CHAPTER 4. MEDICAL SCIENCES

LEFT VENTRICULAR REMODELING IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME AND OBESITY

Andreieva Iana[1]

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Abstract. The aim of the study: to estimate the structural changes of LV among people with unrecognized OSAS and different body mass. **Materials and methods.** The study involved 74 patients with OSAS. All subjects were divided into two groups: with obesity and with normal body weight. 20 healthy people were included in the control group. Each patient underwent a clinical evaluation, 24-hour ambulatory blood pressure monitoring, cardiorespiratory monitoring, transthoracic echocardiography. Pearson correlation analysis, univariate and multivariate regression analysis were performed. **Results:** Ten patients from all enrolled subjects were diagnosed with LV hypertrophy. Estimated LVM and LVMI increased in group I in comparison with the group II and control group. Significant differences between group II and control group concerning LVMI and LVM weren`t admitted. A significant difference for PWT_d and IVS_d were observed in group 1 and group 2, compare to control group. Increasing body mass index and increasing level of hypoxia lead to impairment of diastolic dysfunction. Diastolic dysfunction was diagnosed in 17 patients with OSAS and obesity. All patients with diastolic dysfunction have second or third stage of obesity and severe OSAS. Patients with concentric hypertrophy had the significantly lowest E/A in comparison with patients without hypertrophy or with concentric remodeling. The LVMI was positively correlated with DI even after adjustment for the BMI. The LVM correlate with mean SaO_2 and the lowest SaO_2. The univariate regression analysis showed that the lowest SaO_2, DI, AHI were associated with LVMI. **Conclusions:** 1. OSAS and

[1] Candidate of Medical Sciences, Associate Professor at Department of Therapy, Physiotherapy, Balneology and Occupational Medicine,
SI "Medical Academy of Postgraduated Education of Ministry of Health of Ukraine", Ukraine

obesity are associated with high LVM, LVMI, a deterioration of the diastolic function of the LV and prevalence of concentric LV remodeling. The LVM, LVMI and level of DD were increased parallel to an increasing in the OSAS`s severity and the degree of obesity. 2. There were admitted statistically significant differences for PWT_d and IVS_d among patients with OSAS without obesity and healthy people. All patients with established DD had 1 grade diastolic dysfunction (impaired relaxation). 3. The lowest SaO_2, DI, BMI were associated with changes of LVMI, LVM, PWT_d and IVS_d according to the results of regression analysis. A positive correlation between DT, BMI and DI, and the negative correlation with $minSaO_2$ have been established. IVRT correlated only with the DI, and the index E/A – with BMI. In multivariable regression analysis, DI was a predictor of diastolic dysfunction and LVH in patients with OSAS and obesity.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) characterized by recurrent episodes of complete or partial obstruction of the upper airway during sleep, has widely gained interest since its initial description more than 40 years ago [10, p. 355]. In the adult population, the prevalence of OSA is estimated to be ~25%, and as high as 45% in obese subjects. Obesity predisposes to and potentiates OSAS. The prevalence of OSAS and its consequences are likely to increase in light of the current obesity epidemic. Recent estimates suggest that 60% of the adult population in industrialized countries is overweight (BMI $\geq$ 25 kg/m^2) and at least 30% is obese (BMI $\geq$ 30 kg/m^2) [12, p. 85]. Sleep fragmentation is an important consequence of OSAS; whether such interrupted sleep results in pathophysiologically similar mechanisms such as sleep deprivation is not known. Experimental sleep deprivation, as well as self-reported short sleep (< 6 h/night), have been linked to metabolic dysregulation independent of obesity and OSA, suggesting important interactions between these conditions and increasing the complexity of their treatment [13, p. 1074].

OSAS is associated with hypertension, insulin resistance, atrial fibrillation, stroke, and increased cardiovascular disease (CVD) morbidity and mortality. Disruption of sleep leads to increased sympathetic activation, metabolic changes, vasoconstriction, acute tachycardia, acute blood pressure elevation that results in increased left ventricular (LV) afterload [12, p. 86].

Repeated apneas and hypopneas during the night have pronounced physiological effects in patients with OSAS [16, p. 946]. Reductions in ventilation cause alveolar hypoxia and hypercapnia. Pulmonary artery pressures increase because of pulmonary artery vasoconstriction related to alveolar hypoxia and because of increased blood return to the right heart secondary to negative intrathoracic pressure. Right ventricular overload can cause paradoxic movement of the intraventricular septum to the left and decrease left ventricular (LV) compliance. In addition, the negative intrathoracic pressure increases LV afterload and LV work. These changes can cause transient LV dysfunction. All these events are associated with increased sympathetic activity [15, p. 384].

OSAS is the most common form of sleep-disorder breathing. Whereas LV dysfunction is a known cause of central sleep-disorder breathing, it has been postulated that OSAS might be an independent risk factor for LVH and LV dysfunction. Left ventricular hypertrophy (LVH) is one of the well-knowing CVD risk factors and often associate with OSAS [13, p. 1075]. However, how OSAS impacts on LV remodeling isn`t completely clear. On the one hand, LVH could be as a result of the OSAS itself. Some studies have shown that LVH is a common complication of OSAS and even without the potential cardiovascular disease, left ventricular systolic and diastolic dysfunction (LVSD and LVDD) and LVH were associated with OSAS. LVMI strongly correlate with OSAS severity and prevalence of LVH among patients with severe OSAS is high [3, p. 93]. But other authors claim that LVH could be caused by the OSAS comorbidities such as hypertension, obesity and metabolic deregulations, and the LVMI differ significantly only between the patients with the OSAS who suffer from hypertension, obesity, and/or diabetes mellitus [12, p. 87]. Furthermore, obesity is an additional risk factor for development of LVH and increasing of CVD risk. At the same time, continuous positive airway pressure therapy for 6 months resulted in significant regression of LVH as measured by interventricular septal thickness but not LV posterior wall thickness in one study, whereas decreased interventricular septal thickness was observed along with improved LV function in another study [4, p. 494].

However, in the initial stages of the disease, we hypothesize that mechanical effects of obstructive events mainly create ventricular pressure overload that by itself might lead to slowed ventricular relaxation and cardiac remodeling. So, **the aim of the current study** was to estimate the

structural and functional changes of LV among people with unrecognized OSAS with and without obesity.

2. Materials and methods

Subjects for this study were recruited from 418 consecutive adults with OSAS who underwent overnight cardiorespiratory monitoring between November 2011 and August 2017. All subjects didn`t have previous treatment of OSAS. Our present research was approved by the clinical research ethic committee of SI "Zaporizhia Medical Academy of Post-Graduate Education Ministry of Health of Ukraine". Written informed consent was obtained from all patients.

Each patient underwent a clinical evaluation during consultation, biological tests, electrocardiogram (CardioSens, XAI-Medica, Ukraine), 24-hour ambulatory blood pressure monitoring (ABPM – 04, Meditech, Hungry). Hypertension was defined as blood pressure ≥125/80 mmHg during ABPM and/or use of antihypertensive medication. When first stage of investigation was completed, patients with hypertension, diabetes mellitus or any other known cardiac and renal diseases, with central sleep apnea were excluded from the study. Finally, 174 (117 men and 57 woman) eligible patients were enrolled. All these patients underwent transthoracic echocardiography.

Body mass index (BMI) of the patients were calculated as weight divided by height square ($kg \cdot m^2$). According to BMI, all subjects were divided into two groups. The first group includes participants with obesity (BMI ≥30 $kg \cdot m^2$) (46 subjects), the second group – with normal body weight (28 subjects). Twenty healthy people were included in the control group. The mean age and gender were similar between the groups.

Self-reported sleep duration on weekdays was obtained from answers to the following question: "How many hours do you sleep on average during a 24-h period?" The response categories ranged from "≤5 h" to "≥11 h" at intervals of one hour. Sleep duration was classified as short (9 h), based on the joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society [8, p. 6]. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS) previously translated and validated in Russian [9, p. 543]. ESS results range from 0–24 with high scores reflecting high levels of sleepiness and excessive daytime sleepness was defined as an ESS ≥10 [8, p. 9]. In addition, participants were classified by the risk of having sleep apnea using the Berlin Questionnaire, which

consist of three categories related to risks and symptoms of sleep disorders (i.e., snoring, stop breathing, tiredness and fatigue, falling asleep and high blood pressure and/or BMI). Participants were classified at high risk of sleep apnea if they reported two or more categories with a positive score.

Cardiorespiratory monitoring was conducted for OSAS diagnosis on Somnocheck 2.0 (Weinmann, Germany). All participants were recorded for at least 8 hours. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. According to the American association of sleep medicine [8, p. 7], the severity of OSAS was classified as mild ($5 \leq AHI < 15$ events/hour), moderate ($15 \leq AHI \leq 30$ events/hour) and severe (AHI > 30 events/hour). Desaturation index (DI) was defined as the percentage of sleep time with oxygen saturation < 90%.

Clinical characteristic of enrolled patients are shown in table 1.

Table 1

Clinical characteristic of enrolled patients

Parameters	Group 1 (n=46)	Group 2 (n=28)	Group 3 (n=20)
Male/Female (n)	117/57	20/8	14/8
Mean age (years)	36,5±6,8	41,6±7,2	36,8±6,7
BMI (kg/m^2)	33,2±4,3	23,5±3,6	23,1±3,3
SBP (mmHg)	128,3 ±10,6	118,2±7,7	112,3±6,9
DBP (mmHg)	79,4±9,3	72,9±6,5	73,1±6,2
AHI (events/per hour)	21,3 ±4,1	18,2±3,3	2,5 ±1,0
Mild OSAS (n)	20	11	0
Moderate OSAS (n)	21	11	0
Severe OSAS (n)	13	6	0
DI (per hour)	22,6±5,8	13,5±5,4	1,1±0,4
Minimum SaO_2 (%)	82,3±6,4	87,4±4,5	97,4±1,5
Mean SaO_2 (%)	92,9 ±5,6	96,5±3,2	98,3±1,2
Sleep duration (%)	6,2±4,2	5,5±2,7	6,9±1,1

Transthoracic echocardiography was performed with Siemens ACUSON X300 ultrasound machines, with a 1,75 MHz probe. Basic measurements of LV dimensions in diastole and systole, thicknesses of interventricular septum (IVS_d) and left ventricular posterior wall (PWT_d), and left ventricular

mass (LVM) was measured by the M-mode technique according to European Association of Cardiovascular Imaging [14, p.418]. The surface area of the body and left ventricular mass index (LVMI) was calculated. LVH was defined as LVMI ≥ 125 g/m2. LV geometry was categorized into 4 groups: normal structure (LVMI<125 g/m2 and RWT<0,45), eccentric hypertrophy (EH, LVMI ≥ 125 g/m2 and RWT<0,45), concentric remodeling (CR, LVMI<125 g/m2 and RWT ≥ 0,45), and concentric hypertrophy (LVMI ≥ 125 g/m2 and RWT ≥ 0,45). Left atrial, end-systolic diameter was measured in M-mode in the parasternal long axis view. LV diastolic function was evaluated by transmitral Doppler using the pulsed Doppler technique with 2D guidance in apical four-chamber view. The following diastolic parameters were measured or calculated from at least three consecutive beats: E wave (peak flow velocity in early diastole); A wave (peak flow velocity at atrial contraction); and the E/A ratio. The mitral deceleration time (DT), isovolumic relaxation time (IVRT) and the valsalva manoeuvre were used to distinguish the different filling patterns if necessary. A normal pattern was defined as E/A > 1 and normal DT (160–240 ms); impaired relaxation was defined as E/A < 1 and DT > 240 ms; a pseudonormal pattern was defined as E/A 1–1.5, DT > 240 ms and reversal of the E/A ratio (to < 1.0) by valsalva manoeuvre; and a restrictive pattern was defined as E/A > 1.5 and DT < 160 ms. All echocardiograms were performed by the same experienced echocardiographer.

Statistical analysis. The quantitative variables were expressed as means ± SD. Categorical variables were presented as percentages. The differences in each variable were evaluated by the Student's *t*-test for continuous variables and the $\chi 2$ test for categorical variables. The relationships between parameters were evaluated by Pearson correlation analysis and univariate regression analysis. Multivariate logistic regression analysis using statistically significant variables from the univariate analysis was performed to identify variables that were independently associated with LVH and left ventricular diastolic dysfunction (LVDD). A *P*-value < 0.05 was considered to indicate a statistically significant difference between groups. Calculations were performed using SPSS-software (Version 13.0; SPSS, Chicago, IL).

3. Results

The demographic, cardio-monitoring and echocardiographic parameters were compared between the groups (table 2).

Table 2

Echocardiographic measures in obtained patients

Parameters	Group 1 (n=46)	Group 2 (n=28)	Control group (n=20)	P
LA, cm	2,74±0,38	2,72±0,41	2,66±0,23	P_{1-3} – 0,088 P_{2-3} – 0,074
LVM, gr	189,7±35,15	141,3±23,2	127,56±21,74	P_{1-3} – 0,013 P_{2-3} – 0,058
LVMI, gr/m^2	92,11±28,15	71,66±15,90	61,14±11,28	P_{1-3} – 0,008 P_{2-3} – 0,066
PWT_d, sm	1,11±0,14	0,93±0,17	0,79±0,12	P_{1-3} – 0,024 P_{2-3} – 0,074
IVS_d, sm	1,13±0,15	0,86±0,17	0,76±0,13	P_{1-3} – 0,028 P_{2-3} – 0,018
E, sm/sec	63,47 ± 9,60*	68,70 ± 8,67	73,22 ± 5,25	P_{1-3} – 0,031 P_{2-3} – 0,066
A, sm/sec	64,2 ± 9,2	62,4 ± 12,1	56,4 ± 9,5	P_{1-3} – 0,108 P_{2-3} – 0,098
E/A, y.o.	0,92 ± 0,33*	1,09 ± 0,42	1,30 ± 0,26	P_{2-3} – 0,078 P_{1-3} – 0,011
IVRT, мс	208,7 ± 16,4*	199,3 ± 20,4*	177,3 ± 15,6	P_{1-3} – 0,034 P_{2-3} – 0,006
DT, мс	90,2 ± 6,9*	86,7 ± 9,5	76,4 ± 10,2	P_{1-3} – 0,022 P_{2-3} – 0,067
FV, %	55,80 ± 2,46	56,24 ± 2,88	56,45 ± 3,10	P_{1-3} – 0,122 P_{2-3} – 0,104

Estimated LVM was increased in group I in comparison with the group II and control group (268,7 ± 65,15, 161,3 ± 43,2, 127,56 ± 21,74, respectively, P=0,008; 0,005). LVMI (g/m) was also significantly increased in patients with obesity and OSAS (47 ± 1,8 vs. 40 ± 1,5, P < 0.01). Significant differences between group II and control group concerning LVMI and LVM weren`t admitted. The LVMI was increased parallel to an increasing in the OSAS severity in the groups I and II, but that increasing failed to constitute statistical significance in group II (P = 0,095).

Ten patients from all enrolled subjects were diagnosed with LV hypertrophy. Nine (90 %) of these patients were in group I. All these patients had severe OSAS (AHI, (36,55±8,41) e/h). Concentric remodeling was diagnosed in 9 patients (8 patients from group I and 1 patient from group II) and concentric hypertrophy was observed in one patient. In comparison with

group without LVH patients with diagnosed LVH have higher level of AHI (38,2 ± 17,8 vs. 24,6 ± 13,3) and DI (6,3 ± 3,2 Vs. 18,6 ± 8,8) (P = 0,011).

According the results of assessment of left ventricle diastolic function in groups, 34 (45,9 %) out of all patients with OSAS had an impaired LV relaxation. Patients with a diastolic dysfunction were older and had higher clinic BP and HR rates. 26 (81 %) subjects had abnormal ABPM. Prevalence of nocturnal hypertension was higher in patients with impaired LV diastolic function than in those with normal LV function (80 % versus 67 %; p = 0,042). Half of the patients with impaired LV relaxation had a non-dipper pattern (42 % of normal LV function subjects; p = 0,714).

Statistically significant differences were found between the diastolic dysfunction parameters in patients with moderate and severe SOAS and patients of control group. In patients with moderate SOAS, the peak A was higher on 13,3 % (P < 0,05) compared with the control group and on 11,1 % compared to the group 2 (P < 0,05). In subjects with group 1, peak E was lower on 24,3 % (P < 0,05) compared with control group and on 22,4 % when compared with group 2 (P < 0,05). Peak A was increased in all groups compared to the control group, but these changes were true only in the group 1. The ratio of E/A decreased with an increase in the severity of OSAS and was the lowest in the group 1- by 36,9 % lower than in the control group (P < 0.05) and by 37,9 % lower compared with the group 2 (P < 0,05). A significant difference was also established between values of the IVRT in the groups 1 and 2 (P < 0,05). According the results of analysis of the IVRT, an increase in the index in patients with groups 1 and 2 was observed at 11,9 % and 15,3 % respectively, in comparison with the control group (P < 0,05). Also, IVRT significantly differed in groups 1 and 2 (P < 0,05).

Thus, LVDD was diagnosed in 4 (8 %) patients in the group 2 and in 17 (36,9 %) patients in the group 1. All patients had grade 1 diastolic dysfunction (impaired relaxation).

According to the assessment of the diastolic functions in patients with different stages of obesity, a significant deterioration of the diastolic function of the left ventricle was established with an increase in obesity. There was no significant change in diastolic function in patients with 1 degree of obesity and OSAS when compared with the group of patients with 2 grade of obesity and the control group. For patients with 2 degree of obesity, compared with the control group, a significant decrease in the IVRT and an increase in the DT, a decrease in the ratio of E/A, an increase in the

Table 3

Echocardiographic measures in patients with different stages of obesity

Показник	Patients with obesity and OSAS (n = 46)			Control group (n = 20)
	Obesity 1 stage (n = 21)	Obesity 2 stage (n = 16)	Obesity 3 stage (n = 9)	
FV, %	57,92 ± 3,44	56,25 ± 3,22	55,02 ± 3,92	56,45 ± 3,10
P_C	0,312	0,118	0,096	
LA, cm	3,09 ± 0,32	3,28 ± 0,55	3,52 ± 0,54	2,66 ± 0,23
P_C	0,101	0,042	0,011	
LVM, gr	153,2 ± 26,4	159,9 ± 20,4	183,2 ± 25,5	127,5 ± 21,7
P_C	0,067	0,031	0,012	
LVMI, gr/m^2	71,18 ± 12,73	82,08 ± 11,23	97,11 ± 18,14	61,14 ± 11,28
P_C	0,088	0,026	0,041	
PWT_d, sm	0,89 ± 0,11	0,91 ± 0,13	1,15 ± 0,14	0,79 ± 0,12
P_C	0,126	0,055	0,042	
IVS_d, sm	0,89 ± 0,10	1,03 ± 0,11	1,18 ± 0,10	0,76 ± 0,13
P_C	0,086	0,001	0,001	
E, sm/sec	67,71 ± 8,64	63,47 ± 9,60	55,42 ± 9,11	73,23 ± 5,25
P_C	0,211	0,006	0,001	
A, sm/sec	61,3 ± 9,2	65,9 ± 8,7	70,4 ± 9,1	56,4 ± 9,5
P_C	0,087	0,062	0,041	
E/A, y.o.	1,18 ± 0,42	1,08 ± 0,23	0,80 ± 0,27	1,30 ± 0,26
P_C	0,211	0,052	0,009	
IVRT, мс	197,1 ± 17,2	210,6 ± 17,1	219,3 ± 16,2	177,3 ± 15,6
P_C	0,042	0,013	0,003	
DT, мс	84,2 ± 9,2	88,3 ± 7,2	98,7 ± 10,4	76,4 ± 10,2
P_C	0,068	0,034	0,001	

time delayed blood flow of early diastolic filling of the left ventricle and the IVRT was established. Diastolic dysfunction was diagnosed in 51 % of patients with OSAS and obesity of 2 degrees.

Among the structural changes in the LV in patients with obesity of 2 degrees, in comparison with the control group, a significant increase

was found only in the PWT_d. In this case, the presence of LVH was found in 1 (6 %) of patients in this group. In the analysis of diastolic function indicators in the patients with obesity of 3 degrees, reliable changes in the diastolic function were found when compared with the control group and with obesity of grade 3. Among the structural changes compared with the control group, a significant increase in LVM, LVMI, PWT_d, and IVS_d ($P < 0.05$) were established. LVH was established in 8 patients from this group (1 patient had concentric hypertrophy and 7 – concentric remodeling of the left ventricular myocardium).

In our study, a comparative analysis of the state of left ventricular diastolic function in patients with different types of left ventricular hypertrophy was performed. The IVRT was reduced in patients with concentric remodeling and concentric hypertrophy when compared to those without left ventricular hypertrophy. Also, there was a decrease in the ratio of E/A, especially with concentric hypertrophy, but the values of the DT of the LV and IVRT did not significantly differ between the groups.

Statistically significant positive correlations were detected between the BMI and cardio-respiratory parameters – AHI, mean SaO_2, the lowest SaO_2, and DI $SaO_2 < 90\%$ ($r = 0,232$, $P = 0,003$; $r = 0,44$, $P = 0,010$; $r = 0,284$, $P = 0,01$; and $r = 0,381$, $P = 0,007$, respectively). The LVMI was positively correlated with DI ($r = 0,744$, $P = 0,011$) even after adjustment for the BMI ($r = 0,273$; p value = 0,042). There were no statistically significant correlations between the LVMI and the AHI ($r = 0,164$, $P = 0,082$). The LVM correlate with mean SaO_2 ($r = -0,228$, $R = 0,06$), and the lowest SaO_2 ($r = -0,189$, $P = 0,06$). Positive significant correlation was detected between PWT_d and DI ($r = 0,354$, $P = 0,001$) and non-significant correlation was detected between IVS_d and AHI ($r = -0,263$; $P = 0,072$). A correlation analysis showed that E/A was significantly related to age ($r = -0,522$; $P < 0,001$), clinic DBP ($r = -0,274$; $P = 0,022$) and SBP ($r = -0,287$; $P = 0,008$), AHI ($r = -0,418$; $P = 0,007$), DI ($r = -0,224$; $P = 0,009$) and mean SaO_2 ($r = 0,415$; $P < 0,001$) but not to LVMI. In the subgroup of non-obese subjects, E/A ratio was significantly correlated to age ($r = -0,413$; $P < 0,001$), mean nocturnal SaO_2 ($r = 0,349$; $P < 0,017$) and clinic DBP ($r = -0,231$; $P = 0,038$). According results of correlation analysis between structural indices and the state of diastolic function of the LV, it was found that in patients with OSAS and obesity, the LVMI correlated with E/A, the delayed blood flow of early diastolic filling of the left ventricle and IVRT (r = -0,572, 0,484, 0,612,

respectively, P < 0.05). In addition, the LVMI correlated with AHI, DI and min SaO_2 (r = 0,582, 0, 535, -0,317, P < 0.05) in patients from group 1.

The univariate regression analysis with dependent variable as LVMI showed that the lowest SaO_2, DI, AHI were significant associated with LVMI (table 4).

Table 4

Results of univariate regression analysis (LVMI)

Independent variables	OR (CI 95%)	P
Age, years	1,31 (1,05-1,56)	0,021
Gender (male)	0,88 (0,53-1,11)	0,067
BMI, kg/m^2	1,05 (0,99-1,28)	0,001
AHI, events/per hour	1,16 (0,93-1,31)	0,072
DI, per hour	1,42 (1,18-1,95)	0,033
Mean SaO_2, %	0,84 (0,62-1,26)	0,216
Min SaO_2, %	1,62 (1,13-1,93)	0,029
SBP, mmHg	0,81 (0,68-0,98)	0,114
DBP, mmHg	0,93 (0,76-1,18)	0,046

The univariate regression analysis with dependent variable as E/A showed that age, AHI, DI, BMI and LVMI were independent predictors of E/A (table 5).

Table 5

Results of univariate regression analysis (E/A)

Independent variables	OR (CI 95%)	P
Age, years	1,14 (0,95-1,33)	0,001
Gender (male)	0,71 (0,44-0,98)	0,283
BMI, kg/m^2	1,05 (0,99-1,28)	0,001
AHI, events/per hour	1,07 (0,88-1,12)	0,016
DI, per hour	1,09 (0,87-1,56)	0,042
Mean SaO_2, %	0,8 (0,52-1,14)	0,324
Min SaO_2, %	0,74 (0,44-1,03)	0,161
SBP, mmHg	0,99 (0,95-1,66)	0,021
DBP, mmHg	0,96 (0,84-1,22)	0,010
LVMI, gr/m^2	1,13 (1,02-1,22)	0,004

According result of correlation and univariate regression analysis, all final multivariate regression models were adjusted for age, SBP and gender. To construct the final model, we use stepwise input of the variables to the regression model.

In case of using the LVMI as dependent variables, BMI, the lowest SaO_2, mean SaO_2, AHI and DI were performed to assess the contribution of these variables in LV changes. A 1% decrease in the lowest SaO_2 saturation was associated with a LVMI increase of 2,5 gr (P=0,02), increase in IVS_d of 0,08 cm (P<0,05) and an increase in PWT_d thickness of 0,03 cm. An increase DI in 1 % lead to increasing of LVMI of 2.6 gr and PWT_d thickness of 0,05 cm.

In case of using the E/A as dependent variables, age, AHI, DI, BMI and LVMI were tested in a multi-factor regression model. After adjusting for age, sex and BMI, the final regression model demonstrated that only the DI was an independent predictor of LV diastolic dysfunction in OSAS and obesity patients (Table 6).

Table 6

Results of multivariate regression analysis (E/A)

Independent variables	OR (CI 95%)	P
Age, years	1,08 (0,96-1,26)	0,005
Gender (male)	1,16 (0,95 – 1,42)	0,024
BMI, kg/m^2	1,04 (0,96-1,22)	0,037
AHI, events/per hour	0,95 (0,82-1,20)	0,084
DI, per hour	1,12 (1,09-1,42)	0,023
LVMI, gr/m^2	1,06 (1,04-1,31)	0,062

4. Discussion

OSAS has important influences on cardiac functions such as left/right ventricular dysfunction, cardiac arrhythmia, and pulmonary hypertension [11, p. 106]. Although, the mechanism of impairment in myocardial contraction and relaxation seen in patients with OSAS is poorly understood. OSA may increase cardiac risk due to an imbalance of myocardial oxygen demand and supply as a result of hypoxemia, hypercapnia, and increased sympathetic activation occurring during apnea [1, p. 1978].

The results of our analysis highlight the importance of hypoxia severity, not just the AHI, in promoting cardiac remodeling. Diseases, such as hyper-

tension, obesity, and diabetes mellitus, which often accompany OSAS, also contribute to the development of LVH. In our study, cardio-vascular and endocrine diseases were excluded. Furthermore, both groups of patients with OSAS were significantly different according BMI and severity of OSAS. The majority of patients with obesity (50%) were in the severe OSAS group. Because of the compelling evidence of a causal link between OSAS and hypertension, we believe that it would be inappropriate to include hypertensive patients in our study since the causal pathway underlying LVH and DD from OSAS may well influence the results.

In our study, the severe OSAS patients had more hypoxic duration in their sleep compared with the moderate and mild OSAS groups. LVM and LVMI were slightly higher in severe OSAS patients, whereas they were within normal limits in mild and moderate OSAS patients. Moreover, severe OSAS patients had slight LVH. Our study did not define the mechanism underlying LVH; however, LVH could be caused by intermittent blood pressure surges, and/or nocturnal hypoxemia. Tamisier R. et al. [1, p. 1976-1978] reported echocardiographic evidence of LVH in 50% of patients with an AHI > 20 per hour compared with 21,4 % in those with an AHI < 20 per hour.

Results of our study have confirmed in some other studies. The Wisconsin Sleep Cohort Study [6, p. 1189-1192] showed a significant association with baseline AHI severity and LVH, but relationships became non-significant when BMI was added to the model. Mean SaO_2 and DI were independent predictors of LVM and LVMI in adjusted logistic regression models in this study. In our study we confirm a stronger correlation for DI than for AHI. We didn't obtain significant difference for mean SaO_2 for all participants of our study and differences were significant only for patients with severe OSAS. Furthermore, in the study of Seyed Hashem Sezavar et al. [12, p. 34-38] LV hypertrophy not only occurred more frequently in those with severe OSAS (66%), but an increase in the LVMI was strongly correlated with a rise in the DI even after adjustment for the BMI. All patients with LVH in our study have severe OSAS. But hypertension patients didn't exclude from these studies [7, p. 5-7] and that fact could influence the results.

Our subjects didn`t affect by blood pressure than those of other studies in differentiating their effects on LV geometry, which might highlight the importance of sleep-disordered breathing, particularly hypoxia expressed

by DI among the patients who are at high risk for LV remodeling. In our study, we found that OSAS and obese patients had DD, but only patients with severe OSAS and obesity had reduced ejection fraction, others had normal LVEF. In contrast, Altintas N. et al. [15, p. 385-388] suggested that OSAS may be a direct cause of daytime LV systolic dysfunction. However, several cross-sectional studies concordant with our results have demonstrated that the daytime EF was normal in patients with OSAS and did not significantly differ between patients with OSAS and control subjects. In theory, the discordance between our study and N. Altintas's study may be because of our relatively small sample size or perhaps because of a high risk of technical failure of echocardiography in patients with severe obesity. We would advocate for future studies using radionuclide angiography or cardiac magnetic resonance in a large group of OSAS patients.

LVDD is considered as a preclinical stage of heart failure, is a risk factor for the development and progression of heart failure, and significantly reduces survival even in the asymptomatic patients [13, p. 1078]. In our study, an assessment of changes in left ventricular diastolic function in patients with a comorbid OSAS and obesity, whose significance in the development of diastolic dysfunction was proven.

According to the results of the comparative analysis of the state of diastolic function in patients with OSAS without obesity and practically healthy persons with normal body weight, reliable differences are established only between IVRT and the peak E. But the absence of changes in other indicators of the functional state of the left ventricle is not a reliable criterion for DD. In the comparative analysis depending on the degree of obesity, reliable changes were made for all indicators of diastolic function in patients with 3 degree of obesity compared with the control group. In addition, 57% of patients with obesity of the 3 degree had diastolic dysfunction. In conducting the correlation analysis of indicators in this group of patients, strong connections were established between BMI and the IVRT ($r = 0,622$, $P < 0,05$). Thus, the results may indicate a deterioration of the diastolic function with an increase in obesity even in young and adolescent patients without cardiovascular disease. The number of patients diagnosed with diastolic dysfunction has increased by almost 2 times with the addition of obesity to OSAS. All patients with diagnosed diastolic dysfunction had 1 grade of dysfunction, indicating violation of left ventricular myocardial relaxation.

The mechanisms underlying diastolic dysfunction in OSAS patients are not clear; however, elevations in nocturnal blood pressure and sympathetic nervous system activity in OSAS subjects create ventricular pressure overload. It could be speculated that as it occurs in other processes, such as chronic hypertension and aortic stenosis, increased pressure overload at the cellular level would mainly result in decreased levels of sarcoplasmic reticulum calcium adenosine triphosphotase pump, and increased phospholamban. This process could slow the removal of calcium from the cytosol, which leads to impaired ventricular relaxation. However, the pressure overload causes activation of multiple cellular signals that create myocardial tissue hypertrophy and interstitial fibrosis, increasing passive stiffness. Indeed an impaired coronary flow reserve would cause silent ischemia, worsening ventricular active relaxation when left ventricular diastolic pressure begins to rise.

Another plausible mechanism to explain the presence of diastolic dysfunction is related to futile inspiratory efforts [5, p. 976-980] These efforts result in exaggerated negative intrathoracic pressure, which leads to an increase in left ventricular transmural pressure and hence after-load without increasing blood pressure. Another consequence of the increased negative intrathoracic pressure is the leftward shift related to enhanced venous return and right ventricle dilatation. All of the aforementioned effects of the enhanced negative intrathoracic pressure have been demonstrated to affect left ventricular filling [7, p. 6-7]. It is difficult to define how each of those mechanisms affects diastolic function in a single OSAS patient because of their complex interactions.

A number of studies have been conducted in which the association of diastolic dysfunction with hypoxic indicators of OSAS has been studied. The results of our study are partly consistent with the results of these studies. For example, Damy T. et al. [11, p. 103-108] had found that the presence of moderate to severe OSAS is associated with diastolic dysfunction. At the same time, the degree of deterioration of the diastolic function correlated only with the increase of the AHI, in contrast to our study, which established a correlation between IVRT, DT and DI, and between IVRT and min SaO_2. Also in the study, Damy T. et al. some patients with severe OSAS had 2 grade of diastolic dysfunction, as opposed to the results of our study, where all patients had 1 grade of diastolic dysfunction. It should be noted that the study Damy T. et al. included individuals who had risk factors

for diastolic dysfunction, namely, arterial hypertension, diabetes mellitus, dyslipidemia, which could affect the outcome of the study and determine the differences in the results of the studies.

Wang J. et al. [3, p. 93-98] analysis of changes in left ventricular diastolic function in different types of myocardial remodeling in patients with OSAS. The results of this study found that wave E was significantly lower in the group of patients with a concentric and eccentric type of left ventricular hypertrophy; E/A ratio was significantly lower in concentric remodeling of the myocardium and concentric left ventricular hypertrophy. According to the correlation and regression analysis in Wang J. et al. a close relationship was established between structural changes in the myocardium and diastolic dysfunction indices. These data partly coincide with the results of our study, in which all patients with concentric hypertrophy and remodeling of the left ventricle showed a deterioration of the diastolic function. The relationship between structural changes in the LV and diastolic function has not been proven in a regression analysis in our study. Differences can be due to inclusion in the study J. Wang et al. patients with arterial hypertension, which has a significant effect on the structural and functional changes of the LV.

Bodez D. et al. [4, p. 494-503] used the global standardized approach to assessing primary diastolic dysfunction in a cohort of patients with OSAS and demonstrated the presence of diastolic dysfunction in 37% of patients with OSAS. However, hypoxia indices at OSAS did not demonstrate sufficient predictive capacity for diastolic dysfunction of the left ventricle in a multivariate regression analysis, in contrast to our study, where DI was an independent predictor of diastolic dysfunction. In addition, AHI reliably correlated with the volume of the left atrium in a study of Bodez D. et al., as opposed to our study, where no reliable changes were found between these indices. We assume that the differences between the results of studies may be due to differences in the method of echocardiography.

Changes in cardiac hemodynamics with intermittent hypoxia and obesity have been well studied in rats. The results of these studies can be explained indirectly by the echocardiographic changes found in our study. According to Danica L. et al. [7, p. 1-7] a significant contribution to the damage to the left ventricular myocardium in the OSAS increases transmural pressure in the left atrium and the left ventricle due to fluctuations of intracranial pressure occurring during the episode apnea / hypopnea as a result of useless respiratory efforts.

When obesity, one of the leading pathogenetic factors is the increase in circulating blood volume, which affects left ventricular preload [2, p. 423-429; 17, p. 155-159]. Thus, it can be assumed that prolonged variations in pressure and volume with combined OSAS and obesity result in structural and functional changes in the ventricles of the heart, leading to deterioration of diastolic function and heart failure in these patients [3, p. 93-98]. The experimental results described explain the signs of left atrial dilatation found in our study, and the overload and degradation of left ventricular relaxation.

Changes in cardiac hemodynamics with intermittent hypoxia and obesity have been well studied in rats. The results of these studies can explain indirectly some echocardiographic changes which were found in our study. According to Danica L. et al. [7, p. 1-7] the increase of transmural pressure in the left atrium and the left ventricle due to fluctuations of intracranial pressure occurring during the episode apnea/hypopnea as a result of useless respiratory efforts have a significant contribution to the damage to the left ventricular myocardium in the OSAS [7, p. 1-7]. Obesity is one of the leading pathogenetic factors in the increase in circulating blood volume, which leads to left ventricular preload [2, p. 423-429; 17, p. 155-159]. Thus, it can be assumed that prolonged variations in pressure and volume in patients with comorbid OSAS and obesity result in structural and functional changes in the heart ventricles, leading to deterioration of diastolic function and heart failure in these patients [3, p. 93-98]. The experimental results described the signs of left atrial dilatation the overload and degradation of left ventricular relaxation which were found in our study.

But, our study has several limitations. Our study was a cross-sectional study, and included small amount of subjects, that could distort results. There were considerably fewer female patients and patients older 65 years meeting our criteria, that also could influence study`s results. We had a relatively small sample size and thus we were likely underpowered for some of our assessments particularly in subgroup analyses. We also realize that a number of covariates are present such that we are unable to distinguish the effects of severe OSAS from those of hypoxemia. Ultimately, we acknowledge that control of BMI and hypertension in future studies as well as controlled interventional studies will be required to show the isolated effect of AHI on the measured parameters and to draw rigorous conclusions. However, we believe that our data represent an important addition to the

published studies based on their novelty and the hypotheses that we have generated for subsequent research.

Prospects for further research. It is planned to study the changes of the structural and functional parameters of the heart among patients with OSAS, hypertension, diabetes, establish their prognostic role in LVH against the background of overweight and obesity.

5. Conclusions

We found that the OSAS may result in left ventricular dysfunction a strong positive correlation was observed between geometry and function of LV and severity of OSAS. Since the ventricular function provides prognostic information in patients, the results from this study should be further confirmed with several longitudinal studies.

1. OSAS and obesity are associated with high LVM, LVMI, a deterioration of the diastolic function of the LV and prevalence of concentric LV remodeling. The LVM, LVMI and level of DD were increased parallel to an increasing in the OSAS`s severity and the degree of obesity.

2. There were admitted statistically significant differences for PWT_d and IVS_d among patients with OSAS without obesity and healthy people. Concerning LVMI and LVM, no statistically significant differences were admitted.

3. Manifestations of DD were recorded in 36,9 % of patients with OSAS and obesity. All patients with established DD had 1 grade diastolic dysfunction (impaired relaxation).

4. The lowest SaO_2, DI, BMI were associated with changes of LVMI, LVM, PWT_d and IVS_d according to the results of regression analysis. A positive correlation between DT, BMI and DI, and the negative correlation with $minSaO_2$ have been established. IVRT correlated only with the DI, and the index E/A – with BMI.

5. In multivariable regression analysis, DI was a predictor of diastolic dysfunction and LVH in patients with OSAS and obesity.

The authors have no conflicts of interest to disclose.

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