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# Prognosis and cardiovascular morbidity and mortality in prospective study of hypertensive patients with obstructive sleep apnea syndrome in St Petersburg, Russia

**Authors' Contribution:**

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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## Summary

**Background:**

To assess the impact of obstructive sleep apnea-hypopnea syndrome (OSAHS) on prognosis and cardiovascular morbidity and mortality in relation to other major cardiovascular risk factors.

**Material/Methods:**

This prospective study recruited 234 patients from an out-patient clinic. Based on the Berlin questionnaire, 147 patients (90 males, mean age 52.1±10.4 years) with highly suspected sleep breathing disorders were included in the study. Based on cardiorespiratory monitoring, patients were divided into 2 groups: 42 patients without sleep breathing disorders (SBD), and 105 patients with OSAHS. Among these, 12 patients started CPAP therapy and formed the third group.

**Results:**

The mean follow-up period was 46.4±14.3 months. Event-free survival was lowest in the untreated OSAHS patients (log rank test 6.732, p=0.035). In the non-adjusted regression model, OSAHS was also associated with a higher risk of cardiovascular events (OR=8.557, 95% CI 1.142–64.131, p=0.037). OSAHS patients demonstrated higher rates of hospitalization compared to the control group without SBD (OR 2.750, 95%CI 1.100–6.873, p=0.04).

**Conclusions:**

OSAHS hypertensive patients, and in particular, according to our model, patients with severe OSAHS (AHI >30/h), are at higher risk of fatal and non-fatal cardiovascular events. Moreover, untreated OSAHS patients demonstrate higher rates of hospitalization caused by the onset or deterioration of cardiovascular disease.

**Key words:**

**obstructive sleep apnea • prognosis • mortality • hypertension**

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## BACKGROUND

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is considered to be an independent risk factor for cardiovascular diseases [1–12]. According to data of cohort prospective [13] and large population [10] studies, the prevalence of fatal cardiovascular events is higher in patients with OSAHS [14–16]. Recent studies have shown a relationship between sleep breathing disorders and cardiovascular morbidity and mortality [15,17–19]. Peker et al. (2006) demonstrated a 5-fold increase in the risk of coronary heart disease. Marin et al. (2005) analyzed a large male cohort and concluded that patients with severe OSAHS are at higher risk of fatal and non-fatal cardiovascular events compared to healthy people and those with regular snoring. The beneficial effect of CPAP therapy was also documented [20]. However, some authors try to explain increased mortality in OSAHS patients by concomitant diseases rather than sleep breathing disorders [16]. Contributions of other cardiovascular risk factors (such as obesity and metabolic disorders) that are common for OSAHS patients, and their relation to outcome, are still not clear. None of the previous studies included a cohort of OSAHS patients from Russia.

Our study aimed to assess the impact of OSAHS on prognosis and cardiovascular morbidity and mortality in relation to other major cardiovascular risk factors. We focused on hypertensive patients because OSAHS is known to be closely connected to the development of hypertension [21] and resistance to antihypertensive therapy [12], and in most cases in our center OSAHS is diagnosed in patients with already abnormal blood pressure levels.

## MATERIAL AND METHODS

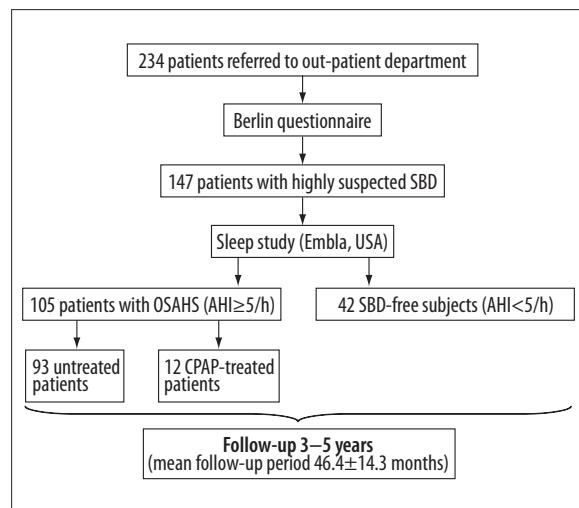
### Study population and design

#### *Selection of patients*

From May 2003 to March 2007 we selected 234 patients from a cohort referred to the out-patient department of Almazov Federal Heart, Blood and Endocrinology Centre with newly diagnosed or uncontrolled hypertension according to the following inclusion criteria: arterial hypertension (diagnosed if systolic blood pressure [SBP] and/or diastolic blood pressure [DBP] were 140 and 90 mmHg or higher, respectively, or if the patient was on antihypertensive therapy).

Patients were not included if they:

- had a concomitant significant cardiovascular pathology (coronary artery disease [angina pectoris] class II or higher), severe arrhythmia, congestive heart failure, valvular disease or cardiomyopathy;
- had other factors or diseases predisposing to OSAHS, such as congenital and acquired (rheumatoid arthritis, etc.) anatomical changes, visceral cranium abnormalities, macroglossia, vocal fold paralysis, diseases leading to pharyngeal lymphoid tissue proliferation (Hodgkin's lymphoma, AIDS), endocrine diseases (acromegaly, hypothyreosis), or neurological diseases (stroke, myasthenia, myotonic dystrophy, metabolic myopathy, amyotrophic lateral sclerosis, Guillain-Barré Syndrome, amyloidosis, diphtheritic, alcoholic and diabetic polyneuropathy);



**Figure 1.** Study design.

- had severe concomitant diseases (chronic liver or kidney diseases, cancer);
- were found to have a severe cognitive deficit that could confound the sleep examination.

Further selection was based on the results of a sleep breathing disorder questionnaire (Berlin Questionnaire [22]), and daytime sleepiness assessment by the Epworth scale [23]. The study enrolled only patients with suspected OSAHS. As a result, 147 patients (90 males and 57 females) aged 23–80 years (mean age 52.1±10.4 years) were included into the study (Figure 1).

All recruited patients signed the informed consent after full explanation of the procedure, which complied with the Declaration of Helsinki and the ethics policies of the institutions participating in the study.

#### *Assessments and study groups*

All patients completed a baseline questionnaire to collect data about personal and medical history, heredity, and lifestyle. Every patient underwent physical examination, including measurement of anthropometric parameters (height, weight, body mass index; waist, hip and neck circumferences) and vital signs (HR and blood pressure, BP). Patients who smoked 1 or more cigarettes per week were considered smokers. Patients were considered to be alcohol-users if they consumed 3 or more units of alcohol per week. Three or more sessions of aerobic exercise (30 minutes or longer) per week was considered to be the normal level of physical activity.

All patients underwent cardiorespiratory monitoring by Emblette Pds (Embla, USA) and the following parameters were recorded: snore, nasal flow, thoracic and abdominal excursions, body position, blood oxygen saturation, and heart rate. All recordings were evaluated manually by a specialist in polysomnography. Apnea was defined as an episode of airflow cessation lasting for at least 10 seconds. Hypopnea was defined as an episode of a decrease in airflow of more than 50% compared to baseline, lasting for >10 seconds, combined with a decrease in oxygen saturation

**Table 1.** Baseline group characteristics.

	Control group without SBD (n=42)	OSAS group		P (95% CI)
		OSAS untreated group (n=93)	CPAP-treated group (n=12)	
Sex, male	22 (52.4%)	59 (63.4%)	9 (75%)	0.295
Heredity	19 (54.3%)	51 (61.4%)	4 (44.4%)	0.544
CHD	12 (28.6%)	30 (32.3%)	5 (41.7%)	0.696
Thyroid pathology*	2 (4.8%)	4 (4.3%)	2 (16.7%)	0.222
Glucose metabolism impairment	7 (16.7%)	25 (26.9%)	6 (50.0%)	0.062
Among them:				
Diabetes mellitus	6 (14.3%)	22 (23.7%)	5 (41.7%)	0.137
Glucose tolerance impairment	1 (2.4%)	3 (5.3%)	1 (8.3%)	0.27
Smoking	20 (47.6%)	46 (49.5%)	5 (41.7%)	0.901
Alcohol use	20 (47.6%)	45 (48.4%)	4 (33.3%)	0.634
Aerobic physical activity	8 (24.2%)	23 (28.4%)	1 (11.1%)	0.637
Median (range of deviation)				
Age, years	50.7 (32.0–80.0)	54.0 (23.0–79.0)	55.2 (36.0–72.0)	0.26
BMI, kg/m <sup>2</sup>	33.1 (22.2–47.8)	34.6 (21.9–49.6)	34.6 (25.8–43.5)	0.11
Neck circumference	40.0 (35.0–46.0)	44.0 (39.0–49.0)	41.0 (40.0–41.0)	0.054
Hypertension duration, years	10.5 (2.0–30.0)	10.0 (0.3–35.0)	7.0 (5.0–30.0)	0.47
SBP	150.0 (110–180)	160.0 (110–260)	150.0 (130–180)	0.13
DBP	90.0 (60–120)	94.0 (70–140)	95.0 (80–105)	0.21
AHI, episodes per hour of sleep	1.8 (0.3–4.9)	24.3 (5.7–102.0)	59.5 (28.0–108.0)	<0.0001
Epworth scale, score	6.5 (3–13)	9.0 (3–23)	10.5 (6–19)	0.20

\* - thyreotrophic hormone level remained unchanged.

SBD – sleep breathing disorders; OSAS – obstructive sleep apnea syndrome; CPAP – continuous positive airway pressure; CHD – coronary heart disease; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; AHI – apnea/hypopnea index.

of ≥4% [14]. Sleep apnea/hypopnea syndrome was diagnosed if the patient had 5 or more events of apnea and hypopnea per hour of sleep (apnea-hypopnea index, AHI). Apnea was classified as obstructive if simultaneous excursions of the thorax and abdomen were registered, and was classified as central if no respiratory muscle effort was observed. Sleep apnea was classified as mild if the patient had 5–14.9 apnea or hypopnea events per hour, as moderate if AHI was 15–29.9 per hour, and severe if AHI was >30 per hour of sleep session.

Based on the results of the sleep study, patients were divided into 2 groups (Figure 1), with baseline characteristics shown in Table 1. Forty-two patients without sleep breathing disorders (SBD), with AHI <5 per hour [median 1.8 (0.3–4.9)], formed the control group, and 105 patients with AHI 5 and more episodes per hour constituted the OSAS group (no cases of central sleep apnea were diagnosed). Twenty-seven out of 105 patients (26%) had mild OSAS (AHI 10.9 [5.7–14.9] events per hour of sleep), 28 (27%)

– moderate OSAS (AHI 22.5 [15.4–29.3] events per hour of sleep), and 50 (47%) patients – severe OSAS 9AHI 51.0 [32.0–108.0] events per hour of sleep).

The groups did not differ by age, BMI, neck circumference, hypertension stage and duration, by the prevalence of hyperglycemia or diabetes, thyroid pathology (thyreotrophic hormone level remained normal), smoking, alcohol use and by physical activity level at baseline (Table 1).

A CPAP therapy session was offered (we used Auto-CPAP-devices ResMed, Australia; Respiration, USA, and ViPAP-III-device, ResMed, Australia) to anyone diagnosed with OSAS to evaluate its efficacy and assess the necessary therapeutic pressure. Out of 105 patients with SBD, 51 (48.6%) underwent the CPAP therapy test, but most refused to use CPAP therapy at home due to the high cost of the device (23 [45.1%] patients) and the inconvenience of the method (911 [21.6%] patients); in addition, 5 patients (9.8%) failed to get a fitting mask. Twelve (23.5%) patients who

**Table 2.** Antihypertensive therapy at baseline and at follow-up

	<b>OSASH untreated at baseline (n=93)</b>	<b>OSAHS untreated at the end (n=82)</b>	<b>Non OSAHS at baseline (n=42)</b>	<b>Non OSAHS at the end (n=41)</b>	<b>CPAP at baseline (n=12)</b>	<b>CPAP at the end (n=11)</b>
Monotherapy	38	14	25	24*	3	0**
2 drugs	41	26	14	4	4	4
3 drugs	10	20	3	4*	3	2
4 and more drugs	4	16	0	1*	2	1
Without therapy	0	6	0	8*	0	4

\* p<0.01 as compared to OSAHS at the end; \*\* p<0.001 as compared to non-OSAHS at the end.

started CPAP therapy at home formed the third group (Figure 1): 11 patients used autoCPAP-devices and 1 subject used a BiPAP-device. Most patients in this group were males (75%, 9 men), and AHI was higher in this group compared to OSAHS patients who did not use a CPAP.

All patients obtained counseling regarding lifestyle changes including weight loss, smoking cessation, alcohol use (the importance of drinking alcohol not later than 4 hours before sleep was emphasized) and use of sedative medicines. Change of body position during sleep was advised to all untreated OSAHS patients.

At baseline, antihypertensive therapy was prescribed to all patients with achievement of target blood pressure level (<140/90 mm Hg). Baseline therapy in CPAP-treated and untreated OSAHS patients did not differ by intensity or by components (p>0.05) (Table 2).

#### Follow-up and endpoints

Three-to-five year follow-up was initially planned. Patients' status and compliance with medical advices were assessed twice per year by telephone; if necessary, visits to the clinic were arranged. Efficacy of CPAP therapy and the condition of the device were assessed once in 6 months during a visit to the clinic using an appropriate software package (ResScan, ResMed, Australia; EncorePro, Respirationics, USA). It was considered effective if AHI was lower than 10 episodes per hour of session, and the mean nightly usage was more than 5 hours [24]. Antihypertensive therapy was assessed by clinic chart reviews and by direct patient interviews.

The primary endpoint was a composite of cardiovascular death, fatal/non-fatal myocardial infarction and stroke. If fatal events occurred, information about the circumstances and the date of death was obtained from the relatives, and the causes were assessed by analyzing the medical records in the medical institution and/or from death certificates. The non-fatal events were recorded by medical documentation. The secondary endpoint included hospitalization resulting from a new onset or deterioration of cardiovascular disease. Frequency of hospitalization and readmission was also assessed. The reasons for hospitalization were determined from the medical records. We also analyzed the changes in anthropometric parameters in untreated OSAHS and non-OSAHS patients – BMI, waist and neck circumferences, and changes in antihypertensive treatment.

Sleep breathing disorders are believed to be a risk factor for glucose and insulin metabolism impairment [25,26]; thus, we also assessed the new cases of glucose tolerance impairment and diabetes mellitus.

#### Statistics

Baseline and final data are presented as median and range of deviation or as mean and standard deviation (SD); categorical variables are expressed as numbers and percentages. Histograms, Kolmogorov-Smirnov and Shapiro-Wilk statistics, skewness and kurtosis analyses were used for distribution assessment. Baseline characteristics were compared using the Mann-Whitney U test and the Kruskall-Wallis criteria for continuous variables; the  $\chi^2$  test and Fisher exact test were used for categorical variables. Kaplan-Meier analysis with the log-rank test was used to estimate survival between the groups, and the odds ratio (OR) was calculated using the Cox proportional hazards model. Cox regression was used to estimate the OSAHS impact on time to cardiovascular events. ORs were considered significant when the 95% confidence intervals (CI) did not include the value of 1; and the p value of <0.05 was considered to be statistically significant. All statistical analyses were performed using a statistical software package (Statistica for Windows version 7.0, StatSoft Inc., U.S. è SPSS version 16.0 software; SPSS, Inc., Chicago, IL).

#### RESULTS

By March 2009, 8 patients from the 147 originally enrolled into the study were lost to follow-up because they had moved to another area. The mean follow-up period was 46.4±14.3 months. All 12 patients from the third group showed good compliance with the CPAP therapy, with mean nighttime device usage being 6.04±1.4 hours.

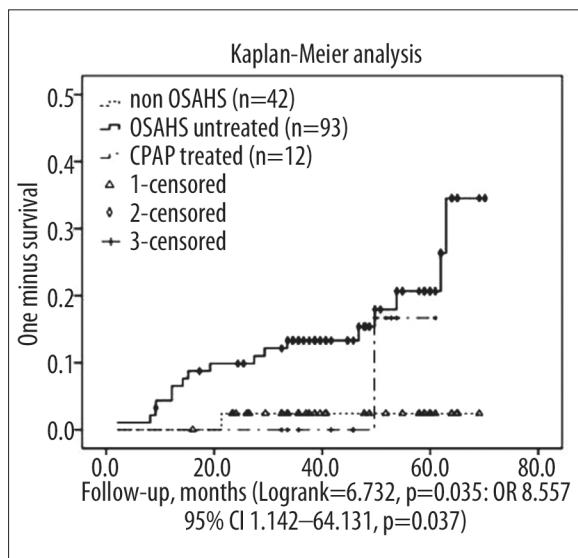
Overall, 23 events (15.6%) were registered, including 13 (8.9%) deaths, of which 11 (84.6%) occurred in males. One (7.7%) fatal event (sudden cardiac death) occurred among the CPAP-treated patients, 1 death from non-cardiac disease was observed in a patient without SBD, and 11 (84.6%) fatal events, including 1 non-cardiac death, occurred in the untreated OSAHS patients (Table 3).

Out of 10 non-fatal events, 5 were strokes and 4 were myocardial infarctions (MI), all observed in untreated OSAHS patients. One MI occurred in the control group. No non-fatal cardiovascular events were registered in the CPAP-treated

**Table 3.** Cardiovascular events distribution in the study groups.

<b>Underlying cause</b>	<b>Non-OSAHS (n=42)</b>	<b>OSAHS untreated (n=93)</b>	<b>CPAP-treated (n=12)</b>	<b>Total (n=147)</b>
<b>Fatal outcomes</b>				
Myocardial infarction, n	0	4	0	4
Sudden cardiac death, n	0	5	1	6
Congestive heart failure, n	0	1	0	1
Non-cardiac death, n	1	1	0	2
Total, n	1	11	1	13
<b>Non-fatal events</b>				
Myocardial infarction, n	1	4	0	5
Stroke, n	0	5	0	5
Total, n	1	10	1	21

OSAHS – obstructive sleep apnea syndrome; CPAP – continuous positive airway pressure.

**Figure 2.** Survival in OSAHS and SBD-free patients.

group (Table 3). The risk of fatal/non-fatal MI did not differ significantly from the control group (OR=3.859, 95% CI 0.467–31.892; p=0.273).

However, incidence of primary combined endpoint (cardiovascular death, fatal/non-fatal MI and stroke) differed significantly between the groups ( $P=7.145$ ,  $p=0.023$ , Fisher exact test). The risk estimated by the Monte Carlo test was higher in untreated OSAHS patients (20.4%) than in the control group (2.4%) (OR=9.293 95% CI 1.194–72.363,  $p=0.012$ ); however, no difference was found as compared to CPAP-treated patients (OR=3.727, 95% CI 0.215–64.474,  $p=0.398$ ). This might be due to the small sample size of the CPAP-treated group, which made it difficult to draw any definitive conclusions. There was no discrepancy between CPAP-treated patients and the control group (OR=0.379, 95% CI 0.045–3.127,  $p=0.690$ ).

Event-free survival (by Kaplan-Meier method) was lowest in the untreated OSAHS patients (log rank test 6.732,  $p=0.035$ ) (Figure 2).

In the non-adjusted regression model, OSAHS was also associated with a higher risk of cardiovascular events (OR=8.557, 95% CI 1.142–64.131,  $p=0.037$ ). The relationship between the variables (sex, age, BMI, duration of hypertension, smoking, alcohol use, physical activity level, family history of cardiovascular diseases, current coronary heart disease, glucose metabolism) and survival was assessed by Cox regression analysis (Table 4). The time-dependent model showed that only severe OSAHS was associated with poor outcome (OR=9.203 95% CI 1.176–72.002,  $p=0.034$ ), while presence of moderate and mild OSAHS did not affect survival (OR=8.588 95% CI 0.999–73.82,  $p>0.05$ , and OR=4.205 95% CI 0.437–40.434,  $p>0.05$ ). In the adjusted model, the impact of severe OSAHS was significant even when adjusted to the above-mentioned variables ( $p=0.04$ , Table 4).

Moreover, OSAHS patients demonstrated higher rates of hospitalization compared to the control group without SBD. Thirty-three untreated OSAHS patients were hospitalized (and 12 of them required readmission), while only 7 patients from the control group required hospitalization (OR 2.75, 95% CI 1.100–6.87,  $p=0.04$ ). There were 3 hospitalizations registered among CPAP-treated patients, and 1 of these patients required readmission (compared to untreated patients OR=0.606 95% CI 0.15–2.395,  $p=0.54$ ).

New onset of diabetes was registered in 4 untreated OSAHS patients, as well as 2 cases of glucose intolerance, compared to 2 (4.8%) cases of glucose intolerance impairment in the control group ( $p>0.05$ ).

There were no significant changes between baseline and final values of BMI ( $33.6 \pm 6.3$  and  $34.2 \pm 6.6$  kg/m<sup>2</sup> respectively,  $p>0.05$ ), waist circumference ( $107.3 \pm 14.1$  and  $109.6 \pm 13.7$  cm,  $p>0.05$ ), and neck circumference ( $41.8 \pm 4.5$  and  $41.9 \pm 5.1$  cm,  $p>0.05$ ) in control group, as well as in OSAHS patients

**Table 4.** The impact of variables on survival.

	OR (95% CI)	P*
AHI <5 per hour	REF	0.139 (REF)
AHI 5–14.9 per hour	8.588 (0.999–73.82)	0.50
AHI 15–29.9 per hour	4.205 (0.437–40.434)	>0.05
AHI ≥30 per hour	9.203 (1.176–72.002)	<b>0.034</b>
Sex	5.302 (0.632–44.496)	0.12
Age	1.017 (0.923–1.120)	0.74
BMI	1.038 (0.893–1.206)	0.62
Coronary heart disease	4.710 (0.943–23.534)	0.06
Duration of hypertension	1.026 (0.955–1.101)	0.49
Glucose metabolism impairment	0.619 (0.132–2.895)	0.54
Family history	3.464 (0.698–17.187)	0.13
Alcohol use	7.621 (0.968–60.002)	0.054
Smoking	1.153 (0.202–6.576)	0.87
Physical activity	1.515 (0.251–9.133)	0.65

\* P-value indicates statistical significance by Cox regression. AHI – apnea/hypopnea index; BMI – body mass index.

(BMI  $35.4 \pm 5.2$  cm at baseline and  $35.3 \pm 5.8$  kg/m $^2$  by 2009, p>0.05; waist circumference, respectively,  $116.9 \pm 13.4$  and  $117.1 \pm 15.9$  cm, p>0.05; and neck circumference  $43 \pm 2.7$  and  $44.1 \pm 3.1$  cm, p>0.05).

By 2009 most of OSAHS patients were on combination antihypertensive therapy (Table 2), while the majority (60%) of non-OSAHS subjects continued monotherapy (p<0.001). Thirty-six (44%) OSAHS patients compared to 5 (12%) controls took 3 or more antihypertensive drugs (p<0.05). There was also a difference in the distribution by classes of antihypertensive drugs. By 2009, 76 (93%) OSAHS patients and 32 (29%) non-SBD patients (p=0.012) took angiotensin converting enzyme inhibitors/angiotensin-2-receptor antagonists. Beta-blockers were prescribed to 63 (77%) OSAHS patients compared to 10 (24%) patients in the control group (p<0.001). By 2009, intensity of antihypertensive therapy in CPAP-treated and untreated patients with SBD was comparable. This finding might be due to the small size of the CPAP group, limiting the analysis and requiring further investigation.

## DISCUSSION

We tried to avoid the main limitations of other trials: determination of sleep apnea according to questionnaires that cannot be compared to the results based on the sleep study; inclusion of patients with severe cardiovascular pathology, diabetes mellitus, severe congestive heart failure or history of stroke [13,17], which can compromise the outcome history; and inclusion of patients with both central and obstructive sleep apnea, which does not allow comparison with the results of other OSAHS studies [10].

Our study also has several important limitations: the lack of randomization between the groups makes it observational,

the follow-up period was relatively short (in one-third of patients it was less than 3 years), no sleep studies were performed during the follow-up period, and we do not know if all the patients in the control group remained OSAHS-free and vice versa. One of the main limitations is the sample size of the CPAP-treated group. This can be explained by the fact that the majority of patients in Russia are still not mentally ready to use CPAP devices regularly (only 11.4% of patients with verified SBD agreed to this treatment in our study), even those with severe OSAHS, who should receive CPAP-therapy according to international standards.

Nevertheless, the present study appears to be the first performed in the Russian population, and is focused on hypertensive patients without known cardiovascular events.

The major finding is the impact of OSAHS on cardiovascular outcome. Our results showed that only severe OSAHS was associated with negative outcome. This finding corresponds to the recent publication of Valham et al (2008) – in a 10-year follow-up, SBD patients (n=392) with verified coronary heart disease had a significantly higher risk of stroke, correlating with desaturation index >5% and AHI  $\geq 15$  episodes per hour of sleep, independent of demographical, anthropometric, clinical and lifestyle parameters. Valham et al. (2008) failed to find any relationship between SBD and major cardiovascular events, which could be due to the older population with male predominance.

In our study the rate of fatal and non-fatal cardiovascular events was significantly higher in OSAHS hypertensive patients as compared with the SBD-free group, and in the adjusted regression model was associated with the severity of SBD. Thus, the risk of cardiovascular events in the Russian population of OSAHS patients was 9 times higher than in SBD-free subjects. Mean event-free survival in the OSAHS

group was 60.1 months (95% CI 55.9–64.2). However, only patients with severe SBD appeared to be at higher cardiovascular risk independent of lifestyle and other factors (sex, age, BMI, duration of hypertension, smoking, alcohol use, physical activity level, family history, current coronary heart disease, glucose metabolism impairment), while the prognosis in patients with mild-to-moderate OSAHS was comparable to the SBD-free group. It should be emphasized that all patients in our study had obstructive sleep apnea, and the central causes, as well as concomitant diseases predisposing to SBD, were excluded.

In our study the prognosis in CPAP-treated patients did not differ from the untreated OSAHS patients, though other authors showed a clear beneficial effect of CPAP therapy on the risk of recurrent cardiovascular events [20] and rates of fatal and non-fatal cardiovascular events and hospitalization [29]. Our results could be explained by the sample size of the CPAP-treated group, due to the limited availability of CPAP therapy in Russia. We speculate that with a bigger group we could expect to find differences and to form more definitive conclusions.

There have been only a few studies analyzing hospitalization rates in OSAHS patients. In 1 study, CPAP therapy reduced urgent hospitalization rates [30], and another study included combined endpoint analysis of deaths and hospitalizations, but the cause of hospitalizations was not verified [29]. We demonstrated a higher rate of hospitalization due to the onset or deterioration of the cardiovascular disease in OSAHS patients compared to the SBD-free group.

Our results show the need for a multiple combination antihypertensive therapy in OSAHS patients. These data support other publications showing the high prevalence of resistant hypertension in OSAHS [12,28].

We did not intend to verify the possible underlying mechanisms leading to high mortality in patients with SBD. The higher prevalence of resistant hypertension demonstrated in our study can be one of the reasons for worse outcome in the OSAHS group. The data on no long-term changes in BMI may indicate that the effect was not related to obesity. Lipid changes were not assessed, and could be an important issue.

## CONCLUSIONS

Our results confirmed that OSAHS hypertensive patients, in particular patients with severe OSAHS (AHI >30 episodes per hour of sleep), are at higher risk of fatal and non-fatal cardiovascular events. Moreover, we demonstrated higher rates of hospitalization were caused by the onset or deterioration of cardiovascular disease in untreated OSAHS patients, and higher prevalence of resistant hypertension.

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