



Predictors of heart rhythm disturbances in hypertensive obese patients with obstructive sleep apnea

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Abstract

Objective To assess the incidence and predictors of heart rhythm and conduction disturbances in hypertensive obese patients with and without obstructive sleep apnea (OSA). **Methods** This is an open, cohort, prospective study. Out of 493 screened patients, we selected 279 hypertensive, obese individuals without severe concomitant diseases: 75 patients without sleep-disordered breathing (non-SDB group), and 204 patients with OSA (OSA group). At baseline, all patients underwent examination, including ECG, Holter ECG monitoring, and sleep study. During follow-up (on 3, 5, 7 and 10th years; phone calls once per 6 months), information about new events, changes in therapy and life style was collected, diagnostic procedures were performed. As the endpoints, we registered significant heart rhythm and conduction disorders as following: atrial fibrillation (AF), ventricular tachycardia, atrioventricular block (AV) 2–3 degree, sinoatrial block, significant sinus pauses (> 2000 ms), and the required pacemaker implantation. **Results** The median follow-up was 108 (67.5–120) months. The frequency of heart rhythm disorders was higher in OSA patients (29 cases, $\chi^2 = 5.5$; $P = 0.019$) compared to the non-SDB patients (three cases; OR: 3.92, 95% CI: 1.16–13.29). AF was registered in 15 patients ($n = 12$ in OSA group; $P = 0.77$). Heart conduction disturbance developed in 16 patients, without an association with the rate of coronary artery disease onset. Regression analysis showed that only hypertension duration was an independent predictor of AF (OR: 1.10, 95% CI: 1.04–1.16; $P = 0.001$). In case of heart conduction disturbances, apnea duration was the strongest predictor ($P = 0.002$). **Conclusions** Hypertensive obese patients with OSA demonstrate 4-fold higher incidence of heart rhythm and conduction disturbances than subjects without SDB. Hypertension duration is an independent predictor for AF development, while sleep apnea/hypopnea duration is the main factor for heart conduction disorders onset in hypertensive obese patients with OSA.

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Keywords: Atrial fibrillation; Cardiovascular morbidity; Cardiovascular prognosis; Heart conduction disorder; Obstructive sleep apnea

1 Introduction

Sleep-disordered breathing (SDB), notably obstructive sleep apnea (OSA), is characterized by the repetitive apneas and/or hypopneas associated with intermittent hypoxia, hypoxemia and hypercapnia, sleep fragmentation due to the frequent arousals, intrathoracic pressure fluctuations, and sympathetic overactivity.^[1] SDB is highly prevalent in general population, and a tendency towards increase for the last two decades had been recently shown.^[2,3] Both the preva-

lence and severity [apnea-hypopnea index (AHI): 14.3 (7.0–27.2) vs. 7.6 (2.9–15.9) episodes/h, $P < 0.0001$] tend to increase in the elderly population compared to the middle-aged subjects.^[2]

SDB is known to be associated with cardiovascular diseases, and the increasing pool of evidence suggests a strong relation between sleep apnea and heart rhythm disturbances. This relation is partly supported by the shared risk factors, such as obesity, elderly age, male sex, smoking, etc. The main underlying mechanisms include intermittent hypoxemia leading to electrical instability, autonomic imbalance, swings of the intrathoracic pressure.^[1] The following potential factors are also discussed: genetic changes, atrial and ventricular remodeling including structural (atrial dilation, ventricular hypertrophy and dilation), electrical (atrial conduction slowing) and molecular remodeling (changes in atrial connexin-43 expression, potassium channel mRNA expression), and others.^[4–10] The association between atrial

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fibrillation (AF), heart conduction disorders and SDB is also confirmed by the observational studies which showed high rates of their coexistence exceeding 50%.^[11,12] However, the results of the prospective studies are controversial.^[13] In addition, few observational cohort studies failed to confirm the relationship.^[14,15] Moreover, the data on the clinical predictors of AF and conductive disorders in sleep apnea patients is rather scarce.

Therefore, the objective of the study was to assess the incidence and predictors of heart rhythm and conduction disturbances in hypertensive obese patients with and without concomitant obstructive sleep apnea.

2 Methods

The study was designed as an open, cohort, prospective study (Figure 1). The study protocol was approved by the Local Ethical Committee of the Almazov National Medical Research Centre. All patients signed informed consent before inclusion.

Median duration of follow-up: 108 (67.5–120.0) months

Visits
Baseline 1 yrs 2 yrs 3 yrs 4 yrs 5 yrs 6 yrs 7–10 yrs

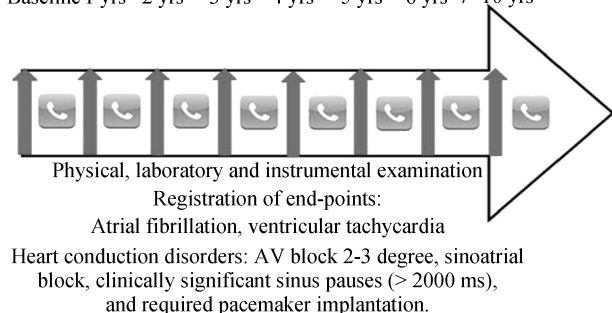


Figure 1. Study design.

2.1 Inclusion/exclusion criteria and group characteristics

Among patients who underwent sleep study at the Almazov National Medical Research Centre during 2002–2006 years according to electronic health records database, we selected those who fulfilled the following inclusion criteria: age 18–70 years old, with verified hypertension [blood pressure (BP) \geq 140/90 mmHg or antihypertensive drug intake] lasting for more than one year before inclusion; with witnessed sleep apneas and/or snore; overweight [body mass index (BMI) \geq 25 kg/m²]; who signed informed consent. The patients were excluded in case of severe cardiovascular diseases (coronary artery disease, CAD) presented by angina pectoris II functional class or higher; myocardial infarction in past; heart failure NYHA II or higher functional class, known significant heart rhythm disorders, cardiomyopathy of various origin; those, who used non-inva-

sive ventilation [continuous positive airway pressure (CPAP) users]; severe concomitant diseases affecting prognosis (liver and kidney pathology, oncological diseases, systemic diseases); type 1 or 2 diabetes mellitus at baseline; evident secondary sleep apnea (inherited facial abnormalities, severe ear-nose-throat diseases, oropharyngeal lymphoid hypertrophy, endocrine diseases, neurologic diseases, etc); and severe cognitive decline.

From 2002 to 2006, 493 patients with suspected sleep-disordered breathing were evaluated at the sleep lab at the Almazov National Medical Research Centre, and 294 patients met inclusion/exclusion criteria (Figure 2).

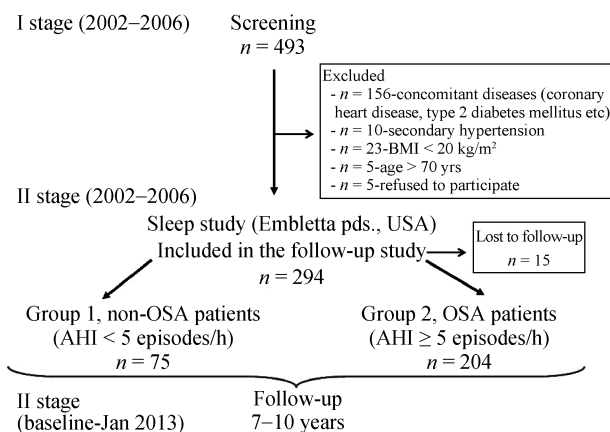


Figure 2. Patient selection. AHI: apnea-hypopnea index; BMI: body mass index; OSA: obstructive sleep apnea.

2.2 Endpoints and follow-up

After informed consent was signed, an individual visit schedule (visits on 3, 5, 7 and 10th years; phone calls once per 6 months) was planned. Non-scheduled visits were performed when necessary. In case of failure to contact (2012–2013), the most recent known data were used. Follow-up was estimated from inclusion date to the date of the last visit and/or the date of the last known information (obtained from patients' relatives or physicians, from medical records, i.e., dates of cardiovascular events). The patients lost to follow-up during the first year of the study were excluded from the analysis.

In this analysis, we assessed the frequency of significant disorders of heart rhythm and conduction. As the endpoints, we registered clinically significant heart rhythm and conduction disorders as following: AF/atrial flutter (paroxysmal, persistent, permanent), ventricular tachycardia, atrioventricular (AV) block 2–3 degree, sinoatrial block, clinically significant sinus pauses (> 2000 ms) based on the routine ECG and Holter ECG (HM ECG) monitoring, and the required pacemaker implantation.

2.3 Procedures

At baseline, all patients underwent interview, sleep study, physical examination, anthropometric measurements, office BP measurement, ambulatory BP monitoring (ABPM), biochemistry (lipids, glucose, creatinine, estimated glomerular filtration rate, and albumin urine excretion), ECG, and echocardiography. Moreover, secondary hypertension was excluded according to the available at that time [national (2001)^[16] and European guidelines (2007)^[17]: ultrasound of kidneys and adrenal gland, kidney scintigraphy when needed, Doppler of renal arteries, aldosterone-renin ratio, computer scans of adrenal glands, cortisol, catecholamine and metabolism levels in blood and urine].

At follow-up, information about new events, changes in therapy and life style was collected. Physical examination, office BP, anthropometry measurements, ABPM, HM ECG, echocardiography treadmill-test (when needed), and biochemistry tests were performed.

The questionnaire was developed at the Almazov National Medical Research Centre and included personal data, questions about risk factors and life style (based on WHO questionnaires), hereditary factors, concomitant diseases and therapy, sleep disorders including sleep apnea (based on the Berlin questionnaire, Epworth sleepiness scale).^[18,19]

Physical activity was considered low when physical training was performed less than twice per week. Smoking status was assessed at the moment of examination and in past. Regular alcohol use was considered in case of alcohol intake once per week and more frequent.

Heart rate was assessed at auscultation during 30 s. BP was measured in a sitting position on the right arm, three times with the 1-min interval. Mean of two last measurements was calculated (in accordance with the valid national guidelines). Anthropometric parameters (height, weight, body mass index by Quetlet formula, waist (WC) and hip (HC) circumferences, WC/HC ratio, neck circumference) were assessed.

Sleep study was performed by a portable cardiorespiratory device (Embletta pds., Medcare, Iceland), which allows to register up to nine parameters simultaneously, including respiratory excursions, oronasal air flow, snore pulseoximetry, body position, air pressure, and movements. The data were analysed with the use of software “Somnologica for Embletta” (Iceland). Semi-automatic analysis was performed and verified by the experienced sleep specialist. The sleep period was defined based on the patients’ diary. Apnea was considered when there was a $\geq 90\%$ drop in oronasal airflow lasting for 10 s and more. Hypopnea was scored when there was a $\geq 50\%$ reduction in oronasal flow associated with at least 4% desaturation. AHI was calculated as

the total number of apneas and hypopneas divided by the sleep duration (in hours). Depending on the severity, three degrees are distinguished: AHI 5.0–14.9 episodes/h, mild SDB; AHI 15.0–29.9 episodes/h, moderate SDB; AHI ≥ 30 episodes/h, severe SDB. We also assessed the number of desaturations, mean and maximal apnea duration (s), and mean and minimal oxygen saturation (%).^[20]

ECG was registered after 5 min of rest. Heart rhythm, heart rate, sinoatrial and atrioventricular conduction, signs of heart dilation and hypertrophy were assessed. Holter ECG monitoring was performed during 24-h (12-channel ECG, “Inkart”, Russia). The sleep time was defined according to the diaries. KTRResult software (“Inkart”, Russia) was used to analyze the data. Rhythm, heart rate, heart rhythm and conduction disorders were evaluated during wakefulness and sleep. At follow up, “Kardiotekhnika-04–3R(M)” (“Inkart”, Russia) device was used, which allows simultaneous registration of 12-channel ECG, pneumogram, spirogram, snoring, pulseoximetry and activity. Heart ultrasound was performed to exclude systolic dysfunction (ejection fraction), to assess the size of the heart chambers, to exclude valve disease, etc.

Blood samples were taken after 12-h fasting. Blood was centrifuged, and blood serum was frozen at -80° . The following parameters were analyzed: glucose, total cholesterol, high-density lipoproteins, triglycerides (Hitachi-902, Japan; reagents by Roche-Diagnostics, Switzerland). Level of low-density lipoproteins (LDL) was calculated by the Friedwald equation: $LDL = total\ cholesterol - HDL - triglycerides/5$.^[21] Glomerular filtration rate (GFR) was calculated by the MDRD equation:^[22]

$GFR = 32,788 \times Creatinine^{-1.154} \times Age^{-0.203} \times \kappa$, where Creatinine is measured in $\mu\text{mol/L}$, and κ is a coefficient which is equal to 0.742 for females.

2.4 Statistical analysis

Quantitative parameters are shown as mean \pm SD or as median (interquartile range) depending on the distribution type (assessed by Kolmogorov-Smirnov test). Nominal variables are presented as frequencies and/or as percentages. Chi-square test and Fisher exact test were applied to compare frequencies in different groups. For related samples McNemar test was used. Quantitative variables were compared by Mann-Whitney (two groups) or Kruskal-Wallis (> 2 groups) tests, ANOVA or Wilcoxon test were used for the related samples.

Correlation Spearman analysis was used to evaluate the associations between variables. For predictors assessment, paired and multiple logistic regression (with stepwise inclusion) was applied. The occurrence of AF/conduction disorder

der was included as a dependent variable. Among potential factors, the following variables were assessed: age at the baseline, sex, smoking, alcohol consumption, the presence of left ventricular hypertrophy, hypertension duration, beta-blockers use, renin-angiotensin-aldosterone system (RAAS) blockers use, apnea-hypopnea index, desaturation index, mean oxygen saturation, mean and maximal duration of apneas-hypopneas. Only those parameters which appeared to be significant (at $P \leq 0.01$ by simple regression analysis) were included in the multiple regression model. The factors associated with ventricular tachycardia in the studied cohort were not evaluated due to the low number of cases.

$P < 0.05$ was considered significant. In all tests, two-sided criterion was applied. The rounding was up to the hundredth, in case of borderline values, they were rounded up to thousandth. Statistical analysis was carried out with the use of SPSS 16.0.

3 Results

3.1 Group characteristics

Based on the sleep study, 77 subjects did not have SDB (non-SDB group, AHI < 5 episodes/h), and 217 formed the

SDB group (AHI ≥ 5 episodes/h). In the non-SDB group, two patients were lost to follow-up, while in the SDB group 13 subjects were lost to follow-up during the first months of the study. Therefore, finally, non-SDB group included 75 patients, and SDB group included 204 patients. All patients in the SDB group had obstructive respiratory events.

The groups matched by sex, age, office BP, ratio of smokers, ratio of patients with hereditary cardiovascular factors, self-estimated physical load, alcohol consumption, hypertension duration, and biochemical tests (Tables 1–3). However, OSA patients showed higher weight ($P < 0.001$), BMI ($P < 0.001$), waist circumference ($P < 0.001$) and WC/HC ($P = 0.046$), neck circumference ($P < 0.001$), and higher rate of left ventricular hypertrophy ($\chi^2 = 15.32$, $P < 0.001$).

Regarding antihypertensive therapy at baseline (Figure 3), SDB patients more often ($\chi^2 = 27.9$, $P < 0.001$) required combined therapy to control BP (< 140/90 mmHg). Moreover, they needed more drugs (by one antihypertensive drug) than non-SDB patients on average.

3.2 Dropouts

Dropout rate (due to various reasons, i.e., moving to

Table 1. Baseline characteristics.

Parameter	Non-SDB group, $n = 75$	OSA group, $n = 204$	$P = \text{level}$
Male/female, n	46/29	144/60	$\chi^2 = 1.09$ $P = 0.33$
Age, yrs	48 (42.0; 54.0)	51.0 (45.0; 56.0)	$P = 0.070$
Weight, kg	93.1 \pm 15.7	106.9 \pm 20.7	$P < 0.001$
BMI, kg/m ²	30.4 (26.5; 34.7)	35.0 (31.2; 39.7)	$P < 0.001$
WC, cm	102.8 \pm 16.1	117.1 \pm 13.4	$P < 0.001$
HC, cm	115.4 \pm 18.4	119.9 \pm 14.7	$P = 0.002$
WC/HC	0.90 \pm 0.10	1.00 \pm 0.09	$P = 0.046$
Neck circumference, cm	38.0 \pm 4.7	44.0 \pm 3.6	$P < 0.001$
Office SBP, mmHg	130 (121; 140)	136 (125; 148)	$P = 0.13$
Office DBP, mmHg	80 (70; 90)	80 (60; 90)	$P = 0.87$
Epworth scale, scores	4.0 (3.0; 6.5)	10.0 (6.0; 14.0)	$P < 0.001$
Hypertension duration, yrs	7.0 (3.0; 10.0)	10.0 (5.0; 15.0)	$P = 0.052$
Fasting glucose, mmol/L	5.4 (5.1; 5.9)	5.6 (4.9; 6.0)	$P = 0.51$
Total cholesterol, mmol/L	5.62 (5.10; 6.11)	5.34 (4.68; 6.06)	$P = 0.09$
Low-density lipoproteins, mmol/L	3.62 (3.22; 4.70)	3.42 (2.72; 4.06)	$P = 0.14$
High-density lipoprotein, mmol/L	1.10 (0.87; 1.26)	1.10 (0.95; 1.33)	$P = 0.86$
Triglycerides, mmol/L	1.96 (1.39; 2.19)	1.76 (1.32; 2.49)	$P = 0.90$
Uric acid, $\mu\text{mol/L}$	380.0 (317.5; 439.5)	430.0 (377.0; 491.0)	$P = 0.07$
Creatinine, $\mu\text{mol/L}$	77.0 (67.0; 93.5)	88.0 (71.0; 97.6)	$P = 0.21$
eGFR, mL/min per 1.73 m ²	89.2 \pm 23.1	81.5 \pm 19.3	$P = 0.13$
Ejection fraction (Teicholz)	66.8% \pm 4.3%	64.6% \pm 6.8%	$P = 0.19$

Data are presented as mean \pm SD or as median (interquartile range). BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HC: hip circumference; OSA: obstructive sleep apnea; SBP: systolic blood pressure; SDB: sleep-disordered breathing; WC: waist circumference.

Table 2. Baseline characteristics of life style and other cardiovascular risk factors.

Parameter	Non-SDB group, <i>n</i> = 75	OSA group, <i>n</i> = 204	<i>P</i>
Working people	73	180	$\chi^2 = 9.97$ <i>P</i> = 0.001
Smokers (including past smokers)	33	112	$\chi^2 = 1.74$ <i>P</i> = 0.23
Hereditary (cardiovascular) factor	37	104	$\chi^2 = 2.14$ <i>P</i> = 0.18
Regular physical activity	20	53	$\chi^2 = 0.10$ <i>P</i> = 0.88
Alcohol abuse	37	104	$\chi^2 = 0.001$ <i>P</i> = 1.00
Glucose intolerance	0	4	$\chi^2 = 0.05$ <i>P</i> = 1.00
Presence of left ventricular hypertrophy (either based on ECG or heart ultrasound)	32	151	$\chi^2 = 15.32$ <i>P</i> < 0.001
*Snoring duration, yrs	4.0 (1.5; 7.0)	10.0 (5.0; 20.0)	<i>P</i> = 0.003

Data are presented as *n* or median (interquartile range). *Only patients who gave the answer were included (35%). SDB: sleep-disordered breathing; OSA: obstructive sleep apnea.

Table 3. Sleep study at baseline.

Parameter	Non-SDB group, <i>n</i> = 75	OSA group, <i>n</i> = 204	<i>P</i> -level
AHI, episodes/h	2.2 (1.0; 3.7)	31.2 (15.0; 57.2)	<i>P</i> < 0.001
Desaturation index, episodes/h	2.1 (0.8; 3.6)	27.4 (12.2; 52.5)	<i>P</i> < 0.001
Mean oxygen saturation	94.5% (93.7%; 95.4%)	93.1% (90.9%; 94.6%)	<i>P</i> < 0.001
Minimal oxygen saturation	86.0% (84.0%; 89.0%)	77.0% (70.0%; 83.0%)	<i>P</i> < 0.001
Mean desaturation	4.8% (4.5%; 5.3%)	6.2% (5.3%; 8.7%)	<i>P</i> < 0.001
Duration with saturation < 90%, percent of total sleep time	0.2% (0; 0.9%)	5.7% (1.5%; 24.0%)	<i>P</i> < 0.001
Total duration of snoring, percent of total sleep time	17.4% (6.8%; 37.3%)	23.7% (14.3%; 38.5%)	<i>P</i> = 0.159
Mean duration of apnea-hypopneas, s	19.1 (16.0; 26.5)	23.7 (20.0; 28.2)	<i>P</i> < 0.001
Maximal duration of apnea-hypopneas, s	36.0 (25.0; 61.2)	77.5 (62.3; 99.8)	<i>P</i> < 0.001

Data are presented as *n* or median (interquartile range). AHI: apnea-hypopnea index; OSA: obstructive sleep apnea; SDB: sleep-disordered breathing.

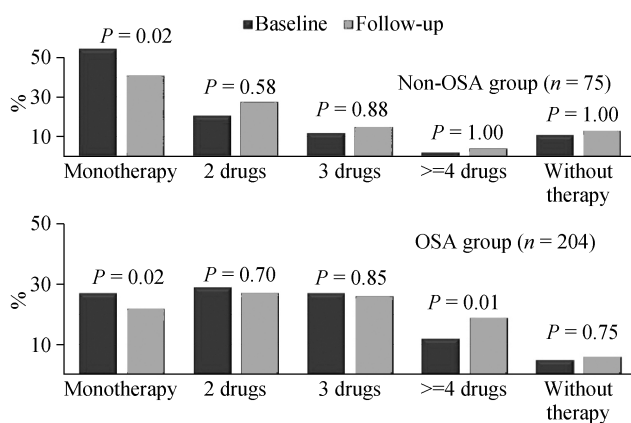


Figure 3. Antihypertensive drugs: baseline and follow-up.

another city, decline of further participation) was similar in both groups and was distributed evenly during the follow-up period. Thus, 91.2% OSA patients and 81.3% subjects from

the comparison group completed 3-year follow-up ($\chi^2 = 2.94$; *P* = 0.09). At 5-year follow-up, the rate was 86.8% and 81.3%, respectively ($\chi^2 = 0.58$; *P* = 0.49); by 7 years 71.6% and 78.6%, respectively ($\chi^2 = 0.18$; *P* = 0.19); and by 10 years 31.4% and 38.7%, respectively ($\chi^2 = 1.01$; *P* = 0.32).

3.3 Mortality

During follow-up, 17 lethal cases were registered, including 13 cardiovascular deaths [mean age of the dead: 55.2 (31–71) years]. The reasons were the following in the OSA group (*n* = 10): two cases of myocardial infarction, one case heart failure progression, six cases sudden cardiac death, one case stroke; and in the comparison group (*n* = 3): one case of myocardial infarction, one case of stroke, and one sudden cardiac death.

3.4 Heart rhythm and conduction disorders

The frequency of heart rhythm and conduction disorders

was significantly higher in OSA patients (29 cases, $\chi^2 = 5.5$; $P = 0.019$) compared to the non-SDB patients (three cases). The odds ratio (OR) = 3.92, 95% CI: 1.16–13.29. Moreover, four patients developed transient AV-block 1 degree at nighttime, but it was not considered an endpoint (Table 4, Figure 4).

Heart rhythm disorders developed more frequently in patients with subsequent onset of CAD: in six patients out of 23 patients with CAD onset, preceding heart rhythm and/or conduction disorders had been diagnosed, compared to only 26 out of 258 patients without CAD ($\chi^2 = 5.36$; OR: 3.149, 95% CI: 1.14–8.69; $P = 0.033$).

3.5 AF/atrial flutter

AF was registered in 15 patients ($n = 12$ in OSA group;

Table 4. Heart rhythm and conduction disorders in the studied groups.

Event	Non-SDB patients, $n = 75$	OSA patients, $n = 204$	Chi-square, P -level
Atrial fibrillation/atrial flutter	3	12	$\chi^2 = 0.36$ $P = 0.77$
Heart conduction disturbances (including AV block II degree, sinoatrial block)	0	16*	$\chi^2 = 6.16$ $P = 0.015$
Pacemaker implantation	0	4	$\chi^2 = 1.47$ $P = 0.35$
Non-sustained ventricular tachycardia	0	5	$\chi^2 = 1.85$ $P = 0.33$
Total	3	29#	$\chi^2 = 5.51$ $P = 0.019$

*Two patients developed both sinoatrial and AV block; #One patient developed permanent atrial fibrillation with the Frederick syndrome at night and monomorphic ventricular rhythm, which required pacemaker implantation; four patients developed several types of heart rhythm and conduction disorders. AV: atrioventricular; SDB: sleep-disordered breathing; OSA: obstructive sleep apnea.

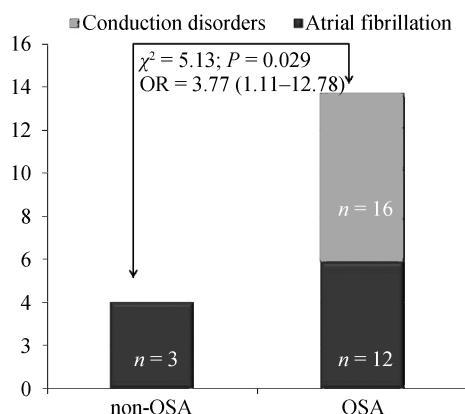


Figure 4. The frequency of heart rhythm and conduction disorders. OSA: obstructive sleep apnea.

$P = 0.77$): among them four cases of permanent AF ($n = 3$ in OSA group and $n = 1$ in non-SDB group). Paroxysmal AF occurred in 11 patients, including one patient who had an increase of AHI from < 5 episodes/h at baseline up to 59 episodes/h at follow-up. CAD was diagnosed in five (21.7%) patients with developed AF, however, AF occurrence preceded CAD (acute coronary syndrome and/or stable angina pectoris) diagnostics. Among 258 patients without CAD, AF occurred in 10 subjects ($\chi^2 = 13.34$; $P = 0.004$; OR: 6.89, 95% CI: 2.13–22.31).

3.6 Heart conduction disturbances

Heart conduction disturbance developed in 16 patients, without an association with the rate of CAD onset: 15 vs. 1 ($\chi^2 = 0.09$; $P = 1.00$; OR: 0.74, 95% CI: 0.09–5.84). There was no association with other cardiovascular fatal/ non-fatal outcomes. Nine patients developed exclusively asymptomatic nocturnal heart conduction disorder, while two subjects with sinoatrial block reported syncope/pre-syncope.

Pacemaker was implanted in four patients (all in the OSA group): DDD in three subjects, in one case the mode is unknown ($\chi^2 = 1.47$; $P = 0.35$). Neither radiofrequency ablation was performed, no CAD was diagnosed in any of these patients.

3.7 Ventricular tachycardia

Non-sustained ventricular tachycardia developed in five OSA patients ($\chi^2 = 1.85$; $P = 0.33$). Exclusively nocturnal ventricular tachycardia was registered in three subjects, and in two of them the paroxysms onset occurred in the end of apnea episodes as shown by the sleep study. There were no signs of CAD in these patients at the time of ventricular tachycardia onset. Later, the rate of CAD was slightly higher in patients with pre-diagnosed ventricular heart rhythm disorders ($\chi^2 = 6.86$; $P = 0.055$).

3.8 Predictors of heart rhythm and conduction disturbances

The analysis of the predictors was performed separately for the AF/atrial flutter and conduction disorders. Ventricular tachycardia was not analyzed separately due to the low number of cases. Based on the simple regression analysis, only duration of hypertension was an independent predictor of AF [OR: 1.10, 95% CI: 1.04–1.16; $P = 0.001$]. Other parameters had no significant impact on the outcome, including age ($P = 0.29$), sex ($P = 0.12$), smoking ($P = 0.19$), alcohol consumption ($P = 0.44$), BMI ($P = 0.26$), left ventricular hypertrophy presence ($P = 0.56$), office SBP ($P = 0.76$), office diastolic blood pressure (DBP, $P = 0.74$), RAAS-blockers intake ($P = 0.56$), AHI ($P = 0.31$),

Table 5. Predictors of heart conduction disturbances based on simple regression analysis.

Parameter	OR (95% CI)	P-level
BMI	1.10 (1.03–1.17)	<i>P</i> = 0.008
LVH presence	3.67 (0.82–16.48)	<i>P</i> = 0.09
Beta-blockers	0.33 (0.09–1.22)	<i>P</i> = 0.10
AHI	1.02 (1.01–1.04)	<i>P</i> = 0.006
Maximal duration of sleep apneas	1.03 (1.01–1.04)	<i>P</i> = 0.001
Mean nocturnal oxygen saturation	0.93 (0.86–1.01)	<i>P</i> = 0.099
Minimal nocturnal oxygen saturation	0.95 (0.91–0.99)	<i>P</i> = 0.019
Desaturation index	1.01 (0.99–1.01)	<i>P</i> = 0.10

AHI: apnea-hypopnea index; BMI: body mass index; LVH: left ventricular hypertrophy.

desaturation index (*P* = 0.48), mean oxygen saturation (*P* = 0.93), and OSA presence (AHI ≥ 5 episodes/h; *P* = 0.55). Predictors of heart conduction disturbances by the simple regression analysis are shown in Table 5.

In case of heart conduction disturbances, multiple step-by-step logistic regression showed the following independent predictors: apnea-hypopnea index (OR: 1.03, 95% CI: 1.01–1.04; *P* = 0.007), and β-blocker intake (OR: 0.29, 95% CI: 0.08–0.98; *P* = 0.047) (Figure 4). However, when apnea duration was included in the model, it appeared to be the only significant factor (*P* = 0.002). Neither minimal/mean oxygen saturation (*P* = 0.88/*P* = 0.68) nor desaturation index (*P* = 0.056) had impact on heart conduction disturbances (Table 6).

4 Discussion

We assessed the role of sleep-disordered breathing for the development of heart rhythm and conduction disturbances which are considered an important cause of cardio-

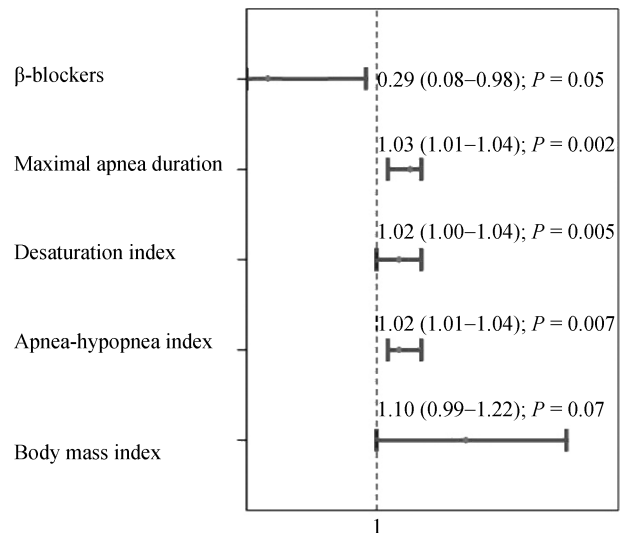


Figure 5. Predictors of heart conduction disturbances in hypertensive obese patients.

vascular mortality. We found a significantly higher incidence of heart rhythm and conduction disorders in hypertensive obese patients with OSA compared to the non-SDB group. The risk of arrhythmic events was 4-fold higher in OSA patients compared to non-SDB group (OR: 3.77, 95% CI: 1.11–12.78, $\chi^2 = 5.13$, *P* = 0.029), which corresponds to the worldwide data.^[11,13] Based on our data, a significant proportion of lethal cases are related to sudden cardiac death (6 out of 10) that can be due to the life-threatening arrhythmias.^[23] However, severe ventricular arrhythmias comprised only minor percentage (17%) of the registered events in our study, which can be attributed to the older age of our sample (over 60 years old by the end of follow-up). Sleep Heart Health Study demonstrated a higher risk of ventricular arrhythmias (but not conduction disorders) in younger patients

Table 6. Predictors of heart conduction disturbances in hypertensive obese patients: the model includes parameters of sleep apnea severity.

Parameter	Model includes AHI, OR (95% CI)	Model includes desaturation index OR (95% CI)	Model includes apnea duration OR (95% CI)
BMI	1.10 (0.99–1.22); <i>P</i> = 0.07	1.08 (1.00–1.17); <i>P</i> = 0.046	1.08 (1.01–1.04); <i>P</i> = 0.070
LVH presence	<i>P</i> = 0.59	<i>P</i> = 0.21	<i>P</i> = 0.36
β-blockers intake	0.29 (0.08–0.98); <i>P</i> = 0.047	0.28 (0.08–0.96); <i>P</i> = 0.043	<i>P</i> = 0.22
AHI	1.02 (1.01–1.04); <i>P</i> = 0.007	-	<i>P</i> = 0.32
Maximal duration of sleep apnea/hypopnea	-	-	1.03 (1.01–1.04); <i>P</i> = 0.002
Mean oxygen saturation	<i>P</i> = 0.54	-	<i>P</i> = 0.68
Minimal oxygen saturation index	<i>P</i> = 0.42	-	<i>P</i> = 0.88
Desaturation index	-	1.02 (1.00–1.04); <i>P</i> = 0.056	-

AHI: apnea-hypopnea index; BMI: body mass index; LVH: left ventricular hypertrophy.

with OSA compared to the elderly ones (younger patients: OR: 9.3, 95% CI: 2.8–30.6; the elderly: OR: 2.0, 95% CI: 1.3–3.1; $P = 0.002$).^[11,13]

In our cohort, paroxysmal and permanent AF comprised the majority of registered events (48%). Experimental studies demonstrated a high probability of AF induction by long apneas (> 1–1.5 min).^[24] The same group of authors prevented AF paroxysms by radiofrequency ablation of ganglia located in the area of pulmonary veins. OSA is common in patients undergoing the operations of pulmonary vein radiofrequency ablation.^[25] They also showed higher risk of post-surgery AF recurrence,^[25–27] which can be decreased by CPAP-therapy. Therefore, some authors suggest to perform sleep studies in all patients undergoing pulmonary radiofrequency ablation, however, OSA presence is not a contraindication for the surgery.^[28]

Follow-up assessment showed no association between either AHI, desaturation index or hypoxemia with AF risk. Only hypertension duration predicted AF occurrence in hypertensive obese patients. Mehra, *et al.*,^[13] also failed to confirm an association between OSA with AF in a fully adjusted model. They showed that in elderly patients, AF is associated rather with central SDB than OSA.

In our cohort, OSA patients with AF onset more often developed CAD later during follow-up. We speculate that AF was the first manifestation of the undiagnosed CAD. OSA is known to contribute to the atherosclerosis progression,^[29] and might increase the risk of heart rhythm disorders. The lack of association between OSA and AF in our study can be also related to the group characteristics, in particular, to the older age group. A meta-analysis (8 studies, 4516 participants with AF) by Qureshi, *et al.*,^[30] demonstrated that CPAP-therapy was more beneficial for AF recurrence prevention after catheter ablation in younger subjects ($P < 0.05$).

The incidence of heart conduction disorders ($n = 16$ in our study), unlike AF, was not associated with the higher risk of subsequent cardiovascular events. Therefore, we hypothesize that heart conduction disorders do not increase cardiovascular risk in hypertensive obese patients with OSA. Our assumption is confirmed by the electrophysiology studies that showed normal function of sinus node and normal atrioventricular conduction in wakefulness in OSA.^[31,32] Moreover, Tilkian AG and Guilleminault C prevented nocturnal sinus bradycardia and asystole in OSAS patients by atropine injection.^[33] These data verify the absence of structural abnormalities of conduction system. However, the number of studies assessing heart conduction in OSAS is rather small.

Intriguingly, unlike AF, the incidence of heart conduc-

tion disorders is associated with AHI in our sample. Maximal duration of sleep apnea/hypopnea [77.5 (62.3; 99.8) s in OSAS patients vs. 36.0 (25.0; 61.2) s in non-SDB group] is an independent predictor of heart conduction disorders, and its significance exceeds that of AHI, oxygen saturation level and desaturation index.

Some authors hypothesize that bradycardia can be protective during long apneas associated with the low oxygen supply.^[34] In these circumstances, pacemaker implantation and heart stimulation can negatively affect myocardial function. CPAP-therapy appears to be the most reasonable option in OSA patients with heart conduction disturbances,^[35] although personalized approach should be implied in decision making. Few case reports demonstrating benefits of CPAP-therapy regarding the lack of nocturnal pacing in OSAS patients with implanted pacemakers, which can help to save the battery and to increase the life of implanted pacemaker.^[32]

Few studies estimated predictors of arrhythmias in SDB. A recent study by Selim, *et al.*,^[14] demonstrated that AHI, and in particular, obstructive events, is the strongest predictor of nocturnal arrhythmias in US veterans. However, the authors did not assess the role of apnea duration. Wu, *et al.*^[36] failed to show the relation between the severity of OSA and bradyarrhythmias in an observational study and stated that heart block does not exclusively occur in severe sleep apnea.

Being at high risk of hypertension and arrhythmias, patients with OSA often require medication therapy. Beta-blockers, which decrease sympathetic activity, appear to be the most appropriate drug class, but might be prejudiced in case of nocturnal bradyarrhythmias. A recent publication by Wolf, *et al.*,^[37] demonstrated that β -blockers are safe and effective regarding the attenuation of apnea-related tachycardia response and are not associated with the increase of bradyarrhythmic responses in hypertensive patients with moderate-to-severe OSA. Our study showed that when adjusted for the sleep apnea duration β -blockers were not associated with the risk of heart conduction disorders, which indirectly confirms the safety of beta-blockers in OSA patients.

Our study has certain limitations. The most important is that we did not assess the efficiency of OSA therapy on arrhythmia development. The access to the CPAP-treatment is complicated in the Russian Federation due to the lack of the reimbursement of the non-invasive ventilation. The dropout rate by the end of the study is rather high. However, the numbers did not exceed those reported by other authors, which can be considered satisfactory. It should be mentioned that in our study the patients did not receive any mo-

netary reward. Importantly, the pre-study duration of sleep apnea is unknown. Self-reported snoring (response rate: 35%) was not associated with the higher cardiovascular risk in the primary analysis, so it was not included in the final model. Possible variability of the evaluated parameters (severity of sleep apnea, apnea-hypopnea index, etc.) can also affect the results of our prospective study. Another limitation typical for the long prospective studies refers to changes in the approaches to the assessment, diagnosis and management of hypertension, heart rhythm disorders, sleep disorders (since 2002), which we tried to overcome by updating the approaches during the follow-up and re-evaluation of the results. Moreover, we included a matching control group followed up within the same time period and the same conditions, because the consideration of all potential predictors is hardly probable.

In summary, hypertensive obese patients with OSA demonstrate high incidence of heart rhythm and conduction disturbances, which is 4-times higher than in subjects without sleep-disordered breathing. The onset of heart rhythm disorders precedes CAD diagnosis in 26%. Hypertension duration is an independent predictor for AF development, while AHI and maximal sleep apnea/hypopnea duration are the main factors for heart conduction disorders onset in hypertensive obese patients with OSA.

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References

- Greenberg H, Lakticova V, Scharf SM. Sleep Breathing Disorders. In *Principles and Practice of Sleep Medicine*, 6th Edition; Kryger M, Ed; 2016; 1110–1124.
- Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015; 3: 310–318.
- Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177: 1006–1014.
- Patel N, Donahue C, Shenoy A, et al. Obstructive sleep apnea and arrhythmia: a systemic review. *Intern J Cardiol* 2017; 228: 967–970.
- Fisser C, Marcinek A, Hetzenecker A, et al. Association of sleep-disordered breathing and disturbed cardiac repolarization in patients with ST-segment elevation myocardial infarction. *Sleep Med* 2017; 33: 61–67.
- Channaveerappa D, Lux JC, Wormwood KL, et al. Atrial electrophysiological and molecular remodelling induced by obstructive sleep apnoea. *J Cel Mol Med* 2017; 21: 2223–2235.
- Gemel J, Su Z, Gileles-Hillel A, et al. Intermittent hypoxia causes NOX2-dependent remodeling of atrial connexins. *BMC Cell Biol* 2017; 18(Suppl 1): 7.
- Jiang N, Zhou A, Prasad B, et al. Obstructive sleep apnea and circulating potassium channel levels. *J Am Heart Assoc* 2016; 5: e003666.
- Gaisl T, Wons AM, Rossi V, et al. Simulated obstructive sleep apnea increases P-wave duration and P-wave dispersion. *PLoS One* 2016; 11: 1–9.
- Iwasaki Y, Xiong F, Naud P, et al. Atrial fibrillation promotion with long-term repetitive obstructive sleep apnea in a rat model. *J Am Coll Cardiol* 2014; 64: 2013–2023.
- Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *Am J Respir Crit Care Med* 2006; 173: 910–916.
- Szymanski FM, Platek AE, Karpinski G, et al. Obstructive sleep apnoea in patients with atrial fibrillation: Prevalence, determinants and clinical characteristics of patients in Polish population. *Kardiol Pol* 2014; 72: 716–724.
- Mehra R, Stone KL, Varosy PD, et al. Nocturnal Arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. *Arch Intern Med* 2009; 169: 1147–1155.
- Selim BJ, Koo BB, Qin L, et al. The association between nocturnal cardiac arrhythmias and sleep-disordered breathing: The DREAM study. *J Clin Sleep Med* 2016; 12: 829–837.
- Porthan KM, Melin JH, Kupila JT, et al. Prevalence of sleep apnea syndrome in lone atrial fibrillation: a case-control study. *Chest* 2004; 125: 879–885.
- Chazova IE, Boitsov SA, Nebieridze DV. In *National guidelines on diagnostics and management of arterial hypertension*, 1st Edition; Moscow, Russia, 2001; 1-37.
- Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; 28: 1462–1536.
- Netzer N, Stoohs R, Netzer C, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 1999; 131: 485–491.
- Johns M. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
- Berry R, Brooks R, Gamaldo C, et al. In *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*, 2nd Edition; American Academy of Sleep Medicine: Darien, USA, 2012.
- Susekov A. Comments to the National guidelines on diagnostics and treatment of dyslipidemia for atherosclerosis prevention. http://old.consilium-medicum.com/media/consilium/04_11/841.shtml (accessed May 7, 2017).

- 22 Levey A, Bosch J, Lewis J, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470.
- 23 Panidis I, Morganroth J. Sudden death in hospitalized patients: cardiac rhythm disturbances detected by ambulatory electrocardiographic monitoring. *J Am Coll Cardiol* 1983; 2: 798–805.
- 24 Ghias M, Scherlag BJ, Lu Z, *et al.* The role of Ganglionated Plexi in apnea-related atrial fibrillation. *J Am Coll Cardiol* 2009; 54: 2075–2083.
- 25 Hoyer FF, Lickfett LM, Mittmann-Braun E, *et al.* High prevalence of obstructive sleep apnea in patients with resistant paroxysmal atrial fibrillation after pulmonary vein isolation. *J Intervent Cardiac Electrophysiol* 2010; 29: 37–41.
- 26 Patel D, Mohanty P, Di Biase L, *et al.* Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: The impact of continuous positive airway pressure. *Circ Arrhythm Electrophysiol* 2010; 3: 445–451.
- 27 Matiello M, Nadal M, Tamborero D, *et al.* Low efficacy of atrial fibrillation ablation in severe obstructive sleep apnoea patients. *Europace* 2010; 12: 1084–1089.
- 28 Tang RB, Dong JZ, Liu XP, *et al.* Obstructive sleep apnoea risk profile and the risk of recurrence of atrial fibrillation after catheter ablation. *Europace* 2008; 11: 100–105.
- 29 Lui MMS, Ip MSM. OSA and atherosclerosis. *J Thoracic Dis* 2012; 4: 164–172.
- 30 Qureshi WT, Nasir U Bin, Alqalyoobi S, *et al.* Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. *Am J Cardiol* 2015; 116: 1767–1773.
- 31 Grimm W, Apelt S, Timmesfeld N, Koehler U. Sleep-disordered breathing in patients with implantable cardioverter-defibrillator. *Europace* 2013; 15: 515–522.
- 32 Simantirakis EN, Schiza SI, Marketou ME, *et al.* Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. *Eur Heart J* 2004; 25: 1070–1076.
- 33 Tilkian A, Guilleminault C, Schroeder J, *et al.* Sleep-induced apnea syndrome. Prevalence of cardiac arrhythmias and their reversal after tracheostomy. *Am J Med* 1977; 3: 348–358.
- 34 Shepard JJ. Cardiopulmonary consequences of obstructive sleep apnea. *Mayo Clin Proc* 1990; 65: 1250–1290.
- 35 Zwillich C, Devlin T, White D, *et al.* Bradycardia during sleep apnea. Characteristics and mechanism. *J Clin Invest* 1982; 69: 1286–1292.
- 36 Wu X, Liu Z, Chang SC, *et al.* Screening and managing obstructive sleep apnoea in nocturnal heart block patients: an observational study. *Respir Res* 2016; 17: 16.
- 37 Wolf J, Drozdowski J, Czechowicz, *et al.* Effect of beta-blocker therapy on heart rate response in patients with hypertension and newly diagnosed untreated obstructive sleep apnea syndrome. *Int J Cardiol* 2017; 10: 4173–4183.

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