment of SAHS has an acute BP-lowering effect, resulting from a substantial reduction in the apnea–hypopnea episodes and hypoxemia, which are particularly prevalent in severe SAHS. Higher intensity and longer duration of hypoxemia with $SatO_2$ less than 85% in minutes results primarily in a

higher nocturnal DBP, which can be improved by CPAP therapy.

4.1. Pathogenetic mechanisms and manifestations of secondary hypertension in SAHS

Secondary hypertension caused by SAHS can be presumed in patients if they have symptoms of sleep-disordered breathing (severe snoring, cephalea, sleep apnea, daytime sleepiness, tiredness, and/or central obesity) or various cardiovascular disorders (arrhythmias, cardiac failure, or pharmacoresistent hypertension), which have been analyzed in several studies [5,18,22-24,27]. Increased vasoconstrictor sensitivity [31,32] and nocturnal diastolic hypertension were observed in patients with SAHS [14,21,26], but these findings could not be proved in some studies due to the small number of patients, low degree of SAHS severity, or higher age of patients with decreased sympathetic-nerve activity [12,16]. Our results also indicate newly detected diastolic, in addition to systolic, hypertension caused by the more severe degrees of SAHS. Because of a very high prevalence of hypertension in patients with SAHS reported in this and other publications, ABPM is indicated in each patient with suspected sleep-disordered breathing to detect early signs of both disorders and their effects.

Sleep fragmentation was independently associated with significantly higher levels of SBP during wakefulness, which was not discernible in adults with an AHI less than 1 per l hour of sleep. Each apnea event per hour of sleep added about 1% to the risk of having hypertension [33]. Moreover, a dose-response association between SAHS at baseline and the presence of hypertension 4 years later was found to be an independent compounding factor [2], which indicates that ABPM has important prognostic potential. In our study PSG parameters correlated with nocturnal more than diurnal DBP. The AHI and AI linearly correlated with the nocturnal diastolic BP, indicating their acute, rather than long-term, effect. However, changes in diurnal and 24-hour AvgBPs suggest that SAHS could contribute to the development of overt secondary hypertension after a period of several years.

Our results confirm the marked BP elevation, particularly in patients with severe SAHS, and could contribute to a better understanding of the complex pathogenic mechanisms of hypertension. Hypoxemia and hypercapnia resulting mainly from apnea–hypopnea episodes initiate progressive activation of the sympathetic nervous system, involving the carotid sinus and aortal baroreceptors [3,4,6,34,35]. Arousal reactions induced by repeated apnea episodes also provoke sympatho-adrenergic activation, despite interruption of hypoxic-hypercapnic stimuli, and they could lead to the elevation of heart rate and BP [3,4]. In addition, the upper-airway stimulation induced by pressure changes caused by snoring, or post-apnea sighs and gasps may evoke reflex tachycardia and vasoconstriction already present in the early stages of SAHS. Similar reflex hypertension is induced by a sniff- and gasp-like aspiration reflex provoked by stimulation of upper-airway rapidly adapting receptors in anesthetized cats [36]. Hypoxia, hypercapnia, re-oxygenation, and sympathetic nerve activation connected with repeated apnea episodes can also disrupt the electrical stability of the myocardium causing arrhythmias [37], and they may contribute to endothelial dysfunction [35]. Extension of intimal-medial thickness in patients with sleep apnea suggests that SAHS is also a potential risk factor for the development of atherosclerosis [20].

Our study has some limitations. The insufficient intensity and duration of CPAP application connected with pressure titration did not eliminate all apnea episodes and thus prevented a complete assessment of the antihypertensive efficacy of CPAP treatment for SAHS. Also, a small number of subjects in groups 1, 2 and 6 (n=11-16) and the inclusion of 4 patients with moderate SAHS in the CPAP-treated group might cause only a border-line significant decrease in some BP parameters. Despite these limitations, our results indicate the major importance of the complex evaluation of nearly 20 ambulatory BP variables selected by comparison with cardiorespiratory indices obtained during parallel PSG examination. Recent results have indicated that an increased risk for SAHS is highly prevalent when assessed by a special Berlin questionnaire, and it is frequently associated with resistant hypertension [38]. ABPM should be evaluated in patients with hypertension to assess and prevent risk of morbidity and mortality [39]. In patients with sleep apnea. a decrease in mean BPs observed by ABPM, together with a reduction of urine normetanephrine secretion and improvement of baroreflex sensitivity after 4 weeks of CPAP therapy, may lower cardiovascular risk by reducing sympathetic-nerve activity [40]. Nighttime BP proved to be a better predictor of death and recurrent cardiovascular events in hypertensive patients with a history of cardiovascular disease [41,42].

In conclusion, SAHS causing marked hypoxemia reflected by significant increases in AHI, AI, duration of $SatO_2$ less than 85% in minutes, and decreases in $AvgSatO_2$, together with arousal-related reflex changes, frequently induces a dose-dependent secondary hypertension. The reflex changes manifest by an increase in nocturnal,

rather than diurnal, and diastolic and systolic BPs, which can be improved by CPAP therapy of SAHS. Therefore, monitoring of BP parameters selected by correlation with parallel recorded PSG indices could be useful for the early detection, complex evaluation of therapeutic success, and prognostic stratification of complications of important, but underestimated, disorders such as AH and SAHS. Nevertheless, further comparative studies are needed for better analysis of this complex and very vital topic.

References

[1] Young T., Palta M., Dempsey J., Skatrud J., Weber S., Badr S., The occurrence of sleep-disordered breathing among middle-aged adults, N. Engl. J. Med., 1993, 328, 1230-1235

[2] Peppard P., Young T., Palta M., Skatrud J., Prospective study of the association between sleep-disordered breathing and hypertension, N. Engl. J. Med., 2000, 342, 1378-1384

[3] Morgan B.J., Crabtree D.C., Palta M., Skatrud J.B., Combined hypoxia and hypecapnia evoked long-lasting sympatetic activation in humans, J. Appl. Physiol., 1995, 79, 205-213

[4] Xie A., Skatrud J.B., Crabtree D.C., Puleo D.S., Goodman B.M., Morgan B.J., Neurocirculatory consequences of intermittent asphyxia in humans, J. Appl. Physiol., 2000, 89, 1333-1339

[5] Hla K.M., Skatrud J.B., Finn L., Palta M., Young T., The effect of correction of sleep-disordered breathing on BP in untreated hypertension. Chest, 2002, 122(4), 1125-1132

[6] Bradley T.D., Tkacova R., Hall M.J., Ando S., Floras J.S., Augmented sympathetic neural response to simulated obstructive apnoea in human heart failure, Clin. Sci., 2003, 104, 231-238

[7] Shamsuzzaman A.S., Gersh B.J., Sommers V.V., Obstructive sleep apnoea complications and cardiovascular disease, 2003, JAMA, 290, 1906-1914

[8] Young T., Peppard P., Palta M., Hla K.M., Finn L., Morgan B., et al., Population-based study of sleep-disordered breathing as a risk factor for hypertension, Arch. Intern. Med., 1997, 157, 1746-1752

[9] Singh J., Larson M., Manolio T., O'Donnell C., Lauer M., Evans J., et al., Blood pressure response during treadmill testing as a risk factor for new-onset hypertension (Framingham Heart Study), Circulation, 1999, 99, 1831-1836

[10] Davies C.W., Crosby J.H., Mullins R.L., Barbour C., Davies R.J., Stradling J.R., Case-control study of 24 h ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects, Thorax, 2000, 55, 736-740

[11] Nieto F.J., Young T., Lind B.K., Sharar E., Samet J.M., Redline S., et al., Association of sleep apnea and hypertension in a large community-based study. JAMA, 2000, 283, 1829-1836

[12] Haas D.C., Foster G.L., Nieto F.J., Redline S., Resnick H.E., Robbins J.A., et al., Age-dependent associations between sleep-disordered breathing and hypertension, Circulation, 2005, 111, 614-621

[13] Pepin J.L., Baguet J.P., Hammer L., Pierre H., Levy P., Mallion J.M., Diastolic diurnal hypertension is a common and underestimated situation in patients with unknown hypertension at time of sleep apnea diagnosis. Sleep Medicine, 2003, 4 Suppl, 1, S1-S56

[14] Baguet J.P., Hammer L., Levy P., Pierre H., Rossini E., Mouret S., et al., Night-time and diastolic hypertension are common and underestimated conditions in newly diagnosed apnoeic patients, J. Hypertens, 2005, 23(3), 521-527

[15] Lavie P., Herer P., Peled R., Berger I., Yoffe N., Zomer J., et al., Mortality in sleep apnea patients: a multivariate analysis of risk factors, Sleep., 1995, 18(3), 149-157

[16] Staessen J.A., Fagard R., Thijs L., Celis H., Arabidze G.G., Birkenhäger W.H., et al., Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension, The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators, Lancet, 1997, 13, 350(9080), 757-764

[17] Donic V., Donicová V., Lesko R., Tomori Z., Screening of sleep apnea from values obtained by monitoring of blood pressure and heart rate variability. Monitorovanie TK a frekvencie srdca ako metóda zisťovania výskytu spánkového apnoe, Sb. Lek., 2002, 103(1), 85-90, (in Slovak)

[18] Logan A.G., Tkacova R., Perlikowski S.M., Leung R.S., Tisler A., Floras J.S., et al., Refractory

Acknowledgements

The study was supported by Slovak Research and Development Agency under the contract No. APVV 20-477/05 and COST Action B-26.

hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. Eur Respir J., 2003, 21(2), 241-247
[19] Yaggi H.K., Concato J., Kernan W.N., Lichtman J.H., Brass L.M., Mohsenin V., Obstructive sleep apnea as a risk factor for stroke and death, N Engl J Med., 2005, 10, 353(19), 2034-2041
[20] Szaboová E., Tomori Z., Donič V., Petrovičová J., Szabó P., Sleep apnoea inducing hypoxemia is associated with early sign of carotid atherosclerosis in males, Respir. Physiol. & Neurobiol., 2007, 155, 121-127
[21] Nagata K., Osada N., Shimazaki M., Kida K., Yoneyama K., Tsuchiya A., et al., Diurnal blood pressure variation in patients with sleep apnea syndrome, Hypertens Res., 2008, 31(2), 185-191
[22] Grote L., Hedner J., Peter J.H., Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension., J Hypertens. 2000, 18, 679-685
[23] Grote L., Hedner J., Peter J.H., Mean blood pressure, pulse pressure and grade of hypertension in untreated hypertensive patients with sleep-related breathing disorders, J. Hypertens., 2001, 19, 683-690
[24] Martinez-Garcia M.A., Gomez-Aldaravi R., Soler-Cataluna J.J., Martinez T.G., Bernacer-Alpera B., Roman-Sanchez P., Positive effect of CPAP treatment on the control of difficult-to-treat hypertension. Eur. Respir. J., 2007, 29(5), 951-957
[25] Penzel T., Mayer J., Peter J.H., Podszus T., Voigt K.H., von Wichert P., Continuous non-invasive blood pressure monitoring in patients with sleep disorders, Physiol. Res., 1992, 41(1), 11-17
[26] Penáz J: Criteria for set point estimation in the volume clamp method of blood pressure measurement. Physiol Res 41(1): 1992. 5-10
[27] Sharabi Y., Scope A., Chorney N., Grotto I., Dagan Y., Diastolic blood pressure is the first to rise in association with early subclinical obstructive sleep apnea: lessons from periodic examination screening, Am. J. Hypertens., 2003, 16(3), 236-239
[28] Hermida R.C., Zamarrón C., Ayala D.E., Calvo C., Effect of continuous positive airway pressure on ambulatory blood pressure in patients with obstructive sleep apnoea, Blood Press Monit., 2004, 9(4), 193-202
[29] Guidelines 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee, J. Hypertens., 1999, 17, 151-183
[30] Verdecchia P., Porcellati C., Schillaci G., Borgioni C., Ciucci A., Battistelli M., et al., Ambulatory blood pressure, An independent predictor of prognosis in essential hypertension, Hypertension, 1994, 24(6), 793-801
[31] Duchna H.W., Guilleminault C., Stoohs R.A., Vascular reactivity in obstructive sleep apnea syndrome. Am. J. Respir., Crit. Care Med., 2000, 161, 187-191
[32] Kraiczi H., Hedner J., Peker Y., Carlson J., Increased vasoconstrictor sensitivity in obstructive sleep apnea, J. App. Physiol., 2000, 89, 193-498
[33] Morell M., Finn L., Kim H., Peppard P., Badr S., Young T., Sleep fragmentation, awake blood pressure. and sleep-disordered breathing in a population-based study, Am. J. Respir. Crit. Care. Med., 2000, 162, 2091-2096
[34] Parati G., Di Rienzo M., Omboni S., Ulian L., Mancia G., Blood presure variability over 24 hours: its different cemponents and relationship to the arterial baroreflex, J. Sleep Res., 1995, 4, 21-29
[35] Phillips B.G., Narkiewicz K., Pesek C.A., Haynes W.G., Dyken M.E., Somers V.K., Effect of obstructive sleep apnea on endothelin-1 and blood pressure, J. Hypertens, 1999, 17, 61-66
[36] Tomori Z., Widdicombe J.G., Muscular, bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. J Physiol., 1969, 200, 25-49
[37] Švorc P., Beňačka R., Petrašová D., Bračoková I., Kujaník S., Effect of systemic hypoxia and reoxygenation on electrical stability of the rat myocardium: Chronophysiological study, Physiol. Res., 2005, 54, 319-325
[38] Gus M., Goncalves S.C., Martinez D., de Abreu Silva E.O., Moreira L.B., Fuchs S.C., et al., Risk for Obstructive Sleep Apnea by Berlin Questionnaire, but not daytime sleepiness, is associated with resistant hypertension: a case-control study, Am J Hypertens., 2008, 21(7), 832-835
[39] Selcoki Y., Uz B., Baybek N., Akcay A., Eryonucu B., The effects of nocturnal dipping on cardiovascular outcomes and proteinuria in essential hypertensive patients, Cent. Eur. J. Med., 2008, 3(3), 279-286
[40] Kohler M., Pepperell J.C., Casadei B., Craig S., Crosthwaite N., Stradling J.R., et al., CPAP and measures of cardiovascular risk in males with OSAS, Eur Respir J., 2008, 32(6), 1488-1496
[41] Fagard R.H., Thijs L., Staessen J.A., Clement D.L., Buyzere M.L., De Bacquer D.A., Prognostic significance of ambulatory blood pressure in hypertensive patients with history of cardiovascular disease, Blood Press Monitor., 2008, 13(6),

325-332

[42] Atanassova P.A., Chalakova N.T., Dimitrov B.D., Diastolic blood pressure cut-off predicts major cerebrovascular events after minor ischaemic stroke: a post-hoc modelling study, Cent. Eur. J. Med., 2008, 3(4), 430-437