ГЕНДЕРНЫЕ РАЗЛИЧИЯ СОДЕРЖАНИЯ В СЫВОРОТКЕ КРОВИ МАРКЕРОВ ВОСПАЛЕНИЯ И АКТИВАЦИИ ТРОМБОЦИТОВ У ПАЦИЕНТОВ С ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ НЕКЛАПАННОГО ГЕНЕЗА

Огуркова О.Н., Лугачёва Ю.Г., Драгунова М.А., Ситкова Е.С.

Научно-исследовательский институт кардиологии – филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия

Резюме. Распространенность фибрилляции предсердий высока и сопоставима у обоих полов. Такие факторы, как различно экспрессируемые биомаркеры крови у женщин и мужчин могут играть определенную роль в возникновении фибрилляции предсердий и развитии тромботических осложнений.

Цель – исследование маркеров воспаления и активации тромбоцитов у больных с фибрилляцией предсердий неклапанного генеза, получающих антикоагулянтную терапию и имеющих в анамнезе тромботические осложнения и пациентов с фибрилляцией предсердий без тромботических осложнений в зависимости от гендерной принадлежности больных.

В исследование было включено 22 здоровых добровольца и 60 пациентов с диагнозом «фибрилляция предсердий», получающих антикоагулянтную терапию, из них у 21 пациента произошло развитие тромботических осложнений. Исследование содержания в сыворотке крови α2-macroglobulin, hsC-reactive protein, fetuin A, α-1-acid glycoprotein, L-selectin, serum amyloid P, adipsin, platelet factor 4 проводили на FLEXMAP 3D, с использованием диагностических тест-систем Acute Phase Panel 3.

Сравнительное исследование содержания биомаркеров продемонстрировало повышенное содержание С-реактивного белка у мужчин и женщин в обеих группах пациентов с фибрилляцией предсердий; снижение фетуина А и L-селектина в группе женщин с тромбозами по сравнению с женщинами без тромботических осложнений и по сравнению со здоровыми женщинами. Половых различий в содержании фетуина А и L-селектина в группе больных с фибрилляцией предсердий без тромботических осложнений и у здоровых добровольцев не обнаружено. Уровень адипсина не имел половых различий в группе пациентов с фибрилляцией предсердий с тромбозами и у здоровых добровольцев, однако он был значительно повышен у женщин без тромбозов. Содержание тромбоцитарного фактора 4 у женщин в обеих группах пациентов превышает значение данного показателя у здоровых женщин, половых различий в группах у пациентов с фибрилляцией предсердий не обнаружено.

Адрес для переписки:

Огуркова Оксана Николаевна
Научно-исследовательский институт кардиологии
634012, Россия, г. Томск, ул. Киевская, 111а.
Тел.: 8 (960) 975-45-44.
E-mail: ogurkovaon@mail.ru

Address for correspondence:

Oksana N. Ogurkova
Cardiology Research Institute
111a Kievskaya St
Tomsk
634012 Russian Federation
Phone: +7 (960) 975-45-44.
E-mail: ogurkovaon@mail.ru

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Низкие уровни фетуина А и L-селектина при одновременном повышении содержания С-реактивного белка и тромбоцитарного фактора 4 приводят к увеличению протромбогенного потенциала и изменению баланса про- и противоспалительных медиаторов в сторону усиления воспаления у пациентов с фибрилляцией предсердий женского пола.

Ключевые слова: фибрилляция предсердий, тромботические осложнения, воспаление, биомаркеры, белки острой фазы, гендерные различия

GENDER DIFFERENCES IN SERUM MARKERS OF INFLAMMATION AND PLATELET ACTIVATION IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

Ogurkova O.N., Lugacheva Yu.G., Dragunova M.A., Sitkova E.S.

Cardiology Research Institute, Branch of Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russian Federation

Abstract. The prevalence of atrial fibrillation is high and comparable in both sexes. Such factors as differently expressed blood biomarkers in women and men may play a role in the occurrence of atrial fibrillation and the development of thrombotic complications.

To study markers of inflammation and platelet activation in patients with atrial fibrillation of non-valvular origin, receiving anticoagulant therapy and having a history of thrombotic complications and patients with atrial fibrillation without thrombotic complications, depending on the gender of the patients.

The study included 22 healthy volunteers and 60 patients diagnosed with atrial fibrillation receiving anticoagulant therapy, of which 21 patients developed thrombotic complications. Serum levels of α2-macroglobulin, hsC-reactive protein, fetuin A, α-1-acid glycoprotein, L-selectin, serum amyloid P, adipsin, and platelet factor 4 were studied on FLEXMAP 3D using Acute Phase diagnostic test systems Panel 3.

A comparative study of the content of biomarkers demonstrated an increased concentration of C-reactive protein in men and women in both groups of patients with atrial fibrillation; decrease in fetuin A and L-selectin in the group of women with thrombosis compared with women without thrombotic complications and compared with healthy women. There were no gender differences in the concentration of fetuin A and L-selectin in the group of patients with atrial fibrillation without thrombotic complications and in healthy volunteers. The level of adipsin had no gender differences in the group of patients with atrial fibrillation with thrombosis and in healthy volunteers, however, it was significantly increased in women without thrombosis. The content of platelet factor 4 in women in both groups of patients exceeded the value of this indicator in healthy women; no gender differences were found in the groups of patients with atrial fibrillation.

Low levels of fetuin A and L-selectin, with a simultaneous increase in C-reactive protein and platelet factor 4, lead to an increase of prothrombogenic potential and to a change in the balance of pro- and anti-inflammatory mediators towards increased inflammation in female patients with atrial fibrillation.

Keywords: atrial fibrillation, thrombotic complications, inflammation, biomarkers, acute phase proteins, gender differences

Introduction

Atrial fibrillation (AF) is one of the most common persistent arrhythmias and is known as a risk factor for the development of heart failure, cerebrovascular events, and sudden cardiac death. An increase in mortality associated with the presence of AF is observed in almost all groups of patients: with coronary heart disease, arterial hypertension, and also in individuals with an isolated form of AF [1]. Every year there is more and more data on the gender characteristics of cardiovascular diseases and factors predisposing to their development. The prevalence of atrial fibrillation is high and comparable in both sexes. Atrial fibrillation is associated with a 6-fold increase in the risk of thrombotic complications and stroke and a 2-fold increase in mortality compared with patients with sinus rhythm [1, 11]. It is now well known that men and women with atrial fibrillation differ in most clinical and demographic characteristics. Factors such as sex hormones or differently expressed blood biomarkers in women and men may play a role in the onset of AF.

Structural and electrophysiological changes in AF include many factors, among which inflammation plays an important role, its participation in the initiation, maintenance and progression of AF has been noted. Activation of the blood coagulation system and platelet aggregation is observed during atrial

fibrillation. In recent years, the relationship between thrombosis and inflammation has been actively studied, since it is known that not only inflammation is accompanied by an increase in the activity of the blood coagulation system, but also thrombosis, in turn, leads to the development of inflammation [2].

To date, the assessment of biomarkers is widely used in the diagnosis of myocardial infarction, heart failure, however, studies on gender differences in the composition of biomarkers in atrial fibrillation are not sufficient. Some biomarkers reflect the pathophysiological process of AF development, while others can be used as markers to predict the risk of thromboembolic complications.

Thus, it seems relevant to us to study gender differences in blood biomarkers in patients with atrial fibrillation in order to gain an understanding of the gender specificity of pathophysiological mechanisms in AF and their possible involvement in the development of thrombotic complications (TC).

Purpose of the study: to study markers of inflammation and platelet activation in patients with non-valvular atrial fibrillation, receiving anticoagulant therapy and having a history of thrombotic complications and patients with atrial fibrillation without thrombotic complications, depending on the gender of the patients.

Materials and methods

The study included 22 healthy volunteers and 60 patients over 18 years old with a diagnosis of atrial fibrillation, verified on the basis of clinical guidelines (ESC 2020 recommendations for the diagnosis and treatment of atrial fibrillation), confirmed by ECG, daily ECG monitoring, receiving anticoagulant therapy. Of these, 21 patients (35%) developed thrombotic complications at the background of adequate anticoagulant therapy. In the presence of indications and in the absence of contraindications, endocardial EPS and RFA were performed using the non-fluoroscopic navigation system CARTO 3 EP (Biosense Webster, USA). Exclusion criteria were as follows: contraindications to anticoagulants, chronic heart failure with a pronounced decrease in left ventricular ejection fraction of less than 40% and significant dilatation of the heart cavities, valvular heart disease, pregnant women or women of childbearing age planning a pregnancy at the time of the study, mentally incompetent patients – neurological conditions. All patients gave their written informed consent for inclusion in the study.

Serum lipid testing (total cholesterol, low density lipoproteins (LDL) cholesterol, high density lipoproteins (HDL) and triacylglycerol) was performed by standard methods on an automatic biochemical analyzer Cobas C311 (Roche Diagnostics, USA). Serum α2-macroglobulin (mg/mL), hsC-reactive protein (hsCRP) (mg/L), fetuin A (mcg/mL), α-1-acid glycoprotein (mcg/mL), L-selectin (mcg/mL), serum amyloid P (SAP) (mcg/mL), adipsin (mcg/mL), platelet factor 4 (PF4) (mcg/mL) was carried out on the equipment of the Center for Collective Use "Medical Genomics" of the Tomsk Research Center FLEXMAP 3D, using diagnostic test systems Acute Phase Panel 3 and MILLIPLEX Analyst 5.1 software (Merck KGaA, Milliplex; Darmshdadt) in accordance to the supplier's instructions. The multiplex analysis technology on the Luminex platform (xMAP® technology) is an important tool for the simultaneous quantification of a complex of different biomarkers in a single sample. The possibilities of xMAP® technology allow performing simultaneous quantitative analysis of a complex of 8 biochemical analytes contained in one blood serum sample of patients with AF and healthy volunteers with high sensitivity. Statistical processing of the obtained results was carried out using the Statistica 10.0 software (StatSoft Inc., USA). Quantitative data are presented medians and 25^{th}; 75^{th} percentiles ($Q_{0.25}$-$Q_{0.75}$), categorical data – in the form of n, % (the number of patients with this characteristic, the proportion of their frequency in the group). The statistical significance of differences between two independent quantitative variables was assessed using the Mann–Whitney U test. Differences were considered statistically significant at $p < 0.05$. Spearman's rank correlation coefficient (Spearman R) was used for correlation analysis.

Results and discussion

All patients were divided into groups: group 1 – patients with atrial fibrillation without thrombotic complications, group 2 – patients with atrial fibrillation with thrombotic complications. Within the group patients were divided by gender – group A – women and group B – men. The patients of the studied groups were comparable by age, gender, functional class of CHF, presence of coronary artery disease, arterial hypertension. The main clinical parameters and medical history of the patients of the study groups are presented in Table 1. Thrombotic complications (TC) in AF without damage to the valvular apparatus of the heart among all patients included in the study were as follows: thrombosis of the left atrial appendage was noted in 10 patients (17%), spontaneous echocontrast II degree in 5 patients (8.3%), cardioembolic stroke – in 3 patients (5%), thrombosis of peripheral arteries – in 1 (2%), thrombosis on the pacemaker electrodes – 2 (4%). The patients of the study groups were also comparable in terms of the frequency of use of the main groups of medications. Prescribed therapy, at the time of inclusion in the study, complied with contemporary recommendations and included standard conventional antiarrhythmic and anticoagulant therapy, as well as therapy for the underlying cardiovascular disease (beta-blockers, statins, angiotensin-converting enzyme inhibitors, diuretics), detailed characteristics are presented in Table 2.

TABLE 1. CLINICAL CHARACTERISTICS OF PATIENTS WITH ATRIAL FIBRILLATION

Parameter	Women without thrombotic complications (n = 18)	Men without thrombotic complications (n = 21)	Women with thrombotic complications (n = 10)	Men with thrombotic complications (n = 11)
Age, years, Me ($Q_{0.25}$-$Q_{0.75}$)	66.5 (61.0-71.0)	56.5 (48.0-64.0)	66.0 (63.0-74.0)	68.0 (60.0-73.0)
Left atrium size, mm, Me ($Q_{0.25}$-$Q_{0.75}$)	39.0* (37.0-45.0)	41.0* (40.0-44.5)	45.5 (40.0-48.0)	47.0 (45.0-50.0)
Form of atrial fibrillation, n (%):				
paroxysmal form	8 (44.4)	10 (47.6)	4 (40)	3 (27.3)
persistent form	10 (55.6)	11 (52.4)	6 (60)	8 (72.7)
Arterial hypertension, n (%)	13 (72.2)	14 (66.7)	2 (20)	1 (9.1)
Coronary heart disease, n (%)	11 (61.1)	10 (47.6)	5 (50)	9 (81.8)
Functional class of heart failure (NYHA), n (%)				
I	5 (27.8)	4 (19.0)	1 (10)	1 (9.0)
II	9 (50)	8 (38.1)	–	4 (36.4)
III	–	2 (9.5)	–	–
Thrombotic complications				
Left atrial auricular thrombosis, n (%)	–	–	2 (20)	8 (72.7)
Spontaneous echocontrasting, n (%)	–	–	5 (50)	–
Right atrial thrombosis, n (%)	–	–	1 (10)	–
Cardioembolic stroke, n (%)	–	–	–	3 (27.3)
Right ventricular electrode thrombus, n (%)	–	–	–	2 (18.2)
Peripheral artery thrombosis, n (%)	–	–	–	2 (18.2)
Total cholesterol, mmol/L Me ($Q_{0.25}$-$Q_{0.75}$)	5.28* (3.91-6.19)	4.10 (3.43-4.72)	3.99 (3.32-4.77)	3.30 (2.99-4.45)
Triacylglycerol, Me ($Q_{0.25}$-$Q_{0.75}$)	1.29 (1.04-1.69)	1.09 (0.87-1.31)	1.12 (0.90-1.34)	1.12 (0.86-1.31)
HDL cholesterol, mmol/L, Me ($Q_{0.25}$-$Q_{0.75}$)	1.39 (1.12-1.56)	1.07 (1.01-1.22)	2.25 (1.50-2.95)	1.51 (1.23-3.00)
LDL cholesterol, mmol/L, Me ($Q_{0.25}$-$Q_{0.75}$)	3.46* (2.14-4.06)	2.43* (1.95-2.92)	1.24 (1.06-1.51)	1.11 (0.88-1.42)
LDL / HDL, Me ($Q_{0.25}$-$Q_{0.75}$)	2.43 (1.92-2.98)	2.06* (1.79-2.73)	3.06 (3.06-3.06)	1.34 (0.80-2.47)

Note. Data are presented as the % and median Me ($Q_{0.25}$-$Q_{0.75}$) for continuous non-normally distributed variables. *, statistical significance of differences between groups of patients with atrial fibrillation without vs with thrombotic complications ($p < 0.05$).

TABLE 2. MEDICATION THERAPY AT THE TIME OF THE STUDY

Parameter	Patients without thrombotic complications Group1 (n = 39)	Patients with thrombotic complications Group2 (n = 21)
Anticoagulant therapy:		
Warfarin, n (%)	8 (20)	8 (38)
Xarelto, n (%)	19 (48)	5 (24)
Pradaxa, n (%)	1 (2)	1 (5)
Eliquis, n (%)	11 (28)	8 (38)
Antiaggregant therapy:		
Aspirin, n (%)	–	2 (9)
Clopidogrel, n (%)	–	2 (9)
None, n (%)	39 (100)	15 (71)
Statins, n (%)	33 (85)	13 (85)
Beta-blockers, n (%)	12 (31)	13 (62)
ACE inhibitors	25 (64)	17 (81)
Diuretics	5 (13)	3 (14)
Antiarrhythmic therapy:		
Propanorm, n (%)	3 (8)	1 (5)
Cordarone, n (%)	6 (15)	7 (33)
Sotalex, n (%)	5 (13)	4 (19)

Note. Data are presented as the absolute value; (%).

A comparative study of the concentration of biomarkers in men and women in groups of patients and in healthy volunteers showed that both men and women in both groups of patients with AF had an increased concentration of C-reactive protein, which is a sensitive and specific laboratory marker of inflammation and tissue damage, the data are presented in Table 3. However, there was no difference in CRP concentration between men and women in groups of patients with AF and in healthy volunteers. When determining the concentration of α2-macroglobulin and α-1-acid glycoprotein in blood no gender differences were found, and their concentration in patients with AF did not differ from the level in the group of healthy volunteers. A decrease in fetuin A and L-selectin concentration was noted in blood serum in the group of women with thrombosis compared to women from the group without thrombotic complications and compared to healthy women. At the same time, in the group with thrombotic complications, the levels of fetuin A and L-selectin in women were reduced compared to men. The concentration of L-selectin in women without thrombotic complications exceeded the value of this indicator compared to healthy women. There were no gender differences in the content of fetuin A and L-selectin in the group of patients with AF without TC and in healthy volunteers.

In women, both from group without TC, and from the group with thrombosis, a reduced concentration of serum amyloid P was observed compared to men. In healthy volunteers there were no gender differences, the data were not statistically significant. One of the key adipokines that have a multidirectional effect on metabolic processes is adipsin secreted by fat cells. Adipsin acts as a regulator of carbohydrate and lipid metabolism possesses the same activity as complement factor D, which is necessary for the normal f activation of the alternative pathway of complement system. Due to this fact, adipsin acts as a link between the energy block of the endocrine system and the humoral block of the immune system [6, 9].

The data of our study demonstrated that the level of adipsin had no gender differences in the group of patients with atrial fibrillation with thrombosis and in healthy volunteers, however, it was significantly increased in women in the group without thrombosis compared to men from the same group, and also compared to women both from the group with thrombosis and the group of healthy volunteers. The proportion of patients included in the study and taking statins to correct lipid metabolism disorders was 87%. Statins are known to have pleiotropic effects: anti-inflammatory, antioxidant, cardioprotective, and antiarrhythmic. They participate in the normalization of body weight and hormonal levels, and lead to an improvement of endothelial function. The antithrombotic effect of statins is realized through the increase of thrombomodulin expression [8, 12]. Of all the examined patients, pronounced disorders of lipid metabolism, in the form of an increase in the content of total cholesterol and LDL cholesterol, were noted in women in the group without thrombosis.

The molecules associated with the cellular link of hemostasis include platelet factor 4, which is released into the plasma from platelet α- granules

TABLE 3. COMPARATIVE ANALYSIS OF ACUTE PHASE PROTEINS IN WOMEN AND MEN

	Patients without thrombotic complications Group 1 (n = 39)		Patients with thrombotic complications Group 2 (n = 21)		Healthy volunteers (n = 22)	
Parameters	**Group A (n = 18)**	**Group B (n = 21)**	**Group A (n = 10)**	**Group B (n = 11)**	**Group A (n = 11)**	**Group B (n = 11)**
hsC-reactive protein (mg/L)	26.33* (14.62-54.5)	27.96* (13.91-41.93)	23.961* (0.00-58.64)	29.01* (14.40-71.76)	16.716 (1.19-21.42)	11.61 (8.162-15.470)
α2-Macroglobulin (mg/mL)	3.81 (2.78-4.94)	3.51 (2.99-4.56)	2.86 (2.58-3.43)	3.55 (2.80-4.98)	2.71 (2.67-4.88)	3.16 (2.25-5.25)
α-1-Acid glycoprotein (mcg/mL)	4.28 (3.20-7.93)	4.19 (3.10-5.27)	3.89 (2.68-4.73)	3.48 (2.62-4.31)	4.16 (2.17-5.13)	3.86 (2.91-4.67)
Fetuin A (mcg/mL)	514.58 (396.12-689.14) ***	444.75 (337.28-623.06)	281.27 (169.720-311.245) * ** ***	375.229 (14.40-71.76)	412.33 (241.8028-478.2000)	448.95 (308.25-597.43)
L-selectin (mcg/mL)	3.075 (2.59-4.08) * ***	2.70 (1.82-3.47)	1.65 (1.09-1.95) * ** ***	2.04 (1.83-2.62)	2.53 (1.781-4.750)	2.54 (1.83-3.32)
Serum amyloid P (mcg/mL)	19.69 (15.93-35.52) ***	24.325 (14.24-31.97)	12.62 (10.63-17.05)	20.21 (11.67-25.14)	23.58 (9.30-27.93)	24.45 (13.83-28.12)
Adipsin (mcg/mL)	40.59 (31.20-47.87) * ** ***	27.83 (20.44-36.18)	32.745 (23.95-40.24)	33.43 (26.76-43.92)	27.04 (19.260-40.005)	27.9 (21.33-37.35)
Platelet factor 4 (mcg/mL)	27.70* (21.4-35.5)	23.10 (17.04-36.03)	21.29* (13.11-24.47)	29.81 (12.81-57.30)	13.90** (8.97-21.76)	21.77 (14.67-47.52)

Note. Data are presented as the % and median Me ($Q_{0.25}$-$Q_{0.75}$) for continuous non-normally distributed variables; *, statically significant groups of patients with atrial fibrillation with a group of healthy volunteers; **, statically significant difference between women and men in the group; ***, $p < 0,05$, statically significant within the group 1 vs group 2.

upon their activation. The content of platelet factor 4 in women in both groups of patients exceeded the value of this indicator in healthy women; no gender differences were found in the groups of patients with atrial fibrillation. However, in the group of healthy volunteers, the level of platelet factor 4 in women was lower than in healthy men. PF4 has high antiheparin activity, as well as the ability to potentiate the aggregation of platelets and erythrocytes. Correlation analysis in patients with thrombosis of the left atrial appendage, revealed a positive relationship between hsC-reactive protein with the size of the left atrium ($r = 0.77$, $p \leq 0.05$). Also, in the group of women with atrial fibrillation and with developed TC, there were statistically significant positive correlations of platelet factor 4 with the parameters of ADP and adrenaline-induced platelet aggregation ($r = 0.94$ and $r = 0.88$, respectively) $p < 0.05$ and inverse relationship of L-selectin concentration with ADP and adrenaline-induced aggregation ($r = -0.82$ and $r = -0.82$, respectively) $p < 0.05$. The level of fetuin A negatively correlated with adrenaline-induced platelet aggregation ($r = -0.90$, $p < 0.05$). Correlation analysis also demonstrated the existence of a relationship between the studied biomarkers and indicators of lipid metabolism. Thus, in the group of men with thrombosis, the level of fetuin A was negatively correlated with the concentration of total cholesterol in blood serum ($r = -0.64$, $p < 0.05$). The concentration of platelet factor 4 had a negative relationship with the level of HDL cholesterol ($r = -0.90$), and there was also a positive relationship with a high correlation

coefficient between the atherogenic index and the size of the left atrium ($r = 0.94$; $p < 0.05$).

The study revealed an imbalance of pro- and anti-inflammatory mediators, as well as gender differences in the content of inflammatory biomarkers and thrombosis markers in groups of patients with atrial fibrillation, as well as their differences compared to healthy volunteers. The most pronounced changes were found in women with thrombotic complications. It is known that in response to the electrical instability of the myocardium, the nervous and endocrine systems change their properties. Heart rhythm disturbances occur under the influence of various pathological conditions, as a result of which the neurohumoral mechanisms of homeostasis are activated. Since the nervous and endocrine systems complement each other, their restructuring triggers the immune system, which in turn can affect the neurohumoral system [1, 2]. Among the biological and immunological markers used to assess active inflammation, a special role is given to C-reactive protein, the protein of the acute phase of inflammation. In our study, the level of hsCRP was significantly increased in all the patients compared to healthy volunteers. In our opinion, these data coincide with other authors' observation that inflammatory processes play a significant role in the onset, maintenance, and preservation of AF [2].

Most cardiovascular diseases are accompanied by an imbalance between the synthesis of pro- and anti-inflammatory mediators. Fetuin A is a negative acute phase protein, and can be considered as a link between chronic inflammation and cardiovascular diseases. Fetuin A is considered to be an anti-inflammatory mediator involved in macrophage deactivation, antifibrotic activity and inhibition of apoptosis of vascular smooth muscle cells, has a proatherogenic effect, increasing insulin resistance, inhibits the production of pro-inflammatory cytokines TNFα and TGF-b, in the vascular system is an inhibitor of the formation of hydroxyapatites in the vascular system. A decrease in its content in the blood is a risk of cardiovascular calcification [3]. Studies investigating the role of fetuin A in cardiovascular disease provide conflicting results. Thus, it was shown that in patients with metabolic syndrome, fetuin A levels positively correlate with CRP, and higher biomarker levels are associated with an increased risk of myocardial infarction and ischemic stroke [4]. Other studies have shown that low concentrations of fetuin A can increase inflammation and overproduction of cardiotoxic cytokines such as tumor necrosis factor [10]. Studies conducted exclusively on patients with coronary artery disease indicate an association between low levels of fetuin A and mitral aortic calcification and stenosis [3]. In our study, a low level of fetuin A in men with thrombosis was negatively associated with lipid metabolism, and a decrease in the level of fetuin A in women with thrombotic complications negatively correlated with an increase in platelet aggregation activity. The effect of fetuin A appears to differ depending on the patient cohort studied, suggesting the need for further study of its role in various cardiovascular diseases.

L-selectin plays a key role in the adhesion of leukocytes to activated endothelium and their migration across the vascular barrier to the lymphoid tissue or area of inflammation. Participating in the regulation of selectin-dependent activation and adhesion of leukocytes, cell adhesion molecules function in various physiological and pathological processes, including the development of cardiovascular diseases. It is known that the level of soluble L-selectin is affected by inflammatory processes in the vascular wall. Circulating L-selectin maintains functional activity by preventing the interaction of leukocytes with L-selectin ligands on endothelial cells, which confirms the hypothesis that circulating L-selectin plays a protective role in the inflammatory process [5].

This hypothesis is consistent with the decrease in the amount of soluble L-selectin in the blood serum obtained in our study in women with atrial fibrillation and thrombotic complications and a negative relationship between its content and platelet aggregation activity. As is known, platelets take the most important and direct part in the reactions of hemostasis and thrombosis. Platelet activation leads to aggregation and exocytosis of the contents of the granules, the production of immunomodulatory molecules. One of the secreted factors is platelet factor 4, a positively charged glycoprotein of the alpha granule of platelets. An increase of the platelet factor 4 content is one of the markers of intravascular activation of platelet hemostasis [7]. Thus, inflammatory factors can contribute to the onset and maintenance of AF, causing structural and electrical atrial remodeling. An increase or decrease in the activity of the interactions between the inflammatory processes and the coagulation system can lead to the fact that coagulation and thrombosis become pathological factors, contributing to the development and progression of diseases.

Conclusion

Our data suggest that low levels of fetuin A and L-selectin, with a simultaneous increase in the content of CRP and platelet factor 4, lead to an increase in prothrombogenic potential and a change in the balance of pro- and anti-inflammatory mediators towards increased inflammation, which plays a role in the pathophysiology of thrombotic events complications in female patients with atrial fibrillation. Thus, our data suggest that the pathophysiological factors for the occurrence of thrombotic complications in atrial fibrillation may differ in women and men. This argues for further detailed and in-depth studies of sex differences in atrial fibrillation to support a gender-based personalized medicine approach.

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Авторы:

Огуркова О.Н. *— к.м.н., научный сотрудник отделения клинической лабораторной диагностики, Научно-исследовательский институт кардиологии — филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Лугачёва Ю.Г. *— к.м.н., врач клинической лабораторной диагностики клинико-диагностической лаборатории, Научно-исследовательский институт кардиологии — филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Драгунова М.А. *— к.м.н., научный сотрудник лаборатории высоких технологий диагностики и лечения нарушений ритма сердца, Научно-исследовательский институт кардиологии — филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Ситкова Е.С. *— к.м.н., старший научный сотрудник лаборатории высоких технологий диагностики и лечения нарушений ритма сердца, Научно-исследовательский институт кардиологии — филиал ФГБНУ «Томский национальный исследовательский медицинский центр Российской академии наук», г. Томск, Россия*

Authors:

Ogurkova O.N., *PhD (Medicine), Research Associate, Department of Clinical Laboratory Diagnostics, Cardiology Research Institute, Branch of Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russian Federation*

Lugacheva Yu.G., *PhD (Medicine), Doctor of Clinical Laboratory Diagnostics, Clinical Diagnostic Laboratory, Cardiology Research Institute, Branch of Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russian Federation*

Dragunova M.A., *PhD (Medicine), Research Associate, Laboratory of High Technologies for Diagnostics and Treatment of Cardiac Arrhythmias, Cardiology Research Institute, Branch of Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russian Federation*

Sitkova E.S., *PhD (Medicine), Senior Research Associate, Laboratory of High Technologies for Diagnostics and Treatment of Cardiac Arrhythmias, Cardiology Research Institute, Branch of Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russian Federation*

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