

Sleep-related breathing disorder is an independent risk factor for uncontrolled hypertension

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Objective To test the hypothesis that sleep-related breathing disorder (SRBD) is associated with poor blood pressure control in hypertensive patients independent from confounding factors such as age, body mass index, alcohol, smoking and daytime blood gases.

Design and methods This cross-sectional study of a sleep laboratory cohort was carried out at the University Hospital Sleep Disorders Centre, Marburg. The study comprised 599 patients referred for a sleep study, all of them with a documented history of systemic hypertension and/or previously initiated antihypertensive therapy. Data were obtained from a clinical interview, two unattended sleep studies and assessment of clinic blood pressure, cholesterol level, alcohol and nicotine consumption and daytime blood gases. The main outcome measure was a post hoc analysis of predictors for poor blood pressure control.

Results Respiratory disturbance index (RDI) was significantly higher in patients with uncontrolled hypertension (blood pressure ≥ 160 and/or 95 mmHg, $n = 463$) than in those with controlled hypertension ($n = 136$) (34.0 ± 26.8 versus 27.0 ± 23.5 , $P < 0.01$). The relative proportion of patients with uncontrolled hypertension increased significantly as SRBD activity increased (χ^2 , $P < 0.05$). Body mass index was the only independent predictor ($P = 0.006$) of uncontrolled

hypertension in the whole study sample. However, in the subset of patients aged ≤ 50 years, RDI ($P = 0.006$) and age ($P = 0.016$) were the only independent predictors. The probability of uncontrolled hypertension increased by approximately 2% ($B = 0.019$, $P = 0.006$) for each RDI unit.

Conclusion SRBD should be considered, in addition to traditional confounders, as a risk factor for poor blood pressure control in younger hypertensive patients (≤ 50 years of age). *J Hypertens* 2000, 18:679–685 © Lippincott Williams & Wilkins.

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Introduction

Sleep-related breathing disorder (SRBD) is a common sleep disorder that affects between 4 and 25% of the adult population [1]. Obstructive sleep apnoea, which is its most common manifestation, is characterized by recurrent upper airway obstruction, increased intrathoracic pressure changes, hypoxaemia and frequent sleep disruption (arousal). Sequelae of SRBD include increased daytime sleepiness, increased risk of traffic accidents, decreased quality of life and probably an increased cardiovascular risk.

Hypertension is an important risk factor for cardiovascular morbidity and mortality [2]. SRBD is common in hypertensive patients [3,4]. It was recognized in the early 1970s that acute cardiovascular changes occur as an immediate consequence of SRBD [5]. Systemic blood pressure increases during apnoea and reaches a maximum, ranging from 150 to 300 mmHg, during the

arousal and hyperventilation period [6]. Acute mechanisms for the alterations in systemic haemodynamics such as hypoxia, increased sympathetic activity, increased intrathoracic pressure changes, substantial increases in peripheral resistance and the arousal from sleep have been identified [6].

There are a number of case-control studies that suggest that not only nocturnal but also long-term cardiovascular homeostasis during daytime is adversely affected by SRBD. Sleep apnoea patients showed an increased pressor response to eucapnic hypoxia [7], an attenuated baroreflex response [8], and a decreased endothelial dilatory function [9] compared with age- and body mass index (BMI)-matched controls. Further evidence for the long-term effects of SRBD on cardiovascular function is obtained from an intervention study [10] that demonstrated a sustained increased sympathetic activation in sleep apnoea patients during day-

time compared with controls; this was significantly reduced after therapy with nasal ventilation during sleep. Although strong evidence for an association between SRBD and hypertension is provided by these case-control studies and by recent work in an animal model of sleep apnoea [11], the causal relationship between SRBD and systemic hypertension remains to be fully established. A recent review of the evidence for a causal relationship between SRBD and poor health outcomes [12] states that SRBD is closely related to obesity and age. SRBD may constitute a separate disease entity or a symptom of obesity and age. Therefore studies on the association between SRBD and cardiovascular sequelae need to be controlled for these important potential confounders.

Blood pressure control in hypertensive patients is poor in many countries [13–16]; mainly due to a lack of awareness of the disease by patients and doctors and the patient's noncompliance with therapy. In fact, it has been suggested that reduced compliance may be caused by drug-related neuropsychological side effects, including drowsiness and fatigue [17,18]. However, these symptoms also constitute clinical signs of increased SRBD activity. Previous studies [3,19] and treatment recommendations in refractory hypertension [20] advocate that SRBD activity may ameliorate poor blood pressure control, but studies in larger cohorts have been lacking.

This study addresses the issue of whether SRBD is related to reduced blood pressure control in a large sample of consecutive patients in a sleep study centre setting.

Method

Subjects

The study design has been described in detail elsewhere [21]. Briefly, the study material consisted of data from 1642 patients consecutively seen in the outpatient department of the Marburg Sleep Disorders Centre, Marburg, Germany, from January 1 1989 to April 30 1992. Patients were referred because of clinical symptoms and signs suggestive of SRBD. Four hundred and fifty-two patients (46 women, mean age 53 ± 11 years, mean BMI 30.0 ± 6.0 kg/m² and mean RDI 36.7 ± 28 events/h) were excluded from analysis for the following reasons: missing data on systolic and/or diastolic blood pressure and/or heart rate ($n = 138$), missing blood gas analysis ($n = 140$), missing data on risk factors such as alcohol or nicotine consumption and cholesterol level ($n = 126$), no data on sleep disordered breathing because of technical failure ($n = 2$), missing self-estimated sleep time ($n = 21$) and sleep time less than 5 h ($n = 25$). Included in the final analysis were 599 patients (51 women, mean age 51 ± 9 years, mean BMI 30.7 ± 5.1 kg/m² and mean respiratory disturbance in-

dex (RDI) 32.4 ± 26 events/h), all with a previous diagnosis and/or treatment of systemic hypertension, out of the remaining 1190 patients.

Protocol

Data on age, sex, race and BMI was collected for each patient. SRBD-related signs and symptoms such as snoring, witnessed apnoeas, excessive daytime sleepiness, and difficulty in staying awake while driving a car were recorded [22]. Smoking habits and alcohol consumption were noted. The medical history was checked for the diagnosis and treatment of systemic hypertension. Blood samples for the determination of total cholesterol level and daytime blood gases were obtained.

Unattended home monitoring of nocturnal breathing using the MESAM[®] 4 device (MAP[®], Munich, Germany) was performed on two consecutive nights. RDI for further evaluation was obtained from the second night study. Time of going to bed, lights out, final awakening, longer periods of sleep interruption and estimated sleep time were assessed using a patient diary.

MESAM[®] 4 device

The MESAM 4 device records oxygen saturation using finger pulse oximetry, snoring using an electric subminiature microphone placed over the larynx, beat-to-beat heart rate analysis and body position using a circular sensor taped just below the sternum. The MESAM 4 device is a validated tool in epidemiological research and clinical routine [23,24].

Blood pressure readings

Blood pressure readings were obtained with the patient in a sitting position after a minimum of 10 min rest, between 0900 and 1100 h, using the World Health Organization standard protocol [25]. Recordings were made on two consecutive days in the outpatient department. The second reading was consistently used for further analysis in order to reduce the 'white coat' effect [26].

Data processing

Significant events of sleep-disordered breathing (apnoea, hypopnoea or upper airway obstruction followed by autonomic arousal) were scored only when there was a concomitant desaturation of $\geq 4\%$ from baseline [24]. The RDI was calculated as the number of events divided by estimated sleep duration in hours. Estimated sleep time was determined based on the information from the sleep diary (time of going to bed, lights out, final awakening, lights on, longer periods of sleep interruption). Subsequently, the MESAM scorer edited this information by checking the heart rate (significant drop and reduced variability when going to bed, abrupt increase and plateau after final awakening)

and body position signal (e.g. change from upright to supine position or vice versa). Evaluations were performed by experienced sleep technicians unaware of the actual blood pressure status of the patient.

All patients were categorized according to their systolic and diastolic blood pressure levels. Because it was in common clinical use at the time of data collection (1989–1992) ‘controlled hypertension’ was defined as blood pressure < 160 and 95 mmHg (definition 1, $n = 136$). A second analysis was performed using a cut-off level < 140 and 90 mmHg (definition 2, $n = 38$) for ‘controlled hypertension’ in agreement with the standards currently in use [27]. According to the definition used, 463 and 561 patients, respectively, were labelled as having ‘uncontrolled hypertension’. Additionally, patients were categorized according to their level of systolic (diastolic) blood pressure into those with 140–149 (90–94), 150–159 (95–99), 160–169 (100–104) and ≥ 170 (≥ 105) mmHg (Tables 1 and 2).

In the assessment of the sleep-disordered breathing, RDI < 5 was considered as not clinically relevant

SRBD ($n = 65$) [28]. Additional categories were chosen: RDI 5–19.9 (mild disease, $n = 182$), RDI 20–39.9 (moderate disease, $n = 143$) and RDI ≥ 40 (severe SRBD, $n = 209$) [21].

Statistics

Results are given as means \pm SD. Statistical analyses were performed using the SPSS software program (SPSS for Windows 7.5, Chicago, Illinois, USA). The difference between two unpaired samples were tested by the Students t test. Intergroup differences in data variability of systolic and diastolic blood pressure as grouping variable were compared using a one-way analysis of variance (ANOVA). Differences between age, RDI and BMI were tested in a post hoc analysis with adjustment for multiple testing using the Bonferroni method. Frequencies of patients in the different categories of SRBD activity were tested using the χ^2 test. All reported P values were two-tailed; $P < 0.05$ was considered statistically significant.

Forward multiple logistic regression with ‘uncontrolled hypertension (blood pressure ≥ 160 and/or 95 mmHg)’

Table 1 Systolic blood pressure control in 599 hypertensive patients

Characteristics	Systolic blood pressure (mmHg)					one-way ANOVA
	< 140	140–149	150–159	160–169	≥ 170	
n	101	104	109	122	163	
SBP (mmHg)	127.4 \pm 6.2	140.8 \pm 1.8	151.0 \pm 2.2	160.6 \pm 1.7	182.7 \pm 14.6	
DBP (mmHg)	88.6 \pm 9.1	95.5 \pm 7.6	99.5 \pm 8.5	101.7 \pm 8.8	109.0 \pm 11.3	
RDI (events/h)	23.9 \pm 21.0	28.7 \pm 24.9	31.7 \pm 25.9	39.0 \pm 28.5*	35.7 \pm 26.9*	$P < 0.001$
BMI (kg/m ²)	28.7 \pm 4.1	30.0 \pm 5.1	30.8 \pm 5.4	31.2 \pm 5.3*	31.7 \pm 5.0*	$P < 0.001$
Age (years)	49.2 \pm 9.9	49.4 \pm 10.0	51.9 \pm 8.6*	52.1 \pm 9.4*	54.8 \pm 8.5*	$P < 0.001$
Alcohol (mmol)	4.4 \pm 7.2	3.5 \pm 6.9	4.4 \pm 7.2	3.5 \pm 4.4	3.8 \pm 5.0	$P < 0.1$
Nicotine (cig/d)	5.2 \pm 9.3	7.2 \pm 13.1	5.2 \pm 10.5	5.5 \pm 11.6	3.7 \pm 8.5	$P < 0.1$
Cholesterol (mmol/l)	5.9 \pm 1.1	5.9 \pm 1.0	6.1 \pm 1.1	6.2 \pm 1.2	6.1 \pm 0.9	$P < 0.1$
P_{aO_2} (mmHg)	78.1 \pm 8.4	77.5 \pm 8.4	77.9 \pm 9.0	76.5 \pm 7.8	77.2 \pm 8.8	$P < 0.1$
P_{aCO_2} (mmHg)	39.2 \pm 5.6	39.7 \pm 6.6	38.4 \pm 3.2	40.0 \pm 6.4	38.5 \pm 3.4	$P < 0.1$

* Post hoc analysis with adjustment using the Bonferroni method: significant difference when compared with patient group with systolic blood pressure level < 140 mmHg ($P < 0.01$). ANOVA, analysis of variance; BMI, body mass index; cig/d, cigarettes per day; DBP, diastolic blood pressure; SBP, systolic blood pressure; P_{aCO_2} , daytime arterial carbon dioxide tension; P_{aO_2} , daytime arterial oxygen tension; RDI, respiratory disturbance index per hour of estimated sleep time.

Table 2 Diastolic blood pressure control in 599 hypertensive patients

Characteristics	Diastolic blood pressure (mmHg)					one-way ANOVA
	< 90	90–94	95–99	100–104	≥ 105	
n	60	107	64	162	206	
SBP (mmHg)	133.2 \pm 15.9	144.7 \pm 14.3	149.0 \pm 15.6	155.4 \pm 15.5	170.7 \pm 20.4	
DBP (mmHg)	79.8 \pm 5.1	90.2 \pm 0.8	95.2 \pm 0.6	100.0 \pm 0.2	112.5 \pm 7.3	
RDI (events/h)	26.2 \pm 24.0	28.6 \pm 23.8	33.2 \pm 27.8	30.7 \pm 26.0	37.3 \pm 27.2*	$P = 0.009$
BMI (kg/m ²)	29.1 \pm 4.4	29.7 \pm 5.6	31.2 \pm 4.7	30.1 \pm 4.7	31.9 \pm 5.2*	$P < 0.001$
Age (years)	50.4 \pm 10.8	53.7 \pm 9.8	50.7 \pm 10.4	51.5 \pm 9.5	51.9 \pm 8.3	$P > 0.1$
Alcohol (mmol)	3.8 \pm 7.7	3.7 \pm 5.3	4.1 \pm 6.8	3.4 \pm 4.8	4.3 \pm 6.7	$P > 0.1$
Nicotine (cig/d)	5.5 \pm 10.2	5.2 \pm 10.4	6.8 \pm 11.7	4.6 \pm 10.4	5.2 \pm 10.7	$P > 0.1$
Cholesterol (mmol/l)	5.7 \pm 1.2	6.1 \pm 1.0	6.2 \pm 0.9	6.1 \pm 1.0	6.1 \pm 1.1	$P > 0.1$
P_{aO_2} (mmHg)	78.4 \pm 6.7	76.4 \pm 9.3	77.4 \pm 7.4	78.2 \pm 8.9	76.9 \pm 8.5	$P > 0.1$
P_{aCO_2} (mmHg)	38.3 \pm 4.0	39.6 \pm 6.0	39.2 \pm 6.2	39.1 \pm 6.2	39.1 \pm 3.4	$P > 0.1$

* Post hoc analysis with adjustment using the Bonferroni method: significant difference when compared with patient group with diastolic blood pressure level < 90 mmHg ($P < 0.05$). ANOVA, analysis of variance; BMI, body mass index; cig/d, cigarettes per day; DBP, diastolic blood pressure; SBP, systolic blood pressure; P_{aCO_2} , daytime arterial carbon dioxide tension; P_{aO_2} , daytime arterial oxygen tension; RDI, respiratory disturbance index per hour of estimated sleep time.

as dependent variable was performed with RDI, age, BMI, gender, alcohol, cholesterol, P_{aO_2} and P_{aCO_2} in the model. Significance was tested using the Wald χ^2 test. The logistic regression was performed for the group as a whole. Because previous data have suggested an age-dependent influence of SRBD on blood pressure control [29], regression analysis was performed in patients grouped by age; 50 years was taken as the cut-off point. Model fit was analysed using the Hosmer and Lemshow test.

Results

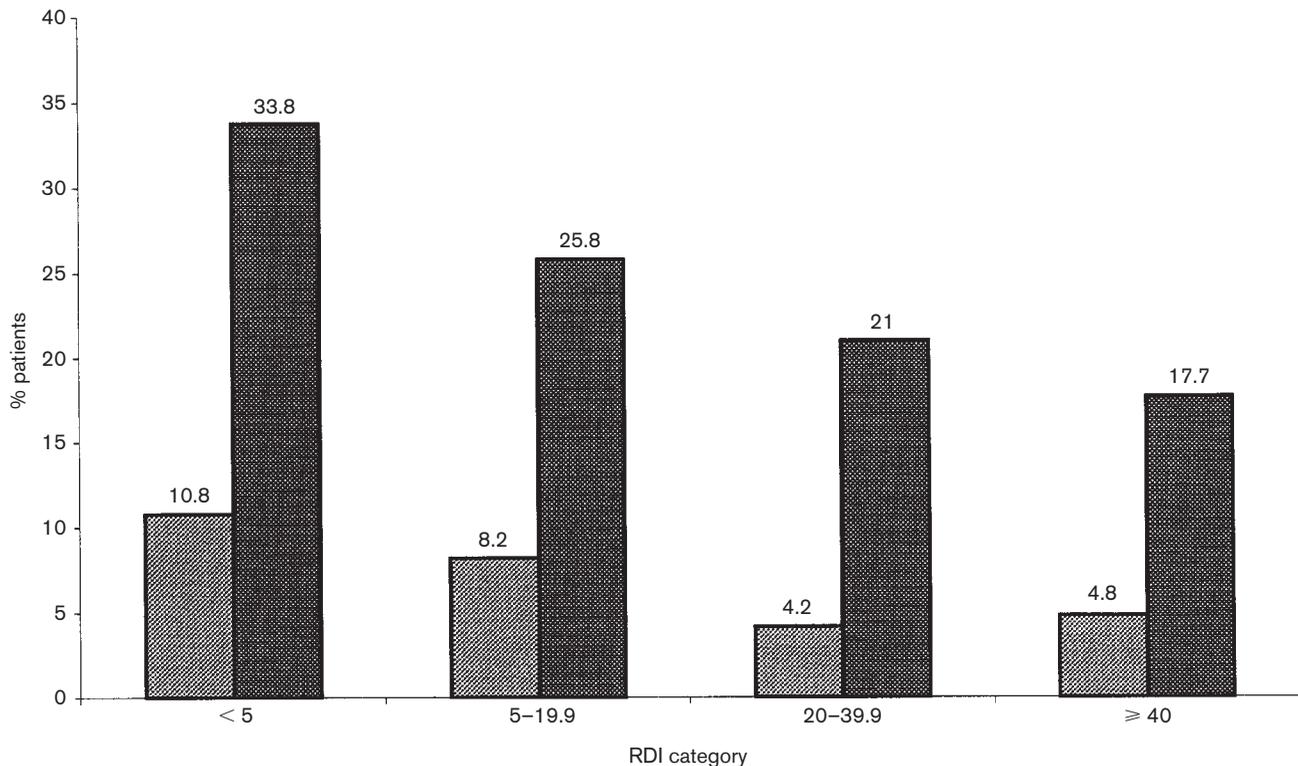
RDI correlated with systolic and diastolic blood pressure ($r = 0.16$, $P < 0.001$). In addition, RDI was significantly higher in patients with uncontrolled hypertension (definition 1, blood pressure ≥ 160 and/or 95 mmHg, $n = 463$) compared with patients with blood pressure $< 160/95$ mmHg ($n = 136$), 34.0 ± 26.8 versus 27.0 ± 23.5 , respectively (t test, $P < 0.01$). With increasing SRBD the proportion of patients with controlled hypertension (blood pressure $< 160/95$ mmHg) was significantly reduced (χ^2 test, $P < 0.05$; Fig. 1).

RDI increased significantly (ANOVA) with higher systolic ($P < 0.01$) and diastolic ($P = 0.009$) blood pres-

sure (Tables 1 and 2). Notably, mean RDI peaked in the systolic blood pressure class > 160 mmHg ($P < 0.001$ compared with < 140 mmHg) and in the diastolic blood pressure class ≥ 105 mmHg ($P > 0.05$ compared with < 90 mmHg) (post hoc analysis adjusted with Bonferroni method). In addition, patients with poor systolic blood pressure control were older and had a higher BMI (Table 1, ANOVA and post hoc analysis, $P < 0.05$). Poor diastolic blood pressure control was associated with higher BMI whereas age was similar over the classes studied (Table 2, ANOVA and post hoc analysis, $P < 0.05$).

Only BMI remained as an independent significant predictor for uncontrolled hypertension (definition 1) in the whole study sample. The probability that patients with a blood pressure ≥ 160 and/or 95 mmHg would have uncontrolled hypertension increased by approximately 6% with each BMI unit (logistic regression, $B = 0.064$, $P = 0.006$; Table 3). In the subset of patients aged ≤ 50 years and with an actual blood pressure ≥ 160 and/or 95 mmHg, each RDI unit increased the probability of having uncontrolled hypertension by approximately 2% (logistic regression, $B = 0.019$, $P = 0.006$; Table 3). In addition, each year of age

Fig. 1



Control of hypertension and sleep-related breathing disorder activity: the frequency of patients with controlled hypertension (■ definition 1, office blood pressure < 160 and 95 mmHg, $P < 0.05$; ▨ definition 2, blood pressure < 140 and 90 mmHg, NS) in four different respiratory disturbance index (RDI) categories.

Table 3 Multiple logistic regression analysis model with uncontrolled hypertension ($\geq 160/95$ mmHg) as dependent variable

Independent continuous variable	Relative risk (odds ratio)	95% CI	P
All patients (<i>n</i> = 553)			
BMI	1.064	1.017–1.112	0.006
Patients 50 years (<i>n</i> = 228)			
RDI	1.019	1.005–1.034	0.006
Age	1.061	1.011–1.114	0.016

Gender, P_{aO_2} , P_{aCO_2} , cholesterol and alcohol consumption were not of sufficient significance to be included in the final model.

independently increased the corresponding probability by approximately 6% (logistic regression, $B = 0.061$, $P = 0.016$). BMI, gender, daytime blood gases, cholesterol and alcohol consumption were not of sufficient significance to be entered in the final model. In the subgroup of patients aged > 50 years no single parameter out of those studied independently predicted uncontrolled hypertension.

Discussion

This study in a large clinical sample of SRBD patients with known hypertension suggests that the sleep and breathing disorder has a stronger and independent impact on poor hypertension control in younger patients than in those over 50 years of age.

Our study assessed the hypothesis that SRBD constitutes an independent risk factor for poor blood pressure control as suggested by previous work in smaller patient samples. Kales *et al.* [3] who investigated a group of 50 hypertensive patients found the most severe sleep apnoea in patients with the highest blood pressure values. In a subsequent study Hirshkowitz *et al.* [30] found that 36% of poorly controlled hypertensive patients fulfilled the criteria of obstructive sleep apnoea compared with only 13% of patients with well-controlled hypertension. Even higher numbers were reported by Isaksson *et al.* [19], who compared 16 patients with refractory hypertension (defined as diastolic blood pressure > 95 mmHg while receiving triple drug antihypertensive therapy) and 16 age-, gender- and BMI-matched responders to antihypertensive drug treatment. Obstructive sleep apnoea was more likely in the refractory hypertensives (56%) than in therapy responders (19%).

Cardiovascular homeostasis appears to be adversely affected by SRBD. Increased catecholamine turnover [10], blunting of baroreflex mechanisms [8] and a reduced endothelial dilatory capacity [9] all involve the pathophysiological mechanisms that may contribute to

this association. It is possible that these mechanisms also, at least in part, explain the increased frequency of refractoriness to antihypertensive therapy in hypertensive sleep apnoeic patients [31].

Low patient compliance with prescribed pharmacological or nonpharmacological treatment is claimed to be a major cause of uncontrolled hypertension [13–17]. In fact, even lower compliance may provide a further explanation for impaired blood pressure control in SRBD patients. This patient group suffers from reduced daytime vigilance and/or excessive sleepiness as a result of apnoea-induced sleep fragmentation [32]. Reduced daytime vigilance and performance, which have been reported as side effects of centrally acting sympatholytic and β -receptor blocking agents [17,18], may further aggravate daytime symptoms in SRBD patients, leading to decreased compliance. Prospective studies with a separate analysis of type, amount and interval of prescribed antihypertensive treatment in SRBD patients and control subjects may clarify this hypothesis.

RDI was an independent predictor for uncontrolled hypertension only in the younger group of patients. The cut-off at 50 years was chosen on the basis of several previous studies that had suggested an increased impact of SRBD on morbidity and mortality in patients aged 50 years and younger. A prospective study showed that snoring, a surrogate marker of sleep apnoea, was an independent risk factor for the development of hypertension only in men aged ≤ 50 years at the 10-year follow up [29]. Lavie *et al.* [33] found an increased influence of SRBD on mortality in men aged 30–50 years. In another study [34] the relationship between mortality and sleep apnoea severity was significant only in patients under 50 years old. Finally, the mean and median ages of the present patient sample were 50 and 51 years, respectively. Considering that age has been identified as a major risk factor for poor control of hypertension in large clinical studies [13,15,35], it might be speculated that the relative contribution of SRBD to incomplete hypertension control is overcome by age-related factors. Such factors may include arterial wall stiffness, which is known to increase markedly with age [36], and age-related increased sympathetic activity [37].

Treatment of sleep apnoea by tracheostomy or nasal continuous positive airway pressure (CPAP) were shown to reduce nocturnal blood pressure and heart rate [38,39]. Recent randomized clinical trials comparing CPAP treatment and placebo tablets [40] or 'sham CPAP' [41] suggested a reduction of daytime blood pressure with therapy. Increased catecholamines were reduced after long-term treatment with nasal CPAP [10] and vascular function and baroreflex control [42]

were clearly affected by SRBD treatment. It therefore appears justified to suggest that treatment of SRBD may lead to improved blood pressure control. Nevertheless, further mechanistic studies and randomized clinical trials are necessary to investigate the interaction between SRBD, different treatment modalities and blood pressure control in hypertensive patients.

The strength of this study is the large size of the study group, which permits standard clinic blood pressure measurements and assessment of traditional cardiovascular risk factors. SRBD was obtained by reliable and sensitive ambulatory measurements on two consecutive nights. Limiting factors include the cross-sectional design, which does not allow an assessment of the directional relationship between SRBD and poor hypertension control. Moreover, the classification of hypertension was based on questionnaire data, medical records, and/or information on prescribed antihypertensive drug treatment. It could be argued that this procedure, rather than classifying hypertension according to current use of antihypertensive drug treatment, may have included patients with less severe hypertension. However, there is no previous data that suggest that such inclusion bias does occur nor that it might have influenced study outcome. We did not perform separate analysis of the type, amount and interval of prescribed antihypertensive treatment because compliance with this treatment is known to vary between 20 and 80% [17,43], causing unpredictable errors in the analysis. Compliance may also vary between two consecutive visits in the outpatient department. In addition, data on the potential interactions between SRBD and antihypertensive treatment are inconsistent. An ACE-inhibitor was reported to decrease SRBD activity [44], and conflicting data were reported for centrally acting sympatholytic drugs and for β -blocking agents [45,46]. A recent comparative study in hypertensive SRBD patients showed no significant difference between atenolol, losartan, enalapril, amlodipine and hydrochlorothiazide in their modest effect on SRBD [47]. However, available protocols dealt only with short- or medium-term (weeks to months) drug intake. Therefore we did not consider the antihypertensive medication actually taken in our analysis.

Finally, the study sample was based on a clinical cohort and thereby reflects clinical management of hypertension in a sleep laboratory setting. It may not be extrapolated to the general population. The control group (patients with an RDI < 5) contains patients with SRBD-related symptoms such as snoring, daytime sleepiness and reported apnoeas. As snoring without apnoea itself is claimed to be a risk factor for hypertension [29], the effect of SRBD on control of hypertension in a general population setting might be even stronger than reflected by our results.

In conclusion, this study demonstrates that in patients aged 50 years or less SRBD constitutes a risk factor for uncontrolled hypertension by increasing the probability by 2% for every RDI unit. Considering that further prospective studies may show that effective treatment of SRBD reduces the need for multiple antihypertensive treatment and improves blood pressure control, screening tools for SRBD may be warranted in the clinical management of patients with poorly controlled systemic hypertension.

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