UDC 616.12-008.331.1-085.82+616-092:612.284.2-085.82

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# EFFECTS OF LONG-TERM CONTINUOUS POSITIVE AIRWAY PRESSURE THERAPY (CPAP) ON EPICARDIAL FAT THICKNESS AND ARTERIAL STIFFNESS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND HYPERTENSION

## Abstract

**Background:** obstructive sleep apnea (OSA) is associated with high prevalence of hypertension, obesity, carbohydrate metabolism impairment and dyslipidemia. However, positive effects of CPAP therapy on epicardial fat thickness of the OSA patient with hypertension are poorly understood and poorly studied. **Study objective:** to investigate 12-month effects of CPAP therapy with auto-adaptation to inhalation and exhalation (A-Flex therapy) of the OSA patient with hypertension and metabolic disorders on epicardial fat thickness (EFT). **Methods:** A single-center prospective study included 310 patients aged 35 to 75 years (45.3 ± 10.4) with night snoring, metabolic disorders, obstructive sleep apnea, hypertension (273 males (88 %) and 37 females (11.9 %)), who signed an informed consent and had the apnea-hypopnea index (AHI) > 5 events/hour. The night polygraphic study (PG) was performed to calculate AHI, oxygen desaturation index (ODI), mean nocturnal saturation ($SpO_2$) by the rules of American Academy of Sleep Medicine (AASM). The calculation of the epicardial fat thickness (EFT), the size and volume of the heart cavities, left ventricular mass index (LVMI) were performed via echocardiography in 2D and M modes. Endothelial function of blood vessels determined by finger test was measured according to peripheral arterial tone (PAT). The reactive hyperemia index (RHI) and augmentation index (AI) was calculated. Optimal level of A-Flex therapy was adjusted at home. AHI, the level of air leakage, average pressure and compliance to CPAP treatment were established in accordance with international requirements. **Results:** after 3 months of A-Flex therapy we found a significant decrease of HOMA-IR –1.09 (95 % CI from –1.74 to –0.96; P=0.021), decrease AI –10.8 % (95 % CI from –13.70 to –4.6; P=0.001), decrease EFT –1.26 mm (95 % CI from –2.2 to –0.95; P=0.001) in mild OSA patients. After 6 months of A-Flex therapy we found a significant decrease of HOMA-IR –2.81 (95 % CI from –3.74 to –1.46; P=0.001), decrease AI –15.6 % (95 % CI from –17.23 to –11.75; P=0.001), decrease EFT –2.15 mm (95 % CI from –3.2 to –1.5; P=0.001) in moderate OSA patients. After 12 months of A-Flex therapy we found a significant decrease of HOMA-IR –4.22 (95 % CI from –5.36 to –2.35; P=0.001), decrease AI –21.05 % (95 % CI from –26.5 to –17.4; P=0.001), decrease EFT –4.0 mm (95 % CI from –5.8 to –2.7; P=0.001) in severe OSA patients. In addition, the data obtained are in good agreement with changes in the clinical picture of the disease: the disappearance of excessive daytime sleepiness, increased motor activity, and normalization of night sleep. **Conclusions:** The 12-month A-Flex therapy in moderate and severe OSA patients with hypertension has a significant therapeutic effect of stabilization systolic and diastolic blood pressure, level of blood lipids and epicardial fat thickness, level of endothelial dysfunction. The 12-month A-Flex therapy has to able to reduce the risks of cardiovascular events in moderate and severe OSA patients with acute metabolic manifestations.

***Key words:*** *epicardial fat thickness, obstructive sleep apnea, metabolic disorders, hypertension, arterial stiffness, CPAP therapy, A-Flex therapy*

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**For citation:** Gorbunova M. V., Babak S. L., Malyavin A. G. EFFECTS OF LONG-TERM CONTINUOUS POSITIVE AIRWAY PRESSURE THERAPY (CPAP) ON EPICARDIAL FAT THICKNESS AND ARTERIAL STIFFNESS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND HYPERTENSION. The Russian Archives of Internal Medicine. 2019; 9(1): 52-59. [In Russian]. DOI: 10.20514/2226-6704-2019-9-1-52-59

**DOI:** 10.20514/2226-6704-2019-9-1-52-59

AASM — the American Academy of Sleep Medicine, AHI — apnea/hypopnea index, LVMI — left ventricular mass index, OSA — obstructive sleep apnea, PG — polygraphic study, EFT — epicardial fat thickness, CRM — Center of Respiratory Medicine, HR — heart rate, EF — epicardial fat

## Introduction

obstructive sleep apnea (OSA) is a disease characterized by interruption of breathing (apnea) and hypoventilation events (hypopnea) during sleep, which result in intermittent hypoxia. The relationship between OSA, vascular risk factors, metabolic disorders and vascular diseases themselves was described in large prospective clinical studies [1,2].

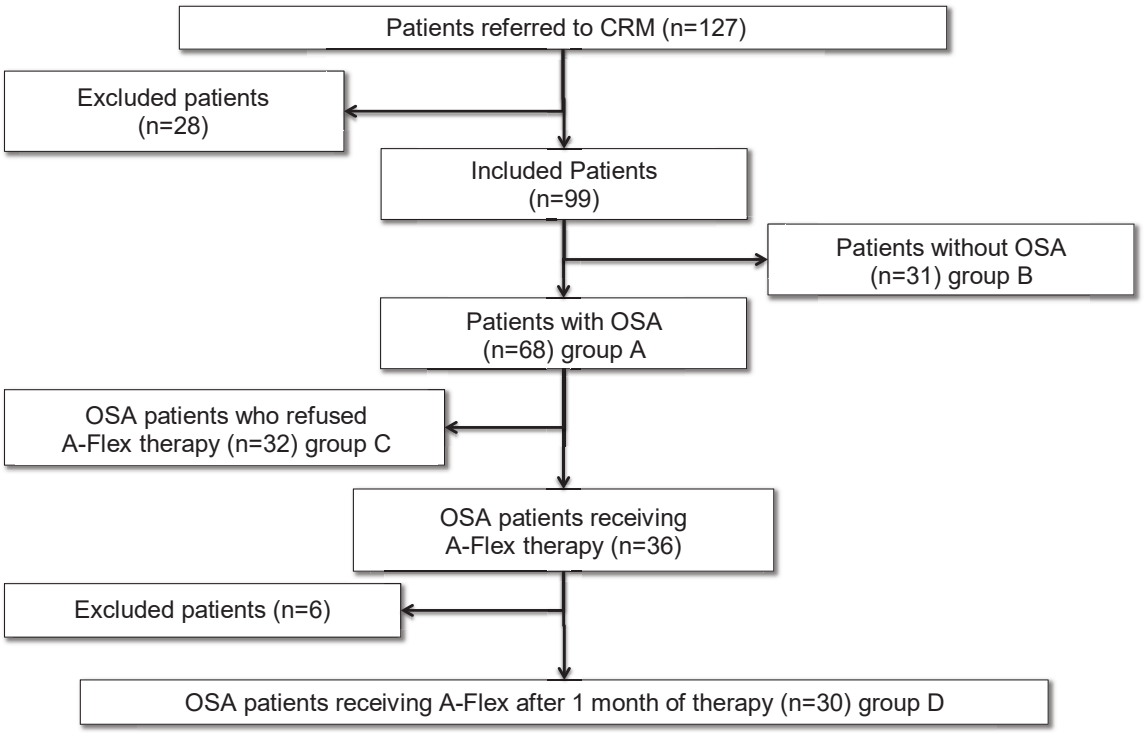
Epicardial fat (EF) is an adipose tissue layer located between the outer myocardial wall and visceral pericardium, particularly behind the right ventricle, in atrioventricular and interventricular grooves. Its weight makes up approximately 18–20 % of the weight of both ventricles; it has common blood supply with the myocardium by the branches of coronary arteries [3]. In case of metabolic disorders, excessive accumulation of EF in OSA turns it into an active endocrine organ, which has lipotoxic, prothrombotic, atherogenic effects on cardiomyocytes and coronary arteries by producing proinflammatory mediators, thus contributing to cardiovascular remodeling [4].

CPAP (Continuous Positive Airway Pressure) therapy with auto-adaptation to the patient's inhalation and exhalation (A-Flex therapy) resolves major pathophysiological effects of OSA, decreases sympathetic drive, intrathoracic negative pressure fluctuation, and reduces left ventricular afterload. In addition, CPAP therapy, possibly by resolving hypoxic events, increases oxygen delivery to tissues, reduces oxygen deficit and is capable of affecting metabolic disorders and EF accumulation in OSA patients with hypertension [5].

## Materials and methods

### *Study design*

A single-center prospective study included 310 patients aged 35 to 75 years (45.3 ± 10.4)



with night snoring, metabolic disorders, obstructive sleep apnea, hypertension (273 males (88 %) and 37 females (11.9 %)), who signed an informed consent and had the apnea-hypopnea index (AHI) > 5 events/hour. All the patients received personalized antihypertensive and lipid-lowering therapy. Depending on severity, OSA patients were divided into group A (n=51, mild OSA), group B (n=91, moderate OSA), and group C (n=168, severe OSA). All the patients received CPAP therapy (A-Flex therapy) in accordance with the American Academy of Sleep Medicine (AASM) guidelines [6] to achieve the optimal correction of OSA with AHI < 10 events/hour. Control follow-up points were follow-up months 0–3–6–12.

### *Patient population*

All the patients underwent physical and complete medical examination with an additional focus on history, symptoms and markers of sleep respiratory disorders. They were interviewed for how long they were gaining weight and when it started, number of attempts to lose weight, administration of weight management medications and/or dietary supplements, dietary habits and daily dietary calories, physical activity. The exclusion criteria were: pregnancy, lactation; type 1 and 2 diabetes mellitus; syndrome-based forms of obesity; severe somatic comorbidity (thyroid function abnormality, renal and hepatic failure, decompensated heart failure, severe hemodynamic cardiac rhythm abnormalities, previous myocardial infarction and stroke within three months before screening, systemic inflammatory disease, cancer); administration of systemic glucocorticosteroids in three months before screening; medical history of mental illness and/or that detected during clinical examination; drug and alcohol dependence; patients with pronounced airway obstruction ($FEV_1$ < 50 %), restrictive disorders (VC < 80 %), daytime arterial blood saturation $SpO_2$ < 90 % ($FiO_2$ = 21 %).

### *Ethical standards*

The study was conducted in the Department of Phthisiology and Pulmonology of the Faculty of General Medicine at State University of Medicine and Dentistry named after A. I. Evdokimov, at the Center of Respiratory Medicine (CRM) and the Hospital of the Russian Central Union of Consumer Cooperatives (39 Losinoostrovskaya Str., bldg. 2, 107150 Moscow, Russia). The study was approved by the Inter-University Ethics Committee of the State University of Medicine and Dentistry named after A. I. Evdokimov.

### *Polygraphic study (PG)*

All the patients underwent a night polygraphic study as per the standardized protocol for cardiovascular monitoring of obstructive sleep apnea in accordance with the American Academy of Sleep Medicine (AASM) regulations and recommendations [7]. SOMNOcheck micro CARDIO (Lowenstein Medical (Weinmann), Germany) with SOMNOlab 2.19 (Lowenstein Medical (Weinmann), Germany) software was used. The study was started at 11.00 p.m. and completed at 7.30 a.m., with registration of the main polygraphic respiratory parameters: 1) mouth-nose air flow and snoring; 2) breathing efforts; 3) recording of $SpO_2$ and heart rate (HR) by pulse oxymetry. The polygraphy findings were processed manually by the qualified personnel of the CRM. Apnea was identified as reduction in the air flow signal by >80 % while maintaining the breathing effort for >10 seconds. Hypopnea was identified as reduction in the air flow signal by >30 % while maintaining the breathing effort for >10 seconds and subsequent desaturation by >4 %. Severity of OSA was determined by the apnea-hypopnea index (AHI) defined as the total number of obstructive apnea and hypopnea per 1 recording hour. Occurrence of 5 < AHI < 15 events/hour was assessed as mild OSA; 15 < AHI < 30 events/hour — as moderate OSA; AHI > 30 events/hour — as severe OSA. The assessment included the nocturnal desaturation level by ODI, i. e., the number of drops of $SpO_2$ > 4 %, as well as mean and minimum nocturnal saturation ($SpO_2$), respectively.

### *Echocardiography*

To calculate epicardial fat thickness (EFT), sizes and volumes of cardiac cavities, left ventricular mass index (LVMI), systolic and diastolic functions of both ventricles, transthoracic echocardiography was performed in 2D and M modes using the Xario 200 ultrasonic scanner (Toshiba, Japan) equipped with a 3.5 MHz transducer. Doppler imaging was carried out using pulsed, continuous wave, color

and tissue Doppler modes. Epicardial fat thickness was determined perpendicularly to the right ventricular free wall in B mode from the parasternal position, along the left ventricular long axis, at end systole, on the line which is at most perpendicular to the aortic ring [8]. For verifying epicardial obesity, criteria of T. Yu. Kuznetsova et al. (2017) were applied: for individuals under 45 years of age — EFT ≥ 5.0 mm; for individuals of 45–55 years of age — EFT ≥ 6.0 mm; for individuals over 55 years of age — EFT ≥ 7.0 mm [9].

### *Endothelial function assessment*

Endothelial vascular function was assessed by the quality of peripheral arterial tone (PAT signal), as determined by the pointing test [10]. Pulse wave amplitude (PWA) was estimated before and during reactive hyperemia (RH) by peripheral arterial tonometry (Endo-PAT2000, Itamar Medical Ltd., Israel). PWA baseline data were collected using finger-ring plethysmographic cuffs to be placed on index fingers of both hands for 5 minutes. Ischemic stimulus was induced by cuff occlusion (shoulder cuff inflation up to systolic pressure of >200 mm Hg for 5 min), and RHI index was calculated as a ratio of mean PWA for a period of 1 minute after cuff deflation to the baseline pre-occlusion PWA. We estimated the augmentation index (AI) defined as a ratio of the shock wave arising from the increase of aortic pressure to the systolic reflected wave [11]. All tests of RHI and AI were performed under standardized conditions (time, room, temperature).

### *Statistical analysis*

The data was analyzed using statistical software, version 6.0 (AnalystSoft Inc., StatPlus). Quantitative data was expressed as mean (M) and standard deviation (SD) (M±SD). Differences between the groups were analyzed using ANOVA for continuous variables. The linear relationship between the variables was measured using the Pearson correlation test. During the final assessment of the findings, we performed the intention-to-treat analysis (ITT analysis). The role of gender, age, BMI, fat distribution, EFT, serum glucose and lipids as AHI-associated variables was tested by the linear regression method using multidimensional models. Chi-squared test ($\chi 2$) was used to compare frequencies in independent samples. Differences in the tested parameters were considered significant at $p < 0.05$. When $0.05 < p < 0.1$, the existence of a statistical trend was estimated.

## Results

Baseline characteristics of the patients are provided in Table 1.

Of the 310 enrolled patients, a total of 294 (94.8 %) patients made every visit and were included in the standardized analysis. Sixteen patients (5.16 %) made only one follow-up visit and were estimated cumulatively only in the ITT analysis. Patients with severe OSA had statistically ($p < 0.05$) high BMI, pronounced nocturnal hypoxemia and metabolic disorders. Hypertension, arterial stiffness, and epicardial fat thickness (EFT) in group B were also statistically higher than in patients with mild and moderate OSA. The average compliance to A-Flex therapy was 5.3 ± 1.6 h/night (high compliance), which allowed full control over sleep apnea events of <10 events/hour and eliminated all risk of potential fatal and non-fatal cardiovascular events.

### *Assessing lipid profile, arterial stiffness, epicardial fat thickness in intention-to-treat (ITT) analyses*

We performed the intention-to-treat analysis (ITT analysis) of the lipid profile parameters (HOMA-IR, cholesterol, LDL cholesterol, triglycerides), arterial stiffness (AI, RHI)), epicardial fat thickness (EFT) among the patients who successfully completed the study and discontinued the therapy ahead of schedule by month 12, as adjusted for age, gender, BMI, presence of cardiovascular diseases and administration of antihypertensive therapy in mild, moderate and severe OSA groups (Tables 2, 3, 4).

In the patients with mild OSA (group A), significant changes in the lipid profile, arterial stiffness, epicardial fat thickness occurred as early as on month 3 of CPAP therapy: HOMA-IR decreased by –1.09 (95 % CI: –1.74 to –0.96; P=0.021), AI decreased by –10.8 % (95 % CI: –13.70 to –4.6; P=0.001), EFT decreased by –1.26 mm (95 % CI: –2.2 to –0.95; P=0.001), and reached the maximum normal by month 12: HOMA-IR decreased by –1.77 (95 % CI: –3.74 to –0.73; P=0.024), AI decreased by –15.1 % (95 % CI: –18.90 to –9.2; P=0.031), EFT decreased by –1.62 mm (95 % CI: –2.5 to –0.97; P=0.001).

***Table 1.*** *Basic characteristics of the studied patients*

| Analyzed parameter | Group A (n=51) | Group B (n=91) | Group C (n=168) |
|---|---|---|---|
| Age (years) | 40.60 ± 5.07 | 44.60 ± 8.30 * | 46.40 ± 9.03 ** |
| Gender (m/f) | 48/3 | 86/5 | 139/29 |
| Body mass index (BMI) (kg/m$^2$) | 32.30 ± 2.30 | 35.80 ± 2.20 * | 37.40 ± 3.60 ** |
| Neck circumference (cm) | 41.30 ± 3.50 | 43.10 ± 3.7 | 44.30 ± 3.8 * |
| Waist circumference (cm): | | | |
| Men | 112.30 ± 8.10 | 118.20 ± 8.60 | 121.40 ± 9.20 * |
| Women | 105.50 ± 10.10 | 108.10 ± 11.20 | 110.3 ± 11.60 * |
| Smokers (n, (%)) | 5 (9.8) | 11 (12.0) | 18 (10.7) |
| Former smokers (n, (%)) | 39 (76.4) | 70 (76.9) | 125 (74.4) |
| Non smokers (n, (%)) | 7 (13.7) | 10 (10.9) | 25 (14.8) |
| **Polygraphic characteristics** | | | |
| Apnea-hypopnea index (AHI) (events/hour) | 9.8 ± 3.90 | 23.4 ± 5.80 ** | 49.8 ± 6.90 ** |
| Oxygen desaturation index (ODI) (events/hour) | 8.7 ± 2.90 | 21.2 ± 4.60 ** | 46.5 ± 4.70 ** |
| Saturation time less than 90 % (TSat_90) (% from total sleep time) | 7.5 ± 1.90 | 16.2 ± 3.20 ** | 27.8 ± 3.40 ** |
| Mean night saturation (Sat mean) (%) | 91.0 ± 1.70 | 86.0 ± 1.90 * | 83.1 ± 2.30 ** |
| Minimum night saturation (Sat min) (%) | 89.0 ± 1.90 | 80.4 ± 3.20 ** | 70.5 ± 4.20 ** |
| Minimum nighttime heart rate (beats/min) | 52.3 ± 3.80 | 49.6 ± 5.20 | 43.1 ± 4.10 ** |
| Maximum nighttime heart rate (beats/min) | 96.2 ± 5.60 | 104.2 ± 6.40 * | 113.2 ± 7.30 ** |
| **Hypertension, arterial stiffness, epicardial fat thickness** | | | |
| Duration of hypertension, years | 7.90 ± 3.80 | 8.20 ± 4.10 | 9.50 ± 2.90 * |
| Systolic BP "office", mm Hg | 146.90 ± 15.60 | 152.30 ± 15.90 | 163.20 ± 17.3 * |
| Diastolic BP "office", mm Hg | 93.40 ± 6.80 | 94.40 ± 6.50 | 99.50 ± 7.1 * |
| Reactive hyperemia index / RHI (reference <1.67) | 1.98 ± 0.21 | 2.11± 0.32 * | 3.30 ± 0.71 ** |
| Augmentation index / AI (%) (reference 18.43–39.97 %) | 39.90 ± 3.9 | 43.80 ± 4.10 | 48.20 ± 4.6 ** |
| Epicardial fat thickness (mm) | 5.10 ± 0.87 | 6.39 ± 0.85 * | 7.98 ± 1.57 ** |
| **Biochemical indicators** | | | |
| Blood glucose on an empty stomach, mmol/l | 5.80 ± 0.50 | 6.10 ± 0.30 | 6.40 ± 0.40 * |
| Glycosylated hemoglobin (HbA1C), % | 5.50 ± 0.50 | 5.70 ± 0.30 | 6.00 ± 0.40 ** |
| HOMA-IR | 4.25 ± 1.72 | 5.53 ± 2.09 * | 6.86 ± 2.14 ** |
| Total cholesterol (mmol/l) | 4.32 ± 0.79 | 4.61 ± 0.81 | 5.21 ± 0.56 * |
| Cholesterol-HDL (mmol/l) | 0.99 ± 0.19 | 0.95 ± 0.15 | 1.09 ± 0.13 |
| Cholesterol-LDL (mmol/l) | 2.20 ± 0.80 | 2.70 ± 0.60 | 2.90 ± 0.40 * |
| Triglycerides (mmol/l) | 1.77 ± 0.61 | 2.11 ± 0.53 | 3.76 ± 0.72 * |

**Note:** * p < 0.05 compared with group A; ** p < 0.01 compared with group A

In the patients with moderate OSA (group B), significant changes in the lipid profile, arterial stiffness, epicardial fat thickness occurred on month 6 of CPAP therapy: HOMA-IR decreased by –2.81 (95 % CI: –3.74 to –1.46; P=0.001), AI decreased by –15.6 % (95 % CI: –17.23 to –11.75; P=0.001), EFT decreased by –2.15 mm (95 % CI: –3.2 to –1.5; P=0.001), and reached the maximum normal by month 12: HOMA-IR decreased by –2.96 (95 % CI: –3.78 to –1.43; P=0.002), AI decreased by –16.0 % (95 % CI: –19.7 to –7.6; P=0.001), EFT decreased by –2.77 mm (95 % CI: –3.6 to –1.5; P=0.001).

In the patients with severe OSA (group C), initial changes in the lipid profile, arterial stiffness, epicardial fat thickness occurred on month 6 of CPAP therapy: HOMA-IR decreased by –3.10 (95 % CI: –5.74 to –2.46; P=0.002), AI decreased by –5.4 % (95 % CI: –7.11 to –3.31; P=0.003), EFT decreased by –4,22 mm (95 % CI: –5.57 to –2.35; P=0.001),

***Table 2.*** *Dynamics of indicators of the group A (n=51)*

| Parsed parameter | 3rd month CPAP | 6th month CPAP | 12th month CPAP |
|---|---|---|---|
| Reactive hyperemia index / RHI | 1.54 ± 0.11* | 1.48 ± 0.27 | 1.42 ± 0.28 |
| Augmentation index / AI (%) | 29.10 ± 4.20* | 25.20 ± 5.40 # | 24.80 ± 9.60 |
| Epicardial fat thickness (mm) | 3.84 ± 0.72* | 3.53 ± 0.88 # | 3.48 ± 0.93 ## |
| HOMA-IR | 3.16 ± 0.23* | 2.64 ± 0.67 # | 2.48 ± 0.98 ## |
| Total cholesterol (mmol/l) | 4.32 ± 0.62 | 4.23 ± 0.68 # | 4.15 ± 0.72 ## |
| Cholesterol-LDL (mmol/l) | 2.21 ± 0.71 | 2.07 ± 0.86 # | 1.95 ± 0.93 ## |
| Triglycerides (mmol/l) | 1.53 ± 0.39 * | 1.52 ± 0.88 | 1.51 ± 0.87 ## |

**Note:** * ρ < 0.05 compared to baseline; # ρ < 0.05 compared with the 3rd month; ## ρ < 0.05 compared with the 6th month

***Table 3.*** *Dynamics of indicators of the group B (n=91)*

| Parsed parameter | 3rd month CPAP | 6th month CPAP | 12th month CPAP |
|---|---|---|---|
| Reactive hyperemia index / RHI | 2.02 ± 0.82 | 1.56 ± 0.52 # | 1.54 ± 0.82 |
| Augmentation index / AI (%) | 38.50 ± 6.20 | 28.20 ± 5.80 # | 27.8 ± 6.8 |
| Epicardial fat thickness (mm) | 5.85 ± 0.59 * | 4.24 ± 0.67 # | 3.62 ± 0.89 ## |
| HOMA-IR | 4.36 ± 2.09 * | 2.72 ± 1.82 # | 2.57 ± 1.83 ## |
| Total cholesterol (mmol/l) | 4.52 ± 0.87 | 4.48 ± 0.91 # | 4.45 ± 0.95 ## |
| Cholesterol-LDL (mmol/l) | 2.62 ± 0.80 | 2.41 ± 0.96 # | 2.24 ± 0.93 ## |
| Triglycerides (mmol/l) | 1.87 ± 0.93 * | 1.77 ± 0.53 # | 1.69 ± 0.98 ## |

**Note:** * ρ < 0.05 compared to baseline; # ρ < 0.05 compared with the 3rd month; ## ρ < 0.05 compared with the 6th month

***Table 4.*** *Dynamics of indicators of the group C (n=168)*

| Parsed parameter | 3rd month CPAP | 6th month CPAP | 12th month CPAP |
|---|---|---|---|
| Reactive hyperemia index / RHI | 3.10 ± 0.85 | 3.00 ± 1.05 | 1.65 ± 0.46 ## |
| Augmentation index / AI (%) | 45.20 ± 5.60 | 42.80 ± 6.02 | 27.15 ± 8.56 ## |
| Epicardial fat thickness (mm) | 7.12 ± 1.38 | 6.75 ± 1.29 # | 3.98 ± 0.83 ## |
| HOMA-IR | 5.92 ± 2.21 * | 3.76 ± 2.18 # | 2.64 ± 0.93 ## |
| Total cholesterol (mmol/l) | 5.15 ± 1.06 | 4.91 ± 1.02 # | 4.70 ± 1.09 ## |
| Cholesterol-LDL (mmol/l) | 2.80 ± 1.12 | 2.61 ± 1.18 # | 2.42 ± 1.13 ## |
| Triglycerides (mmol/l) | 2.12 ± 0.92 * | 1.84 ± 0.82 # | 1.72 ± 0.67 ## |

**Note:** * ρ < 0.05 compared to baseline; # ρ < 0.05 compared with the 3rd month; ## ρ < 0.05 compared with the 6th month

and reached the significant normal only on month 12: HOMA-IR decreased by –4.22 (95 % CI: –5.36 to –2.35; P=0.001), AI decreased by –21.05 % (95 % CI: –26.5 to –17.4; P=0.001), EFT decreased by –4.0 mm (95 % CI: –5.8 to –2.7; P=0.001).

## Discussion

obstructive sleep apnea combined with hypertension and changes in the lipid profile, arterial stiffness, and epicardial fat thickness is a comorbidity, which dramatically increases risks of cardiovascular disorders, particularly in synergism of action. CPAP therapy is a first-line therapy, especially in moderate and severe OSA. We specifically selected patients with moderate and severe OSA who had metabolic disorders, hypertension and visceral adiposity. We focused our attention on them, since such patients were at the highest risk of fatal outcome or cardiovascular complications and often identified as patients with "refractory hypertension and obesity" which do not respond to medication therapy. To avoid possible distortion of the results, we tested only patients with OSA who received neither therapy of any metabolic syndrome components nor CPAP therapy. The important factor was

multi-agent medication therapy of hypertension prescribed to the patients earlier.

Despite the simple design, no blinding, placebo control and randomization of patients, we achieved the minimum effect on the end result through correct formation of the study and control groups and use of the intention-to-treat analysis (ITT analysis). Our findings are fully consistent with a number of studies concerning CPAP therapy impact on normalizing the lipid profile, arterial stiffness, epicardial fat thickness in patients with OSA combined with hypertension [12–14]. The mechanism for normalizing the lipid profile, arterial stiffness, epicardial fat thickness in patients with OSA combined with hypertension is most likely related to resolving fragmented sleep, nocturnal hypoxemia, resultant sympathetic activity [15–18]. This hypothesis is supported by our study as well, when administration of A-Flex therapy for 12 months significantly reduced the epicardial fat thickness (EFT) and arterial stiffness (augmentation index (AI)) to the target ranges, even in the patients with severe OSA (Fig. 1, Fig. 2).

In conclusion, only 12-month long-term CPAP therapy as per A-Flex regimen in the group of patients with moderate and severe OSA who had resistant hypertension and metabolic disorders has shown a significant therapeutic effect on restoring the normal arterial stiffness and epicardial fat thickness and is likely to reduce risks of cardiovascular events.

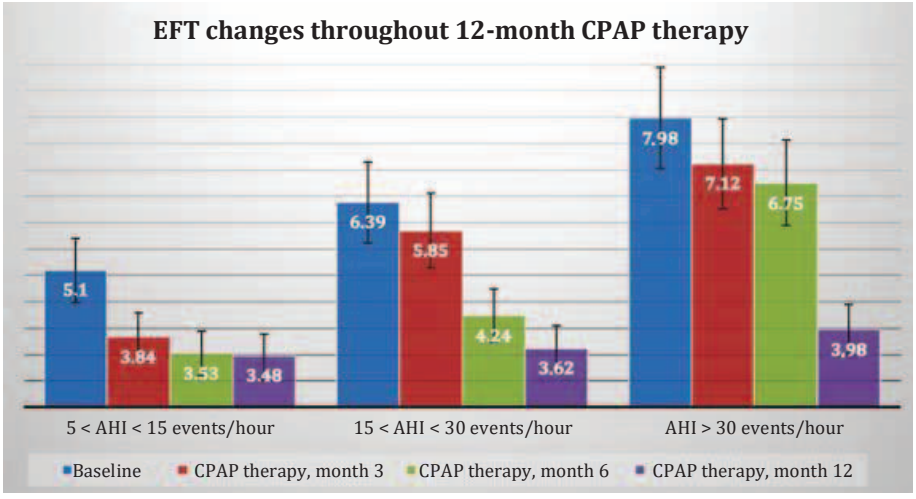



***Figure 1.*** *Diagram of changes in epicardial fat thickness in patients with OSA combined with hypertension of varying severity during CPAP therapy*

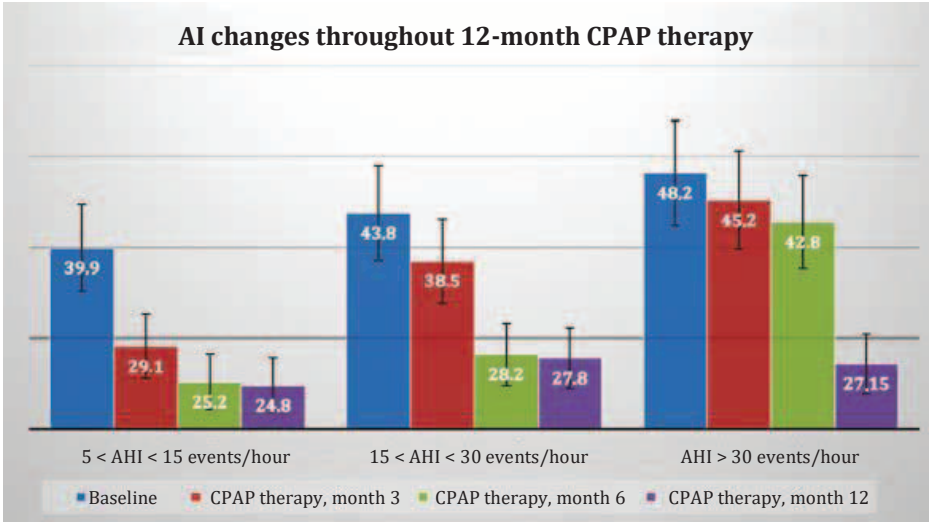



***Figure 2.*** *Diagram of changes in the AI in patients with OSA combined with hypertension of varying severity during CPAP therapy*

**Conflict of interests**
The authors declare no conflict of interests.

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Article received on 25.01.2019
Accepted for publication on 31.01.2019