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# ATRIAL FIBRILLATION COMBINED WITH ARTERIAL HYPERTENSION AND OBESITY PARADOX

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**SUMMARY**

**Purpose.** To study the peculiarities of the clinical course of atrial fibrillation in patients with arterial hypertension and obesity.

**Materials and methods.** 127 patients were observed within the observational cohort studies. Of these, 64 patients with atrial fibrillation, arterial hypertension and obesity in the control group, while the experimental group consisted of 63 patients with atrial fibrillation, arterial hypertension and normal BMI (24.1±2.2) kg/m$^2$. During our work we assessed clinical, anthropometric and laboratory indicators, as well as the results of instrumental examination: ElectroCG; Daily monitoring of ECG, EchoCG. Comparison of binary and categorical indicators was carried out upon an accurate bilateral F test. Statistical hypothesis testing was carried out at critical significance value p=0.05, i.e. the difference was considered statistically significant if p<0.05.

**Results.** Body mass index (BMI) in patients with atrial fibrillation, hypertension and obesity amounted to 35.2±4.6 kg/m$^2$. The average age in all clinical groups was 60.5±9.2 years old, and patients with obesity were significantly younger (p<0.05) – 53.3±6.1 years old than patients with normal BMI – who were 59.8±7.4 years old. Patients with hypertension, atrial fibrillation and obesity often had a persistent form of AF 71%. General assessment of the lipid profile indicated that only patients with obesity and hypothyroidism showed a significantly high level of triglycerides. (p<0.001). There was an increase in NT-proBNP (p=0.001) and galectin-3 (p=0.005). There was a consistent increase of the end-diastolic dimension of the left ventricle in the left atrium; thickening of the left ventricular posterior and the interventricular septum in compared groups proved equivocal, while the LVMMI (p<0.05) was significantly lower in patients with obesity than in the experimental group.

**Conclusion.** The presence of obesity in patients with atrial fibrillation and arterial hypertension adversely affects certain biochemical and ultrasound parameters, however, many of the criteria characterizing cardiovascular risk and prognosis did not reveal significant differences, which requires further in–depth study of this problem and identification of a possible "obesity paradox" in the group of patients with atrial fibrillation, arterial hypertension and obesity.

**Keywords:** *progressing, atrial fibrillation, arterial hypertension, obesity*

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## INTRODUCTION

Obesity along with arterial hypertension (AH) are cardiovascular risk factors the importance of which increases with the presence of cardiac arrhythmias, – atrial fibrillation (AF), in particular [1]. At the same time, available information on the "obesity paradox" suggests its ambiguous effect on the prognosis for cardiac patients and causes interest in studying the obesity factor in people with hypertension and AF. [2]. Obesity is an assumed risk factor for atrial fibrillation (AF) and an independent predictor of the AF progression, that is, the transition from a paroxysmal to a permanent form. It should be noted that the results of some studies prove that overweight and obesity may be associated with a favorable prognosis for cardiovascular diseases. (the so-called "obesity paradox") [3]. To assess the interrelation between adipose tissue parameters and clinical outcomes in patients with AF taking apixaban or warfarin, the results of a randomized ARISTOTLE test were analyzed, which showed that an increase in body mass index or waist circumference is associated with a better prognosis in patients with atrial fibrillation, which confirms – the "obesity paradox" [4].

Multivariant analysis showed that an increase in body mass index (BMI) is associated with a lower death risk. Risk of stroke/embolism was not associated with the BMI, according to the multivariate analysis. (P=0.20). The obese patient's cardiovascular continuum begins as soon as other RFs accelerating this patient's "progress" towards the development of a serious cardiovascular pathology add up to obesity. It is known that atherogenic dyslipidemia in individuals with excess body weight develops 1.5 times more often than in individuals with normal body weight. The increase of body weight by every 10% causes an increase in the level of total cholesterol in the blood plasma by 0.3 mmol/l, which within 5 years increases the risk of developing CVD by 10%. Obesity causes noticeable structural and functional changes in lipoprotein particles. [5].

Hypertension in case of obesity occurs 2.9 times more often [6]. For 80% of men and 61% of women included in the Framingham study, the increase in body weight was namely the cause provoking the development of hypertension. An increase in body weight by 5% over 4 years increased the likelihood of developing hypertension by 30% [7]. The development of hypertension in patients with obesity is directly related to hypervolemia, sodium retention, increased peripheral vascular resistance, hyperactivity of the sympathetic nervous system and the renin-aldosterone-angiotensive system, hyperproduction of leptin and hyperinsulinemia leading to RI. Recently, it has been proven that obesity-caused hypertension goes alongside with an increased level of aldosterone. With obesity, all conditions for the development of endothelial dysfunction are there, which disrupts the balance between the known vasodilator nitric oxide and the powerful vasoconstrictor endothelin-1 [8]. Potentiation of negative effects caused by obesity and hypertension significantly disrupts the structure and function of the heart: the level of pre– and post–stress on the heart increases, especially in individuals with pronounced and lengthy (>15 years) obesity experience; the risk of developing a mixed form of left ventricular hypertrophy (LVH) grows [9]. The increase in body weight is associated with an increase in circulating blood volume and an increase in LV preload. In addition, there is an increase in pressure induced load on the heart. Cardiac output increases in proportion to the increase in body weight. Due to such changes in hemodynamics, myocardial mass growth can be expected. The likelihood of developing LVH increases from 5.5% in people with normal body weight to 29.9% in people with obesity. Hypertension that develops alongside with obesity increases the risk of LVH more than 4 times [10].

Hazard caused by LVH development. Nowadays, LVH is considered to be one of the factors increasing cardiovascular risk, leading to the development of such dangerous heart disorders as chronic heart failure (CHF), cardiac arrhythmia and sudden cardiac death. According to the Cornell and Framingham studies, the risk of CVD in patients with LVH increased by 2–4 times, regardless of age, gender and other RF [11]. Five-year mortality for hypertension patients, combined with LVH, was 35% for men, 20% for women, 50% for the elderly [12]. Any patient suffering from excessive body weight or obesity requires compulsory assessment of the cardiovascular risk (SSR) level in order to develop a treatment strategy for him/her. Taking into account the expansion of our understanding regarding the pathogenesis of obesity and its contribution to the development of CVD, we should assess not only well-known indicators (for example, cholesterol level, blood pressure, smoking, gender), but also the new markers [13]. Changes in the hyperdynamic type of circulation and diastolic dysfunction of the heart, characteristic of obesity, can trigger pathophysiological mechanisms leading to atrial dilatation and, therefore, to the development of AF [14]. The presence of concentric left ventricular hypertrophy (LVH) in obese patients is frequently accompanied by development of ventricular ectopic rhythms [15].

**Purpose.** To study the peculiarities of the clinical course of atrial fibrillation in patients with arterial hypertension and abdominal obesity.

## MATERIALS AND METHODS

127 patients were observed within the observational cohort studies. Of these, 64 patients with atrial fibrillation, arterial hypertension and abdominal obesity, which includes: diabetes mellitus – for 26.7%, hypothyroidism – in 13.3%, COPD – in 4.4% of patients; the experimental group consisted of 63 patients with AF and hypertension with normal BMI (24.1±2.2) kg/m$^2$ and similar frequency of comorbid conditions (diabetes mellitus – in 21.1%, hypothyroidism – 4.6%, COPD – 11.6%) with AF, hypertension and obesity, which was confirmed by BMI >30 kg/m$^2$ and waist circumference/hip width ratio >0.9 (male) >0.85 (female) (Clinical recommendations "Diagnosis, treatment, prevention of obesity and associated diseases," St. Petersburg, 2017). AH of stage 1–3 was diagnosed for 91.1% (Clinical recommendations by the American College of Cardiology (ACC)/American Heart Association (AHA) 2017), diabetes mellitus – in 26.7% (Clinical recommendations "Algorithms of specialized medical care for patients with diabetes mellitus," Moscow, 2017), hypothyroidism – in 13.3% (Clinical recommendations on subclinical hypothyroidism by the European thyroid association, ETA, 2013), COPD – in 4.4% of those examined (Clinical recommendations "Diagnosis and treatment of patients with chronic obstructive pulmonary disease and arterial hypertension," Russian Scientific Medical Association of Therapists (RHMOT), 2017). The experimental group consisted of 63 patients with AF and normal BMI (24.1±2.2) kg/m$^2$ and a similar frequency of comorbid conditions (AH – 83%, diabetes mellitus – in 21.1%, hypothyroidism – 4.6%, COPD – 11.6%). The patients did not much differ in the nature of prescribed therapy, the main components of which were β – adrenoblockers, RAAS blockers, amiodarone. The exclusion criteria were CHD (ischemic heart disease), CKD (chronic kidney disease), liver pathology with impaired function, strokes. During our work we assessed clinical, anthropometric and laboratory indicators, as well as the results of instrumental examination: ElectroCG; Daily monitoring of ECG, EchoCG – Daily monitoring SCHILLER systems (Schiller, Switzerland), EchoCG: transthoracic EchoCG protocol was compiled in accordance with the recommendations of the American Association of Echocardiography (ASE) in M and 2D modes on the Vivid 7 device (General Electric, USA). NT-proBNP using the NTproBNP-EIA-Best reagent kit and galectin-3 EIA method – Bender MedSystems GmbH, (Austria). Statistical analysis: the numerical data were checked for consistency with the normal distribution law by applying the Shapiro-Wilk test. To compare continuous data, the Mann – Whitney U-test was used. Comparison of binary and categorical indicators was carried out upon an accurate bilateral F test. Statistical hypothesis testing was carried out at critical significance value p=0.05, i.e. the difference was considered statistically significant if p<0.05.

## RESULTS

Body mass index (BMI) in patients with AF, hypertension and obesity amounted to 35.2±4.6 kg/m$^2$. The average age in all clinical groups was 60.5±9.2, and patients with abdominal obesity were significantly younger (p<0.05) – 53.3±6.1 than patients with normal BMI – who were 59.8±7.4 years old. Patients with hypertension, atrial fibrillation and obesity often had a persistent form of AF 71%.

General assessment of the lipid profile indicated that only patients with obesity and hypothyroidism showed a significantly high level of triglycerides 4.46 mmol/l [2.41; 5.82], compared to the group without obesity (p <0.001), respectively. The content of brain natriuretic peptide was also studied (NT-proBNP) as well as galectin-3 as markers reflecting the processes of myocardial remodeling and fibrosis in patients with atrial fibrillation combined with arterial hypertension. The NT-proBNP average level for the group with AO 123.8 pg/ml [42.92; 157.02], p<0.001, compared with the group without obesity 67.99 pg/ml [33.5; 115.2]. Despite the fact that all average values fit into the recommended reference interval, the highest values of this indicator are still found in patients with obesity and in 15.9% of them it exceeded reference values (125 pg/ml). The level of galectin-3 in blood serum in patients with hypertension combined with AF and obesity was higher than in patients without obesity. Although it should be noted that in patients with a combination of obesity, this parameter was significantly higher than in those without AO. Thus in the group with AF, AH and obesity, the content of galectin-3 was 29.44 ng/ml [12.7; 97.73], and in the group with FP, AH but without obesity it amounted to 17.8 ng/ml [11.32; 51] (p=0.005). And speaking about the distribution of comorbidity (diabetes mellitus, GP, COPD), the values of this indicator against the reference values are increased in all groups (12 ng/ml) (Fig. 1).

The obtained data confirm the possible role of galectin-3 as a biological marker of myocardial fibrosis and remodeling in patients with AF with the presence of hypertension and obesity.

Attention is drawn to the increased values of the end-systolic and end-diastolic dimensions of the left ventricle, which in patients with obesity were 35.0±0.6 and 58.1±0.5 mm which was statistically insignificant compared to non-obese patients that showed 33.2±0.4 and 59.3±0.2 mm, respectively. The size of the left atrium in patients with obesity amounted to 42.6±0.41 mm, higher than the corresponding value in individuals without obesity 42.0±0.37 mm, however, no statistical significance was found therein. At the same time, the values of the aortic root diameter did not differ much and were 36.1±0.7 mm in patients with obesity, and 35.7±0.3 mm in patients without obesity.

Comparing the thickness of the cardiac chamber walls showed a regular increase in all patients. Thus, the LV posterior wall thickness in patients with obesity was 11.0±0.2 mm, while in patients without obesity it amounted to 11.1±0.1 mm (p<0.632), and the thickness of the interventricular septum in the group with obesity was 11.9±0.1, which is comparable to the group without obesity with 11.8±0.1 mm (p=0.068); no significant difference detected (Tab. 1).

## DISCUSSION

It is known that overweight can have negative health effects. However, the results obtained in new studies show that overweight sometimes has protective properties, in particular: it reduces mortality from cardiovascular causes [16]. Reports based on the administrative database of Denmark (more than 35 thousand patients) have been published, they are devoted to assessing the course and long-term survival for patients with different BMI hospitalized with the first ischemic stroke. In a multivariate analysis, it was discovered that mortality after 2.8 years (on average) was lower among overweight and obese patients, but significantly higher among patients with low BMI, compared to patients with normal BMI. Overweight and obesity were associated with a lower likelihood of repeated stroke in comparison with normal BMI [17]. Another study showed that excess BMI is accompanied by a lower risk of hemorrhagic transformation of ischemic stroke compared to patients with a normal BMI (taking into account demographic and clinical factors and therapy peculiarities) [18]. Referring to the results of both studies, Dr. Kamyar Kalantar-Zadeh [19] notes: the obtained epidemiological data leave no doubt that in some populations a high BMI is associated with an increased development of the metabolic syndrome and a reduced risk of adverse outcomes of cardiovascular diseases, as well as an increase in overall survival, and adds that the findings gained in these studies should not be used to "undermine the feasibility of modern anti-obesity programs conducted on a global scale."

In the present study the evaluation of risk indicators for adverse outcomes of cardiovascular diseases did not reveal a statistically significant difference in patients with AF, AH, and obesity compared to the experimental group, although there are differences in both biochemical and ultrasound indicators. Thus, comparing these two groups, a consistent increase in the left atrium is observed: 42.6±0.41 / 42.0±0.37; increase in the LV end–diastolic dimension: 58.1±0.51 / 59.3±0.22; thickening of the LV posterior wall: 11.0+0.2 / 11.1±0.1 and LV Interventricular septum: 11.9±0.2/11.8±0.1. A decrease of LVMI in patients with obesity may be associated with metabolic processes that can slow down compensatory muscle myocardial hypertrophy.

In this study the role of galectin-3 and NTproBNP, one of the main markers of cardiovascular fibrosis, has been investigated in greater detail. By way of experimenting it was previously determined that galectin-3 promotes the production of active substances, which, in turn, increases collagen synthesis by fibroblasts and leads to the development of myocardial fibrosis [19].

As a result of the analyzing the obtained data, we found out that in patients with obesity combined with AF and AH, the level

**Table 1. Comparative Evaluation of Echocardiography Indicators**

| Indicators | With obesity (n=64) | Without obesity (n=63 | P |
|---|---|---|---|
| Aortic Root diameter, mm | 36.1+0.7 (33.0; 36.5) | 33.4±0.32 (33.0; 36.0) | 0.0424 |
| Left atrium, mm | 42.6±0.41 (38.0; 44.0) | 42.0±0.37(38.0; 42.3) | 0.0624 |
| End-systolic dimension, LA, mm | 35.0±0.62 (32.0; 37.2) | 33.2±0.41 (31.0; 35.0) | 0.0642 |
| End-diastolic dimension, LA, mm | 58.1±0.51 (51.0; 55.0) | 59.3±0.22 (48.0; 52.0) | 0.0650 |
| EF, % | 62.0±0.6 (57.0; 65.0) | 62.9±0.5 (58.0; 66.0) | 0.0876 |
| SF, % | 32.4±0.4 (29.0; 35.0) | 33.7±0.4 (31.0; 34.0) | 0.068 |
| Left ventricular posterior wall, mm | 11.0+0.2 (11.0; 13.0) | 11.1±0.1 (10.0; 11.0) | 0.632 |
| Interventricular septum, mm | 11.9±0.1 (11.7; 13.0) | 11.8±0.1 (10.0; 11.0) | 0.068 |
| LVMMI, g/m$^2$ | 145.6±3.5*(114.7; 148.1) | 193.8±0.8 (110.1; 121.0) | 0.054 |
| SV, % | 80.5±0.3 (69.1; 84.9) | 79.8±0.8 (68.0; 85.0) | 0.3405 |

*Note: * – the differences are significant (at p<0.05) when compared to the corresponding values in the group without LVH according to the Mann-Whitney U-test.*

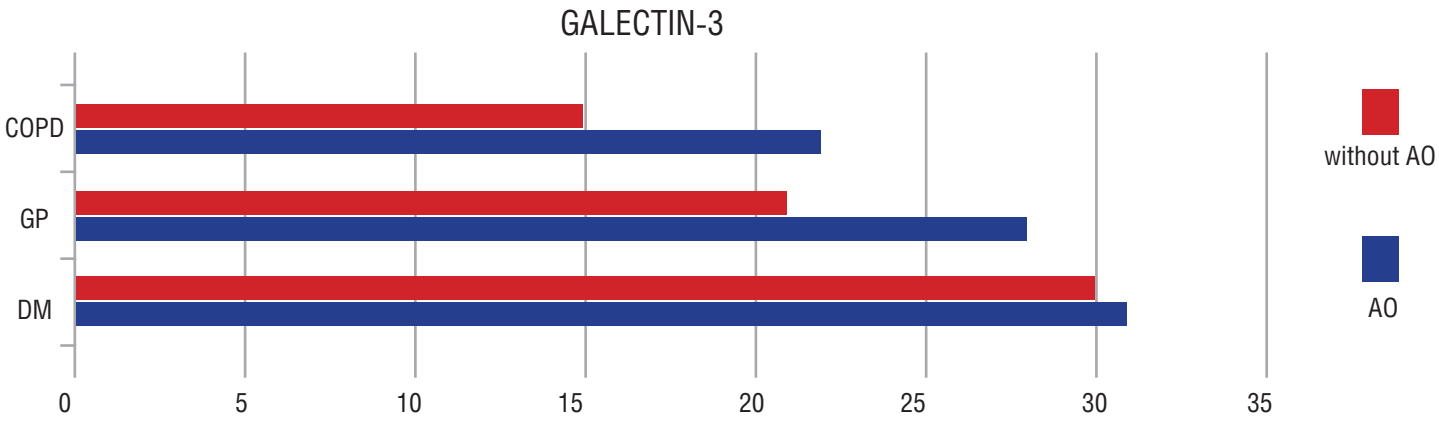


**Figure 1. The level of galectin-3 in various clinical groups**

of galectin-3 is higher than in patients with AF and AH, without obesity. We believe that galectin-3 plays a significant role in the formation of cardiac remodeling at the molecular-cellular level, provoking development of atrial myocardial fibrosis.

It should be stressed that in this study fibrosis markers (NTproBNP, galectin-3) were higher in patients with hypertension, AF and obesity than in patients with AF and hypertension without obesity. The data obtained suggest that high levels of NTproBNP and galectin-3 closely interacting with it are not only markers of myocardial fibrosis, but may also be predictors of the onset and progression of AF in patients with AO. Defining the levels of fibrosis markers in clinical practice can be used to clarify the risk of developing for this arrhythmia syndrome in patients with AO and as a potential target for pharmacological therapy.

For patients with atrial fibrillation on the background of arterial hypertension and obesity, early diagnosis and correction of arterial hypertension, AF and obesity is necessary in order to prevent progressive myocardial damage.

## CONCLUSION

The presence of obesity in patients with atrial fibrillation and arterial hypertension adversely affects individual biochemical and ultrasound indicators, however, many of the criteria that characterize cardiovascular risk and prognosis did not reveal any significant differences, which requires further in-depth study of this problem and identification of a possible "obesity paradox" for the group of patients with AF, hypertension and abdominal obesity.

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