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Role of inflammation, autotaxin and lipoprotein (a) in degenerative aortic valve stenosis in patients with coronary artery disease

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Aim. To study the relationship between the concentration of lipoprotein (a) (Lp (a)) and autotaxin (ATX) in patients with and without degenerative aortic valve stenosis (AoS) in the presence of coronary artery disease (CAD).

Material and methods. The study included 461 patients (mean age, 66±11 years, men, 323), 354 of whom had CAD with stenosis ⩾50% in at least one coronary artery according to angiography. Degenerative AoS was diagnosed with ultrasound. The control group consisted of 107 patients without CAD and degenerative AoS. Concentrations of Lp (a), ATX, lipids and blood cells were measured for all patients.

Results. CAD without degenerative AoS (group 1) was diagnosed in 307 patients, while 47 patients had CAD and degenerative AoS (group 2). Patients in both groups were older than patients in the control group (66±10, 74±8, and 61±13 years, respectively). The ATX level was lower in group 1 (median [25; 75%]: 495 [406; 583] ng/ml) than in the control group (545 [412; 654] ng/ml) or group 2 (545 [476; 605] ng/ml) ($p<0,05$ for all). Lp (a) was lower in the control group (14,5 [5,5; 36,0] mg/dl) than in group 1 (24,9 [9,7; 58,4] mg/dl) ($p<0,005$) and group 2 (23,8 [9,9; 75,7] mg/dL) ($p<0,05$). According to the logistic regression, an increased ATX level, regardless of age and other risk factors, was associated with degenerative AoS only in patients with CAD, while age and neutrophil to lymphocyte ratio were associated with the development of degenerative AoS both in patients with CAD and the general group.

Conclusion. An elevated Lp (a) level is associated with CAD regardless of the aortic valve involvement, while an increased concentration of ATX and neutrophil to lymphocyte ratio in patients with CAD were associated with degenerative AoS regardless of age and other risk factors.

Keywords: degenerative aortic valve stenosis, lipoprotein (a), autotaxin, neutrophil to lymphocyte ratio, coronary artery disease.

Relationships and Activities: none.

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Introduction

Degenerative aortic valve stenosis (AoS) is the most common valvular heart disease in Europe and North America, as well as in Russia. In developed countries, aortic stenosis is the second most common cardiovascular disease (CVD) after coronary artery disease (CAD) and systemic arterial hypertension with a revalence of 0,4% in the general population and 1,7% among people >65 years of age [1]. According to the Russian study, which included 3988 patients, the proportion of patients with AoS under the age of 60 was 0,5% and increased to 5,5% in people over 70 years old [2]. The initial period of the formation of degenerative AoS has similar mechanisms with atherosclerotic changes in both coronary and peripheral arteries [3]. The greatest role among atherogenic lipoproteins in the development of atherosclerosis is played by low density lipoproteins (LDL) and lipoprotein (a) (Lp (a)) [4]. Studies have shown that the accumulation of these atherogenic lipoproteins in the tissue of the aortic valve, as well as local inflammation, play a significant role in the pathogenesis of the formation of degenerative AoS [5]. According to a meta-analysis of a number of studies, statins have no effect on slowing the progression of aortic valve disease [6].

Autotaxin (ATX) — endonucleotide pyrophosphatase/phosphodiesterase 2 — a protein with phospholipase D activity and promoting the formation of lysophosphatidic acid, an active pro-inflammatory agent, is also associated with the development of aortic

stenosis. The performed immunohistochemical study demonstrated the joint localization of ATX, apoprotein (a) and oxidized phospholipids in the tissues of degeneratively altered aortic valves. In addition, ATX activity was found in the Lp (a) fractions isolated from the blood plasma of healthy donors [7].

The aim is to study the relationship between the concentration of Lp (a) and ATX in patients with and without degenerative AoS in the presence of CAD.

Material and methods

In a one-stage, open, single-center study on the basis of the Institute of clinical cardiology of A. L. Myasnikov Federal State Budgetary Institution "National Medical Cardiology Research Center" of the Ministry of Health of the Russian Federation, the patients who underwent inpatient treatment in the period from 2016 to 2018 (n=461) were included. The patients were divided into groups according to the presence of atherosclerotic lesions of the coronary arteries and degenerative AoS. Patients with chronic CAD who had stenosis >50% in at least one of the coronary arteries according to coronary angiography and without changes in the aortic valve according to echocardiography made up group 1 — only 307 (67%) patients. Group 2 consisted of patients with coronary artery disease with varying degrees of severity of degenerative AoS — 47 (10%) patients. The control group — 107 (23%) people, served as patients with unchanged coronary arteries and unaffected aortic valve, but with the possible presence of peripheral atherosclerosis, including with multifocal arterial lesions. The study did not include patients with congenital bicuspid aortic valve, history of rheumatic heart disease, infective aortic endocarditis, cancer accompanied by radiation and chemotherapy, and systemic connective tissue diseases. All patients were on standard drug therapy in accordance with Russian recommendations for their diseases.

The study was carried out in accordance with the principles of the Declaration of Helsinki; written informed consent was obtained from all patients prior to enrollment. The study was approved by the local Ethics Committee.

All patients underwent transthoracic two-dimensional echocardiography and doppler echocardiography to determine the state of the aortic valve. The diagnosis of degenerative AoS was established when the maximum blood flow velocity on the aortic valve >2,0 m/s and the average pressure gradient from the aortic valve >20 mm Hg according to the American guidelines for the management of patients with valvular heart disease.

A general clinical blood test was carried out, as well as determination of the concentration of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL cholesterol) using kits (Biocon, Germany). The concentration of low density lipoprotein cholesterol (LDL cholesterol) was calculated using the Friedwald formula: LDL C=TC-HDL C-TG/2,2 (mmol/l), and the level of corrected LDL C (LDL corr) was also calculated, taking into account the cholesterol contained in Lp (a): LDL C corr=LDL C-0,3×Lp(a)/38,7 (mmol/l), where Lp(a) is the concentration of lipoprotein(a) in mg/dl [8]. The Lp (a) concentration was measured by enzyme-linked immunosorbent assay using monospecific polyclonal ram antibodies against human Lp (a), validated against commercial kits [9]. The level of ATX and C-reactive protein (CRP) in blood serum was determined using kits for enzyme-linked immunosorbent assay (Human ENPP-2/Autotaxin, "R&D", USA and "Vector-Best", Russia, respectively). The neutrophil-lymphocyte index (NLI) was calculated as the ratio of the absolute number of neutrophils to the absolute number of lymphocytes.

Statistical analysis was performed using the "MedCalc" package. Indicators with a normal distribution are presented as means with standard deviations, indicators with a distribution other than normal are presented as a median and values of the 25th and 75th percentiles. The Kolmogorov-Smirnov test was used to determine the normal distribution. To compare the frequency indicators between groups, Fisher's exact test and the χ^2 method were used. Differences were considered statistically significant at $p < 0,05$. Threshold values of various biochemical markers were calculated using the analysis of operating characteristics curves (ROC analysis). To assess the relationship of various factors with the presence of degenerative AoS, we used contingency table analysis and logistic regression methods.

Results

The characteristics of the examined groups are presented in Table 1. Patients from group 2 were older than patients from group 1 and the control group ($p<0,001$ when comparing each group with the control and among themselves). In the groups of patients with coronary artery disease, regardless of the presence of AoS, there was a predominance of the male sex in comparison with the control group. There was no difference between groups 1 and 2 in the presence of diabetes, arterial hypertension, hypercholesterolemia and myocardial infarction, but there were significant differences compared to the control group (Table 1). Most patients with CAD were on statin drug therapy.

The values of total cholesterol, LDL cholesterol and LDL cholesterol in the blood were comparable among patients with CAD, regardless of the presence of AoS, but were significantly lower than in the control group ($p<0,0001$) (Table 1), which is explained by the more frequent use of statins in patients of groups with CAD compared with the control group: 98% vs 80% ($p<0,05$).

Analysis of the concentration of Lp (a) showed that it is higher in patients with CAD (groups 1 and 2) compared with the control group. The concentration of ATX, on the contrary, was significantly lower in group 1 than in the control group or in group 2. At the same time, there was no significant difference between the 2 group, which included patients with AoS, and the control group (Figure 1).

It was noted that at an ATX level of <418,5 ng/ml, which corresponds to the 1st quartile, not a single patient was identified who had both CAD and degenerative AoS at the same time. A quarter of patients from this group had an ATX concentration >606 ng/ml, >70% of patients with an ATX concentration at the 1st quartile level belonged to the group with coronary

Table 1

Groups general characteristics

	Control group CAD- AoS- (n=107)	Group 1 CAD+ AoS- (n=307)	Group 2 CAD+ AoS+ (n=47)	p
Male, n (%)	51 (47%)	240 (78%)	32 (68%)	<0,05 for 1 and 2 vs control
Age, years	61±13	66±10	74±8	<0,001 for 1 и 2 vs control, 1 vs 2
Smoking, n (%)	15 (14%)	83 (27%)	11 (23%)	<0,05 for 1 vs control
Type 2 diabetes, n (%)	19 (18%)	90 (29%)	20 (42%)	<0,05 for 1 and 2 vs control
Arterial hypertension, n (%)	94 (87%)	288 (93%)	43 (91%)	
Hyperlipidemia, n (%)	88 (82%)	288 (93%)	45 (95%)	<0,05 for 1 and 2 vs control
Myocardial infarction, n (%)	2 (2%)	169 (55%)	24 (51%)	<0,001 for 1 и 2 vs control
Statins, n (%)	86 (80%)	302 (98%)	46 (98%)	<0,05 for 1 and 2 vs control
Total cholesterol, mmol/l	5,6±1,7	4,5±1,4	4,4±1,1	<0,001 for 1 и 2 vs control
LDL cholesterol, mmol/l	3,6±1,6	2,6±1,2	2,6±0,9	<0,001 for 1 и 2 vs control
LDL cholesterol corr, mmol/l	3,4±1,6	2,3±1,3	2,3±0,9	<0,001 for 1 и 2 vs control
Lp (a), mg/dl	14,5 [5,5;35,9]	24,9 [9,7;58,4]	23,8 [9,9;75,7]	<0,05 for 1 and 2 vs control
ATX, ng/ml	545 [412;654]	495 [406;583]	545 [477;605]	<0,05 for 2 vs 1 and control
CRP, mg/l	4,1 [3,4;6,1]	5,4 [4,4;6,3]	3,6 [2,7;5,9]	
ESR, mm/h	10 [5;19]	11 [5;21]	20 [10;47]	<0,05 for 2 vs 1 and control
NLI	1,5 [1,2;2,1]	1,7 [1,4;2,3]	2,0 [1,6;3,1]	<0,001 for 1 и 2 vs control, 1 vs 2

Note: ESR is the erythrocyte sedimentation rate. Data are presented as median [25%; 75% percentile] for indicators with a distribution other than normal, when comparing quantitative indicators, the Mann-Whitney U test was used, for indicators with a normal distribution — mean values ± standard deviation or absolute number of patients (%), when comparing quantitative indicators, Student's t-test was used.

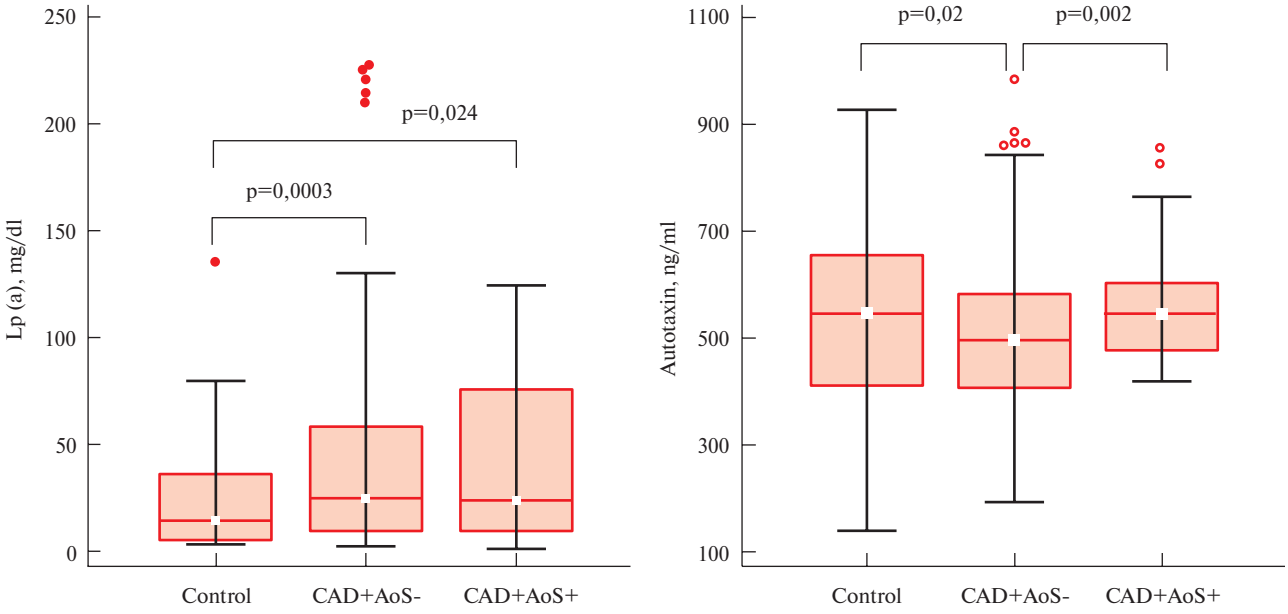

Figure 1 Levels of Lp (a) and ATX in the studied groups of patients.
Note: Data is presented as a Box-and-Whisker plot. Median [25%;75%] — Lp (a) in the group CAD+AoS- was 24,9 [9,7;58,4] mg/dL, in the group CAD+AoS+ — 23,8 [9,9;75,7] mg/dl, and in the control group 14,5 [5,5;35,9] mg/dl. Median [25%;75%] ATX in the group CAD+AoS- 495 [406;583] ng/ml, in the group CAD+AoS + this indicator was 545 [477;604] ng/ml, and in the control group 545 [412;654] ng/ml. AoC — aortic valve stenosis, CAD — coronary artery disease, Lp (a) — lipoprotein (a).

artery disease without AoS. A similar analysis of the distribution of patients relative to the upper and lower quartiles was performed for such indicators as Lp (a) and NLI (Figure 2). The ATX level corresponding to the upper quartile was most often found in patients with combined lesions of CAD and aortic valve, while an increased concentration of Lp (a) was associated with the presence of CAD regardless of the lesion of the aortic valve (Figure 2).

ROC analysis demonstrated a significant relationship between age (sensitivity 74,5%; specificity 65,5%, area under the curve 0,754), NLI (sensitivity

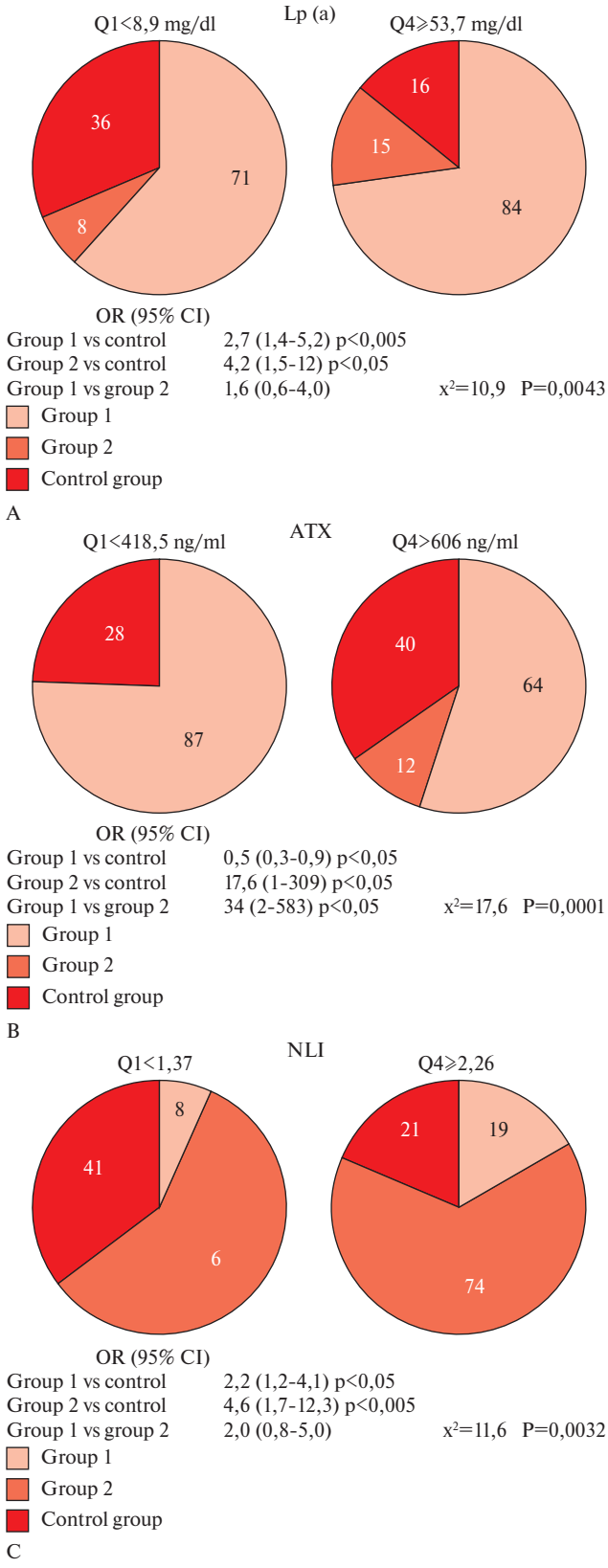

Figure 2 Frequency of CAD and degenerative AoS in patients with low and high levels of Lp (a) — *A*, ATX — *B* and NLI — *C*.

Note: the data are presented as the number of patients from different groups and OR of the presence of aortic stenosis in patients with the level of the studied parameters corresponding to the first (Q1) and fourth (Q4) quartiles of the distribution. ATX — autotaxin, Lp (a) — lipoprotein (a), NLI — neutrophil-lymphocyte index.

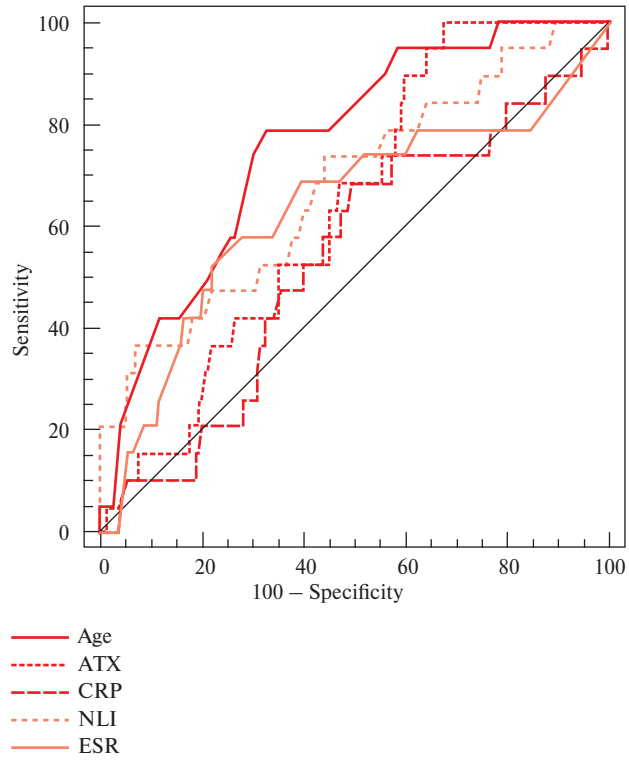

Figure 3 ROC analysis of the relationship between aortic valve lesions and the level of clinical indications and markers of inflammation.

Note: ATX — autotaxin, NLI — neutrophil-lymphocyte index, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein.

36,2%; specificity 90,7%, area under the curve 0,642), ATX concentration (sensitivity 97,9%; specificity 33,82%, area under the curve 0,608) and erythrocyte sedimentation rate (sensitivity 57,9%; specificity 69,4%, area under the curve 0,654) and the presence of AoS in the examined patients (p<0,05 in all cases) (Figure 3).

According to logistic regression analysis, only age — odds ratio (OR)=1,11, 95% confidence interval (CI): 1,07-1,16 and NLI — OR=1,42, 95% CI: 1,16-1,75 (p <0,001 for both comparisons) were independently associated with degenerative AoS both in the general group of the examined patients and in the group of CAD patients. At the same time, in this model, it was not possible to demonstrate an independent relationship between the concentration of Lp (a) and ATX, on the one hand, and the presence of AoS, on the other. When analyzing only CAD patients, an increase in ATX concentration by one standard deviation (138 ng/ml) was associated with the presence of degenerative AoS in patients regardless of age and other risk factors (OR=1,6, 95% CI:1,09-2,2) (p<0,05).

Thus, the specific role of Lp (a) in the development of AoS in patients with already existing ischemic heart disease has not been identified; along with this, it was found that an increased concentration of ATX is associated with the development of AoS in patients with pre-existing ischemic heart disease.

Discussion

Lp (a) is a unique lipoprotein consisting of an LDL-like particle and apoprotein (a) [10]. This indicator was first described >50 years ago as a new genetic variant of LDL. Currently, an increased level of Lp (a) is recognized as an independent risk factor for the development of CAD [11]. In the last few years, Lp (a) has become interesting as a possible risk factor for the development of degenerative AoS [12]. In 2013, according to the results of genome-wide analysis, which included 38 thousand patients, within the framework of the international consortium CHARGE, a significant relationship was revealed between variation in the *LPA* gene and the development of degenerative AoS. The rs10455872 variant in this gene was associated with the development of aortic valve calcification regardless of gender and race [13]. Another large, prospective study EPIC (European Prospective Investigation into Cancer (EPIC) — Norfolk) showed that patients with the highest Lp (a) levels had an increased risk of developing AoS [14]. CCHS (Copenhagen City Heart Study) and CGPS (Copenhagen General Population Study), which included about 78 thousand patients, it was noted that the level of Lp (a) >90 mg/dL was associated with a 2,9-fold increase in the risk of developing AoS [15]. According to the obtained data, the level of Lp (a) was significantly higher in the groups of patients with CAD compared with the control group, regardless of the presence of AoS. Such results, apparently, confirm the leading role of the increased concentration of Lp (a) in early CAD development. Degenerative AoS, as a disease associated with older age, in patients with an elevated Lp (a) level may occur on the background of a previous CAD.

Along with Lp (a), the role of ATX in the development of degenerative AoS was also assessed. According to a "case-control" study by Nsaibia MJ, et al., which is included 300 patients with CAD, it was found that the level of ATX circulating in the blood is associated with the development of degenerative AoS in patients with CAD, and the combination of high ATX activity with a Lp (a) level >50 mg/dL 3,5 times increased the likelihood of developing degenerative AoS [16]. It is important to note that a distinctive feature of our protocol was the study of the control group, which included patients who did not have CAD or AoS. The results are comparable to those of Nsaibia MJ, et al. and are characterized by a significant difference in the level of ATX in patients with coronary artery disease with combined lesions of the aortic valve in comparison with patients with CAD without AoS. There were no significant differences in the average concentration of ATX between patients with AoS and patients in the control group. Thus, only with a combination of an increased level of Lp (a) and ATX, the latter becomes a factor contributing to the development of AoS. This conclusion is confirmed by the results of other studies, in which it was found that ATX is delivered to the tissue of the aortic valve as part of Lp (a). Bouchareb R, et al. demonstrated that ATX activity was increased 4,6 times in the Lp (a) fraction relative to that in the blood plasma of healthy donors. In addition, immunohistochemical analysis of the aortic valve tissue showed that ATX can be produced and secreted by the interstitial cells of the aortic valve, and its expression is associated with markers of inflammation [7].

The inflammatory response is widely discussed as an initiating factor in the development of degenerative AoS. To assess the contribution of inflammation, the authors analyzed NLI as a simple and accessible marker of the systemic inflammatory response. According to the results of several studies, this indicator was associated with the presence of coronary artery disease and AoS [17, 18].

According to our data, NLI is an indicator independent of other CVD risk factors, indicating the presence of AoS in patients with CAD. At the same time, an increased NLI is associated with the identification of both isolated CAD and CAD in combination with AoS compared with the control group, which confirms the role of active inflammation in the development of these CVDs.

According to Song J, et al., NLI and CRP may be new reliable predictors of the development of degenerative AoS; in addition, increased NLI is directly related to the severity of AoS in patients with both tricuspid aortic valve and bicuspid valve [18]. It should be noted that the authors did not find a difference in the CRP level either between the groups differing in the presence of AoS, or in comparison of each group with the control. An increase in CRP is observed in endogenous vascular inflammation accompanying the development of atherosclerosis, as well as in trauma and infection [19]. Since the control group consisted of inpatients with cardiovascular pathology, but without CAD and AoS, some patients had atherosclerotic lesions of peripheral arteries of varying severity. Previously, an association was found between elevated CRP levels and multifocal peripheral arterial disease in women [20], which explains the absence of differences between groups in this study.

Conclusion

The increased level of Lp (a), in contrast to the concentration of ATX, was not associated with the presence of degenerative AoS in patients with coronary artery disease with stenosing atherosclerosis of the coronary arteries. NLI, as a marker of systemic inflammation, demonstrated in this study an association independent of age and other risk factors with degenerative AoS in the presence of CAD.

Relationships and Activities: none.

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