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Biomarkers of inflammation, parameters characterizing obesity and cardiac remodeling in patients with atrial fibrillation and metabolic syndrome

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Aim. To determine the blood level of inflammatory markers, parameters characterizing obesity and cardiac remodeling in patients with atrial fibrillation (AF) in combination with metabolic syndrome (MS).

Materials and methods. This single-stage case-control study included 677 subjects aged 35 to 65 years: patients with MS (n=407), of which 128 patients with AF; comparison group — patients with AF without MS (n=75); control group — practically healthy subjects without cardiovascular diseases and metabolic disorders (n=195).

Results. It was found that the blood concentration of circulating pro-inflammatory biomarkers in patients with AF and MS is higher than in patients with AF without MS: C-reactive protein (CRP) (4,43 (2,68-4,98) and 2,33 (1,08-4,7) mg/L, p<0,0001), interleukin-6 (IL-6) (2,5 (1,28-5,13) and 1,27 (0,68-2,7) pg/ml, p<0,0001) and tumor necrosis factor-α (TNF-α) (5,18 (2,63-7,32) and 3,42 (2,11-5,48) pg/ml, p<0,0001). The serum CRP concentration positively correlates with left (ρ=0,451, p<0,0001) and right atrial (ρ=0,412, p<0,000) volumes, as well as with the waist circumference (ρ=0,503, p<0,001) and epicardial fat thickness (ρ=0,550, p<0,001). Plasma IL-6 and serum TNF-α levels correlated to a lesser extent with parameters characterizing atrial remodeling, but had a strong positive relationship with epicardial fat thickness. According to multivariate analysis, it was found that an increase in the epicardial fat thickness had a greater effect on an increase in blood concentration of CRP, IL-6 and TNF-α, in contrast to other parameters characterizing obesity, such as body mass index and waist circumference.

Conclusion. An increase in the blood concentration of proinflammatory biomarkers CRP, IL-6, and TNF-α is associated with cardiac remodeling and epicardial fat thickness in patients with MS and probably has a pathogenetic role in increasing the AF risk in this cohort of patients.

Keywords: C-reactive protein, interleukin-6, tumor necrosis factor-alpha, atrial fibrillation, metabolic syndrome.

Relationships and Activities: none.

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Atrial fibrillation (AF) — the typically common adult arrhythmia, the prevalence of which has been increasing in recent decades [1]. Non-modifiable risk factors (RF) for AF include male gender, old age, and hereditary predisposition; potentially modifiable causes predisposing to AF include arterial hypertension (AH), obesity, diabetes mellitus (DM), dyslipidemia, obstructive sleep apnea syndrome, chronic heart failure, valvular heart disease, and others [2]. The mechanisms of AF formation are different: the formation of automatism foci in the area of pulmonary veins entry and the circulation of excitation waves in atria, impaired functioning of L-type calcium channels, the formation of dilatation and fibrosis of the left atrium (LA), etc. Once it occurs, this arrhythmia usually anticipates ("fibrillation is born in fibrillation") [3]. However, despite significant advances in understanding the arrhythmogenesis mechanisms underlying the AF formation, the pathogenesis of this arrhythmia is not completely clear. Of particular interest is the possible role of obesity as one of the most common and potentially modifiable AF RF.

The incidence of obesity, as well as AF, progressively increases and takes epidemic form [1]. It should be noted that obesity, especially visceral (abdominal), is often combined with hypertension and metabolic disorders, combined with the concept of "cardiometabolic syndrome". According to the IDF criteria (2005), metabolic syndrome (CMS) is diagnosed in the presence of three or more of the following five factors: abdominal obesity, AH, hyperglycemia or DM, hypertriglyceridemia, and a decrease in the concentration of high-density lipoprotein cholesterol. According to the Atherosclerosis Risk in Communities (ARIC) study, the presence of CMS increases the risk of AF by 1,7 times [4]. AH and abdominal obesity (the most common components of CMS) favor the cardiac remodeling formation, causing dilatation, LP fibrosis, and AF development. However, to date, it is not entirely clear whether AF is a consequence of CMS or whether individual CMS components favor the development of this arrhythmia.

Inflammation plays a significant role in the development and progression of cardiovascular diseases, including AF [5, 6]. In AF, a significant inflammation role has also been established, as evidenced by the data of a meta-analysis conducted by Wu ZK, et al. [7]. Schnabel RB, et al. previously reported 12 markers of inflammation circulating in the blood associated with AF [8]. In AF, the role of two biomarkers of inflammation — C-reactive protein (CRP) and interleukin-6 (IL-6) — has been most studied [9, 10]. In addition to these parameters, the association between AF and tumour necrosis factor-α (TNF-α), interleukin-8 (IL-8) and interleukin-2 (IL-2) was studied [6, 11]. Leukocytosis and distortion of the ratio between neutrophils and lymphocytes is also an indicator of systemic inflammation and oxidative status, which, in turn, favor the AF development [11]. Obesity and CMS are also characterized by asymptomatic chronic inflammation, with these diseases, an increase in the blood of circulating markers of inflammation, including IL-6, CRP, and TNF-α [12, 13].

In AF, the role of not only systemic, but also local inflammation caused by the influence of epicardial adipose tissue (EAT) is discussed. In visceral obesity and CMS, the volume of epicardial fat is increased [14, 15]. In patients with CMS, the increase in EAT thickness estimated by echocardiography, is AF RF [16]. EAT secretes proinflammatory cytokines (TNF-α, IL-6, IL-1β, etc.) [17], which can cause local inflammation and participate in the formation of atrial fibrosis — a substrate for AF development [13, 18]. A meta-analysis conducted by Antonopoulos AS and Antoniades C testifies that a large volume of EAT is associated with AF development [19].

Therefore, it can be believed that the systemic and local inflammation specifically attributed to CMS can cause atrial cardiomyopathy, which can favor AF development [14]. Previously, only a few studies have compared the levels of pro-inflammatory and anti-inflammatory cytokines in patients with AF in combination with CMS with the concentration of these cytokines in patients with isolated AF or with CMS without arrhythmia, and the data from these studies are ambiguous [20, 21]. Based on the fact that the previously published data are contradictory or were obtained according to small samples of patients, this study was conducted.

The study's goal was to determine the levels of biomarkers of inflammation in the blood, parameters that characterize obesity and heart remodeling, in patients with AF in combination with CMS.

Material and methods

In the period from 2014 to 2018, 1307 patients with AF who were hospitalized in the medical department of the university clinic were examined. 721/1307 (55,2%) patients were diagnosed with CAD, 46/1307 (3,5%) with valvular pathology, and 80/1307 (6,1%) patients had inflammatory heart diseases. The one-time cohort examination enrolled patients with isolated AF (n=75) and patients with AF in combination with CMS (n=128) and without structural heart disease. The experimental groups included patients with CMS without AF (n=279), as well as those examined without CMS and AF and without other significant pathology (n=195).

The study was performed in accordance with the standards of Good Clinical Practice (GCP) and the Helsinki Declaration principles. The study protocol was approved by the Ethics Committees of all participating centers. All participants received written informed consent before enrollment.

The study enrolled men and women aged 35 to 65 years. Patients with CMS had 3 or more components of this syndrome diagnosed according to the IDF criteria (2005). The study excluded patients with verified chronic heart failure, heart valve pathology, systemic and oncological diseases, as well as with chronic kidney disease, liver pathology with impaired liver function, thyroid diseases, disorders of cerebral circulation, operations or interventional interventions on the heart in the anamnesis. Acute and exacerbations of chronic inflammatory diseases were excluded in all the examined patients, and patients with an increase in the CRP level determined by a highly sensitive method, >10 mg/l, were not included. The work assessed anthropometric and laboratory parameters, the results of instrumental study methods: electrocardiography, echocardiography (EchoCG). The EchoCG protocol is performed in standard modes on the Vivid 7 device (GE, USA). The thickness of epicardial fat (TEF) was measured over the right ventricle free wall in parasternal position in the diastole in three heart cycles. EAT was identified as a hypoechoic space anterior to the right ventricle free wall, and its thickness was measured between the epicardial heart surface and the pericardium parietal leaf.

All blood serum and plasma samples were centrifuged and stored at a temperature of -40° C, followed by determination of studied biomarkers concentration using standard ELISA test sets. The TNF-α concentration in blood serum was determined by a highly sensitive enzyme immunoassay (Human TNF alpha High Sensitivity ELISA kit, Bender MedSystems, Austria), with a minimum detection threshold of 0,13 pg/ml. The IL-6 concentration in blood plasma was determined by a highly sensitive ELISA test (Human IL-6 High Sensitivity ELISA kit, Bender MedSystems, Austria), with a minimum detection threshold of 0,03 pg/ml. The CRP level in blood serum was determined by a highly sensitive immunoturbidimetric method using COBAS INTEGRA of Roche Diagnostics GmbH, Germany, the minimum concentration of determination is 0,15 mg/l.

All the study results were entered into the original database. The normality of numerical variables distribution was conducted using the Kolmogorov-Smirnov criteria. Depending on type of distribution, the quantitative variables obeying the normal distribution law are represented by the mean value (M) ± standard deviation (σ). For comparison in independent groups of indicators with a normal distribution, the parametric unpaired Student's t-test was used. For the distribution of quantitative indicators that differ from the normal, the data are presented as a median (Me) with the indication of interquartile intervals (25-75%), and for comparison in independent groups of such indicators, the nonparametric Mann-Whitney U-test was used. Multiple comparisons in groups (more than two) in parametric statistics were conducted using univariate analysis of variance (ANOVA), and for nonparametric statistics — the Kruskal-Wallis test. In assessing the correlation coefficient significance, the Pearson's (r) criteria for the normal distribution and Spearman (ρ) criteria for the abnormal distribution of indicators were used. The statistical analysis was performed using the licensed IBM SPSS Statistics software, version 22.0.

Results

The study groups were comparable in gender distribution and did not differ significantly in age. When comparing the parameters characterizing atrium remodeling, it was found that the volumes and volume indices of both atria in patients with AF in combination with CMS are greater than in patients with this arrhythmia without CMS. Differences in the size and volume of atrium in the groups of patients with CMS without AF and CMS with AF were not identified. When TEF comparing, it was found that this index is higher in patients with AF in combination with CMS than in patients with AF without CMS (5,8±2,7 and 3,4±1,6, p<0,0001). In patients with AF without CMS, the TEF index was higher than in healthy subjects (3,4±1,6 and 2,3±0,9, p<0,0001). The main clinical, laboratory and EchoCG characteristics of the examined patients are presented in Table 1.

The concentrations of inflammatory biomarkers in blood serum and plasma in patients with AF in combination with CMS were higher than in patients with AF without CMS: CRP (4,43 (2,68-4,98) and 2,33 (1,08-4,7) mg/l, p<0,0001), IL-6 (2,5 (1,28-5,13) and 1,27 (0,68-2,7) pg/ml, p<0,0001) and TNF-α (5,18 (2,63-7,32) and 3,42 (2,11-5,48) pg/ml, p<0,0001). The levels of these biomarkers are also higher in patients with AF and CMS than in patients with CMS without AF: CRP (4,43 (2,68-4,98) and 2,46 (1,23-3,92) mg/l, p<0,0001), IL-6 (2,5 (1,28-5,13) and 2,12 (1,17-3,56) pg/ml, p<0,0001) and TNF-α (5,18 (2,63-7,32) and 3,5 (2,39-5,6) pg/ml, p<0,0001). The IL-6 concentration in patients with AF without CMS was lower than in patients with CMS without this arrhythmia (1,27 (0,68-

Table 1

Clinical, laboratory, and echocardiographic characteristics of patients with CMS and AF

Parameters	CMS (-), AF (-), n=195, (1)	CMS (+), AF (-), n=279, (2)	CMS (-), AF (+), n=75, (3)	CMS (+), AF (+), n=128, (4)	Statistical significance, p
Age, years	51,3±8,6	53,7±9,3	55,6±6,8	54,3±7,2	p>0,05
Gender, male/female	80/115	125/154	30/45	74/54	p>0,05
BMI, kg/m^2	22,5±4,8	34,1±8,6	24,9±3,5	32,3±6,6	$p_{1,2}$<0,0001; $p_{1,3}$=0,098; $p_{1,4}$<0,0001; $p_{2,3}$=0,003; $p_{2,4}$=0,089; $p_{3,4}$<0,0001
Waist circumference, cm	79,5±8,1	114,8±11,5	86,7±11,7	111,9±13,5	$p_{1,2}$<0,0001; $p_{1,3}$ =0,071; $p_{1,4}$<0,0001; $p_{2,3}$<0,0001; $p_{2,4}$=0,059; $p_{3,4}$<0,0001
Total TC, mmol/l	4,9±0,9	5,4±1,1	4,8±1,2	5,2±1,2	$p_{1,2}$<0,0001; $p_{1,3}$=0,821; $p_{1,4}$<0,0001; $p_{2,3}$<0,0001; $p_{2,4}$=0,689; $p_{3,4}$<0,0001
LDL TC, mmol/l	2,8±0,3	3,4±0,3	3,1±0,3	3,1±0,4	$p_{1,2}$<0,001; $p_{1,3}$<0,001; $p_{1,4}$<0,001; $p_{2,3}$=0,134; $p_{2,4}$=0,289; $p_{3,4}$=0,989
HDL TC, mmol/l	1,6±0,3	1,2±0,3	1,4±0,3	1,1±0,4	$p_{1,2}$<0,001; $p_{1,3}$=0,145; $p_{1,4}$=0,001; $p_{2,3}$=0,089; $p_{2,4}$=0,689; $p_{3,4}$=0,001
TG, mmol/l	1,0±0,3	2,1±0,8	1,3±0,4	1,7±1,2	$p_{1,2}$<0,001; $p_{1,3}$=0,585; $p_{1,4}$=0,001; $p_{2,3}$=0,001; $p_{2,4}$=0,001; $p_{3,4}$=0,001
Glucose, mmol/l	4,7±0,6	6,1±1,2	5,1±0,4	6,0±1,4	$p_{1,2}$<0,0001; $p_{1,3}$=0,087; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,678; $p_{3,4}$=0,001
Echocardiography					
LA diameter, mm	34,9±2,7	44,6±4,2	43,2±2,0	44,5±4,0	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,678; $p_{2,4}$=0,838; $p_{3,4}$=0,345
LA volume, ml	43,2±9,4	81,9±16,6	60,4±19,8	79,9±19,4	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,388; $p_{3,4}$=0,001
LA volume index, ml/m^2	24,3±4,9	39,2±9,7	30,4±9,0	40,1±11,2	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,624; $p_{3,4}$=0,001
RA volume, ml	41,3±8,9	68,5±14,4	57,5±20,6	65,9±14,7	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,457; $p_{3,4}$=0,001
RA volume index, ml/m^2	23,4±4,3	31,9±7,3	29,2±8,8	32,8±7,8	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$=0,314; $p_{3,4}$=0,001
LV MMI, g/m^2	82,6±14,3	105,3±15,3	105,1±17,8	112,9±16,3	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,893; $p_{2,4}$<0,0001; $p_{3,4}$<0,0001
	70,5±12,4	96,3±7,3	82,9±14,7	105,4±12,4	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,001; $p_{2,4}$<0,0001; $p_{3,4}$<0,0001
LV EF, %	64,3±7,1	61,2±6,4	62,4±4,2	60,8±6,2	p>0,05
TEF, mm	2,3±0,9	4,3±2,4	3,4±1,6	5,8±2,7	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,01; $p_{2,4}$<0,0001; $p_{3,4}$<0,0001
Duration of AF, years	-	-	4,9±1,2	4,2±2,2	p>0,05
AF form -	-	40/75 (53,3%)	78/128 (60,9%)	p>0,05	
-	-	20/75 (26,7%)	31/128 (24,3%)	p>0,05	
		15/75 (20%)	19/128 (14,8%)	p>0,05	

Abbreviations: LV MMI — left ventricular myocardial mass index, BMI — body mass index, LDL — low — low-density lipoproteins, HDL — high-density lipoproteins, LA — left atrium, CMS (-) — not available metabolic syndrome, CMS (+) — available metabolic syndrome, RA — right atrium, TG — triglycerides, TEF — thickness of epicardial fat, LV EF — left ventricular ejection fraction, AF (-) — not available atrial fibrillation, AF (+) — available atrial fibrillation, TC — cholesterol.

Table 2

Proinflammatory biomarkers in patients with AF and CMS

Biomarkers	CMS (-), AF (-), n=195, (1)	CMS (+), AF (-), n=279, (2)	CMS (-), AF (+), n=75, (3)	CMS (+), AF (+), n=128, (4)	Statistical significance, p
NLR	1,75 (1,42-2,22)	1,56 (1,26-2,1)	1,71 (1,42-2,14)	1,75 (1,42-2,53)	p>0,05
ESR, mm/h	8,1 (4,5-13,5)	13,5 (7,1-18,0)	11,2 (5,0-15,0)	12,7 (5,0-18,1)	$p_{1,2}$<0,001; $p_{1,3}$<0,001; $p_{1,4}$<0,001; $p_{2,3}$=0,537; $p_{2,4}$=0,787; $p_{3,4}$=0,236
Fibrinogen, g/l	2,9±0,8	3,5±0,8	3,1±0,7	3,3±0,9	p>0,05
CRP, mg/ml	0,57 (0,33-1,19)	2,46 (1,23-3,92)	2,33 (1,08-4,7)	4,43 (2,68-4,98)	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,617; $p_{2,4}$<0,0001; $p_{3,4}$<0,0001
IL-6, pg/ml	0,64 (0,34-1,57)	2,12 (1,17-3,56)	1,27 (0,68-2,7)	2,5 (1,28-5,13)	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,005; $p_{2,4}$=0,022; $p_{3,4}$<0,001
TNF-α, pg/ml	2,22 (0,91-3,38)	3,5 (2,39-5,6)	3,42 (2,11-5,48)	5,18 (2,63-7,32)	$p_{1,2}$<0,0001; $p_{1,3}$<0,0001; $p_{1,4}$<0,0001; $p_{2,3}$=0,266; $p_{2,4}$=0,001; $p_{3,4}$=0,001

Abbreviations: IL-6 — interleukin 6, CMS (-) — not available metabolic syndrome, CMS (+) — available metabolic syndrome, NLR — neutrophil-lymphocyte ratio, ESR — erythrocyte sedimentation rate, CRP — highly sensitive C-reactive protein, TNF-α — tumor necrosis factor-α, AF (-) — not available atrial fibrillation, AF (+) — available fibrillation atria.

Table 3

Correlations of biomarkers with parameters of atrial remodeling in the examined patients

Biomarkers	LA size	LA volume and volume index	RA volume and volume index	LV MMI	LV EF
Neutrophil/ Lymphocyte	-0,01, p=0,852	-0,02, p=0,717 0,03, p=0,609	-0,02, p=0,706 -0,06, p=0,912	0,005, p=0,991	-0,005, p=0,919
ESR, mm	0,07, p=0,209	0,06, p=0,291 0,118, p=0,04	-0,04, p=0,936 0,06, p=0,292	0,037, p=0,514	-0,04, p=0,458
Fibrinogen, g/l	0,075, p=0,332	0,154, p=0,04 0,116, p=0,135	0,102, p=0,205 0,044, p=0,582	0,144, p=0,06	-0,005, p=0,948
CRP, mg/ml	0,486, p<0,0001	0,451, p<0,001 0,326, p<0,001	0,427, p<0,001 0,296, p<0,001	0,412, p<0,0001	-0,124, p<0,0001
IL-6, pg/ml	0,393, p<0,0001	0,342, p<0,001 0,256, p<0,001	0,304, p<0,001 0,229, p<0,001	0,361, p<0,0001	-0,059, p=0,296
TNF-α, pg/ml	0,334, p<0,0001	0,254, p<0,001 0,206, p<0,001	0,221, p<0,001 0,159, p<0,001	0,243, p=0,004	-0,117, p=0,238

Abbreviations: IL-6 — interleukin 6, LV IMM — left ventricular myocardial mass index, LP — left atrium, Nf/Lf — neutrophil-lymphocyte ratio, RA — right atrium, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, LV EF — left ventricular ejection fraction, TNF-α — tumor necrosis factor-α.

2,7) and 2,12 (1,17-3,56) pg/ml, p<0,005), and the concentrations of TNF-α in patients with CMS without AF and AF without CMS did not significantly differ, as shown in Figure 1. The rate of erythrocyte sedimentation in patients in the CMS and AF groups was higher than in healthy subjects, but the average values were within the reference range. Differences in neutrophil-lymphocyte ratio and level of fibrinogen in the examined groups were not established. The data is presented in Table 2.

The correlation analysis of the relationship between the studied inflammation biomarkers and the parameters characterizing atrial remodeling (Table 3), revealed a positive relationship to a greater extent between CRP, IL-6 and TNF-α and the LA size and volume than with the volume of right atrium (RA). According to the results of correlation analysis of inflammatory biomarkers with indicators characterizing obesity, a positive relationship between CRP and IL-6 with body mass index (BMI), waist circumference (WC) and TEF was established. The TNF-α concentration was weakly correlated with BMI and WC, in contrast to the stronger relationship with TEF, as presented in Table 4. The IL-6 and CRP concentrations in blood also correlated more strongly with TEF than with BMI and WC (Figure 2).

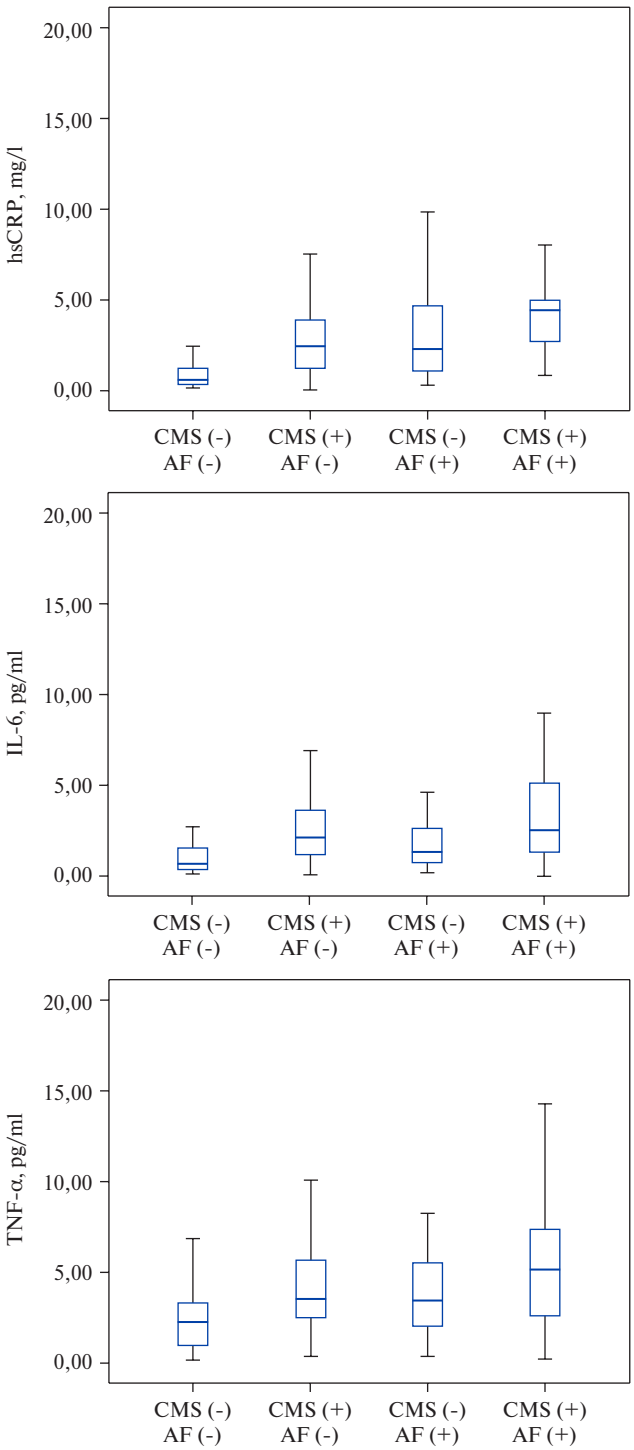

Figure 1. Concentrations of CRP, TNF-α in serum and IL-6 in blood plasma of patients with AF, CMS and practically healthy subjects.
Note: hsCRP — highly sensitive C-reactive protein, IL-6 — interleukin-6, CMS (-) — not available metabolic syndrome, CMS (+) — available metabolic syndrome, AF (-) — no atrial fibrillation, AF (+) — available atrial fibrillation, TNF-α — tumor necrosis factor-α.

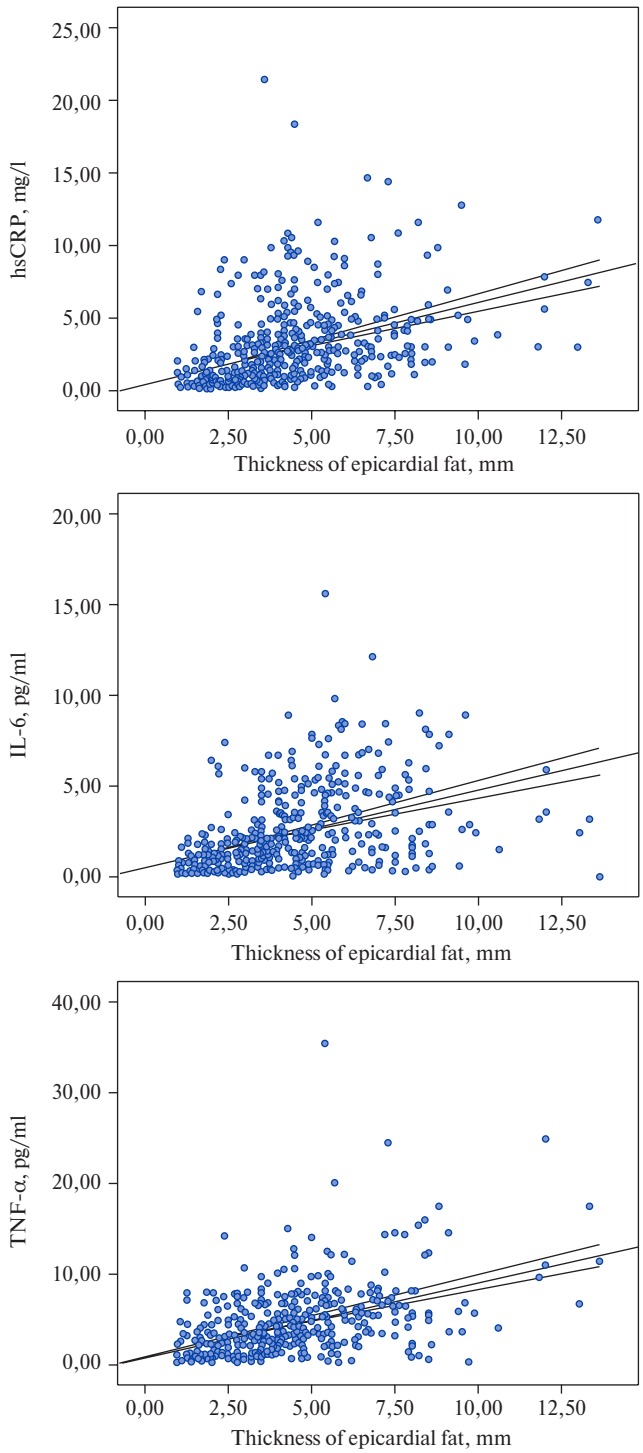

Figure 2. Correlation of inflammatory biomarkers concentrations (CRP, IL-6, TNF-α) with TEF.
Abbreviations: IL-6 — interleukin-6, hsCRP — highly sensitive C-reactive protein, TNF-α — tumor necrosis factor-α.

Multivariate linear regression analysis found that TEF has a statistically more significant effect on the increase in the concentration of CRP, IL-6 and TNF-α than BMI and WC (Table 5). When comparing the concentrations of inflammation studied biomarkers in patients with different TEF, divided by quartiles, it was found that a progressive

Table 4

Correlations of biomarkers with parameters characterizing obesity in the examined patients

Biomarkers	BMI	WC	TEF
Neutrophil/Lymphocyte	-0,122, p=0,02	-0,06, p=0,251	-0,05, p=0,394
ESR, mm	0,129, p=0,02	0,109, p=0,06	0,172, p=0,006
Fibrinogen, g/l	0,241, p=0,0009	0,318, p=0,0002	0,249, p=0,002
CRP, mg/ml	0,504, p<0,0001	0,503, p<0,0001	0,550, p<0,0001
IL-6, pg/ml	0,413, p<0,0001	0,405, p<0,0001	0,525, p<0,0001
TNF-α, pg/ml	0,264, p<0,0001	0,284, p<0,0001	0,508, p=0,0002

Abbreviations: IL-6 — interleukin 6, BMI — body mass index, Nf/Lf — neutrophil-lymphocyte ratio, WC — waist circumference, ESR — erythrocyte sedimentation rate, CRP-C — reactive protein, TEF — thickness of epicardial fat, TNF-α — tumor necrosis factor-α.

Table 5

Linear regression analysis of the influence of parameters characterizing obesity on inflammation biomarkers

Biomarkers	BMI	WC	TEF
CRP, mg/ml	0,208, p=0,003	0,028, p=0,699	0,265, p<0,0001
IL-6, pg/ml	0,001, p=0,985	0,132, p=0,094	0,355, p<0,0001
TNF-α, pg/ml	-0,043, p=0,572	0,06, p=0,446	0,436, p<0,0001

Abbreviations: IL-6 — interleukin 6, BMI — body mass index, WC — waist circumference, CRP — C-reactive protein, TEF — thickness of epicardial fat, TNF-α — tumor necrosis factor-α.

Table 6

Concentrations of inflammatory biomarkers in the blood of the examined patients with different TEF

TEF, quartiles	⩽2,6 mm (Q1)	2,7-3,8 mm (Q2)	3,9-5,0 mm (Q3)	⩾5,0 mm (Q4)	Statistical significance, p
CRP, mg/ml	0,59 (0,32-1,31)	1,23 (0,89-2,99)	2,7 (1,37-4,55)	3,4 (2,03-5,1)	p<0,0001
IL-6, pg/ml	0,61 (0,34-1,34)	1,4 (0,83-2,15)	2,3 (1,22-3,47)	3,34 (1,51-5,34)	p<0,0001
TNF-α, pg/ml	1,83 (0,89-3,19)	2,71 (1,48-4,15)	3,95 (2,81-5,45)	5,65 (3,48-7,89)	p<0,0001

Abbreviations: IL-6 — interleukin-6, CRP — C-reactive protein, TEF — thickness of epicardial fat, TNF-α — tumor necrosis factor-α.

increase in CRP, IL-6 and TNF-α is observed in each TEF quartile, which is presented in Table 6.

Discussion

A large number of studies have been devoted to the role of chronic asymptomatic inflammation in AF development and progression in recent years [3, 6, 11]. Strong evidence of a pathogenetic link between chronic inflammation and AF is that the incidence of AF in diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and others is significantly higher than in the general population [6]. Systemic inflammation also relates to the AF molecular mechanisms development in obesity. Obesity is considered today as a "chronic inflammation" status [22]. Undoubtedly, a relationship between obesity and an increased risk of cardiovascular disease, including AF is largely determined by the high level of inflammatory mediators [23].

The recommendations of the European Society of Cardiology 2020 on the AF diagnosis and treatment contain information on the risk of developing this arrhythmia, including the CMS components: hypertension, obesity, diabetes and dyslipidemia [2]. According to the ARIC study, CMS increases the risk of AF by 1,7 times [4]. The most common CMS components are abdominal (visceral) obesity and AH. Abdominal obesity and CMS are characterized by an imbalance of adipokines, in particular, hyperleptinemia and a decrease in the concentration of protective cytokine — adiponectin. Previously, it was proved that leptin and adiponectin are independently associated with the inflammatory marker

level [13]. CMS is associated with increased levels of proinflammatory cytokines (IL-6, TNF-α), as well as adipokines (leptin, ghrelin), uric acid, and decreased levels of anti-inflammatory cytokines (IL-10) [24].

The literature contains indications of single studies that compared the levels of pro-inflammatory and anti-inflammatory cytokines in patients with AF in combination with CMS and with concentration of these cytokines in patients with isolated AF or with CMS without arrhythmia [20]. In particular, Itani HA, et al. examining the concentration of 13 pro-inflammatory and anti-inflammatory cytokines in a small sample of 71 patients, found that the blood concentration of anti-inflammatory cytokines IL-4 and IL-10 in patients with isolated AF is higher than in patients with CMS or CMS in combination with AF [20]. In the same study, there was a tendency, which did not reach significance, to higher values of proinflammatory cytokines IL-6, TNF-α, and interferon-gamma (IF-γ) in patients with combination of AF and CMS in comparison with isolated AF and isolated CMS [20]. In our work on a large sample (482 patients and 195 examined from the comparison group), it was shown that in patients with AF in combination with CMS, the concentrations in blood plasma of IL-6 and in blood serum of CRP and TNF-α are significantly higher than in patients with isolated arrhythmia or in patients with isolated CMS, and also significantly higher than in patients without arrhythmia, without hypertension and metabolic disorders.

IL-6 — a pro-inflammatory cytokine, synthesized in immune cells, in particular, in macrophages, monocytes and fibroblasts, as well as in non-immune cells — endotheliocyte, vascular smooth muscle cells. IL-6 — the main inflammatory response regulator, which promotes the synthesis in hepatocytes of several proteins of the acute inflammation phase, such as CRP, fibrinogen, etc. [10]. IL-6 stimulates janus kinase/signal transducers and transcription pathway activators (JAK/STAT). Previous studies indicate that IL-6 in plasma is elevated in AF [9, 12, 20]. The high level of IL-6 and other proinflammatory cytokines in the blood in CMS is due to adipocyte dysfunction and is associated with an increase in subpopulation of macrophages in adipose tissue. In turn, proinflammatory cytokines induce insulin resistance. In particular, IL-6 increases insulin resistance, is associated with certain components of CMS, as well as high concentrations of this adipokine are associated with the severity of CMS manifestations [12, 13].

CRP is associated with the level of adipokines, leptin, favors an increase in CRP, and adiponectin suppresses the CRP synthesis and secretion [13]. In our study, the highest values of CRP were diagnosed in patients with AF in combination with CMS. CRP — the most significant indicator of vascular inflammation and is synthesized in the liver in response to stimulating factors, in particular, IL-6, synthesized by macrophages and adipocytes, which explains the low-intensity inflammation characteristic of obesity [13]. Mazidi M, et al. was found that in adults in the USA, the CMS risk was 5,2 times higher in the subjects belonging to the quartile with the highest concentration of CRP in blood plasma, compared with the quartile of subjects with the lowest value of this indicator [25]. In a cohort study conducted in Korea, it was found that a high level of CRP is the AF RF in the population [26]. A large prospective study conducted in China found that patients with CMS combined with elevated levels of CRP (>3 mg/l), in contrast to CMS with CRP ⩽3 mg/l, the AF risk is 1,61 times higher [21]. Previously, it was found that the CRP level is significantly higher in patients with AF with recurrent arrhythmia after radiofrequency ablation of the area of pulmonary veins [6, 8, 11]. However, the pathogenetic relationship between CRP and AF is not fully clear. It is assumed that CRP binds to membranes of cardiomyocytes, activates the compliment, and is a trigger of tissue damage [11].

TNF-α — a cellular signaling protein involved in the inflammatory cascade is secreted by macrophages, lymphocytes, including in adipose tissue, and stimulates the activation of transcription nuclear factor (NF-kB). IL-6 and TNF-α have a proinflammatory effect, stimulate fibroblast differentiation, proliferation, and migration. TNF-α is also a pyrogenic substance and stimulates the CRP synthesis in the liver. In combination with other adipokines, IL-6 and TNF-α also favor the CMS progression, disrupting the regulation of synthesis and release of adipokines and playing a decisive role in the progression of insulin resistance [20]. Similarly to other inflammation markers, TNF-α levels are higher in patients with AF [11].

In this work, positive correlations were found between the concentrations of inflammatory markers in the blood plasma — CRP, IL-6 and the parameters that characterize the heart remodeling — the LA size and volume, the mass index of left ventricle myocardium. These data indirectly confirm the relationship of IL-6 and other inflammation markers with the heart remodeling characteristic of AF, and are consistent with the literature data [20]. High levels of IL-6 are also associated with AF relapse after electrical cardioversion and catheter radiofrequency ablation [7], with thromboembolic complications and outcomes of this arrhythmia [10].

Of particular importance is the fact that our study revealed significant correlations between CRP, IL-6, TNF-α and the parameters characterizing obesity, including those with TEF. At the same time, it was found that in patients with a combination of AF and CMS, the thickness of epicardial fat is significantly greater than in patients with CMS without arrhythmia and in patients with AF without CMS. EAT — a truly visceral adipose tissue directly adjacent to myocardium, including atrial myocardium, which is important in AF formation, especially in patients with visceral obesity [18]. EAT synthesizes a large number of different molecules — pro-and anti-inflammatory adipokines, growth factors, and fibrogenic substances that have paracrine and vasocrine effects on the myocardium [3]. The expression level of most cytokines in EAT is much higher than in visceral fat of a different localization. Macrophages and T-lymphocytes, including those that migrate from EAT to the myocardium, are able to secrete proinflammatory and fibrogenic substances [3]. Consequently, inflammation favors the development of myocardial fibrosis and the formation of electroanatomic substrate for the AF appearance and progression [3]. This position is confirmed by the study of Abe I, et al. (2018), who evaluated the EAT thickness and the severity of LA auricle fibrosis (according to intraoperative biopsy data) in AF, and found that the severity of EAT thickness and fibrosis is associated with the prevalence of LA myocardial fibrosis [27]. In addition, the content of collagen in the LP myocardium positively correlated with the concentration of proinflammatory cytokines in the blood — IL-6, TNF-α [27]. Inflammatory mediators not only stimulate the replacement of cardiomyocytes with fibrous fibers, which is a key mechanism of structural remodeling in AF, but also affect the ion currents in the channels and ATP-regulated pumps, which together is a key link in the AF occurrence. It should be noted that chronic inflammation is not only associated with AF, but also predisposes to the development of thromboembolic complications of arrhythmia [10, 14].

Thus, inflammatory markers are involved in the AF pathogenesis, and the situation with chronic inflammation becomes even more significant when AF is combined with CMS. According to Packer, "atrial cardiomyopathy associated with inflammation" can lead to the development of "atrial fibrillation associated with inflammation" [14].

Study limitations. One of the limitations of this study is the effect of drug therapy, in particular, drugs from the group of statins, on the systemic inflammatory process, and currently it is not possible to assess pro-inflammatory biomarkers in patients without therapy, but in the long term, with a larger data set, such an additional analysis is necessary. Also, a single-stage examination of patients with AF and CMS does not allow to fully study the possible clinical role of inflammatory biomarkers on AF course and treatment tactics, so prospective observation and study of the clinical significance of determining the level of pro-inflammatory biomarkers in patients with CMS and AF are required.

Conclusion

1. The concentration in blood plasma of IL-6, in blood serum of CRP and TNF-α in patients with AF in combination with CMS is higher than in patients with AF without CMS, and higher than in patients with CMS without arrhythmia.
2. TEF in patients with AF in combination with CMS is greater than in patients with AF without CMS, and more than in patients with CMS without arrhythmia.
3. The indices of LP and PP volumes in patients with AF in combination with CMS are higher than in patients with AF without CMS.
4. Correlations were established between inflammatory markers and indicators characterizing visceral obesity, while the IL-6 and CRP concentrations in blood correlated with WC and TEF, and the TNF-α concentration in blood correlated only with TEF.
5. TEF has a greater effect on the IL-6 concentration, CRP, and TNF-α circulating in blood than other indicators that characterize obesity, such as BMI and WC.

Relationships and Activities: none.

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