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Beta-adrenergic receptor reactivity of erythrocyte membranes in patients with left or right atrial dilatation against the background of atrial fibrillation

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ABSTRACT

Hyperactivation of the sympathoadrenal system (SAS) leads to desensitization of β1-adrenergic receptors (β1-AR). This contributes to aggravation of myocardial contractile dysfunction and development of arrhythmias, including atrial fibrillation (AF). An indirect indicator of the viability of β1-AR is β-adrenergic receptor reactivity of erythrocyte membranes (β-ARM).

Aim. To evaluate β-ARM in patients with different forms of AF, including left (LAD) or right (RAD) atrial dilation.

Materials and methods. The sample included 38 patients, 65.8% of whom had paroxysmal AF, 21% had persistent AF, and 13.2% had long-standing persistent AF. All patients received surgical treatment for AF by radiofrequency ablation or cryoablation. LAD was detected in 39.4% of patients, RAD – in 34.2% of patients. Beta-ARM was determined before treatment, as well as at 3 days and at 12 months after ablation.

Results. The groups of patients with different forms of AF, as well as patients with LAD / RAD and without it showed comparable values of β-ARM at different measurement periods. In the group of patients without LAD / RAD, β-ARM increased 3 days after ablation compared to β-ARM before the treatment (p = 0.002 / p = 0.004) and returned to the pre-treatment level after 3 months. At the same time, in the group of patients with LAD / RAD, β-ARM did not significantly change before the ablation and in different periods after it.

Conclusion. In patients with AF without LAD / RAD, we detected an increase in β-ARM 3 days after the ablation compared to the level before the treatment and a decrease in the intensity of SAS 3 months after the surgery. In the presence of LAD / RAD, no changes in the β-ARM were revealed.

Keywords: beta-adrenergic receptor reactivity of erythrocyte membranes, atrial fibrillation, atrial dilatation

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Conformity with the principles of ethics. All study participants signed an informed consent. The study was approved by the local Ethics Committee at Cancer Research Institute of Tomsk NRMC (Protocol No. 208 of 20.01.2021).

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β-адренореактивность мембран эритроцитов у пациентов с дилатацией левого или правого предсердий на фоне фибрилляции предсердий

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РЕЗЮМЕ

Гиперактивация симпатоадреналовой системы (САС) приводит к десенситизации β1-адренорецепторов (β1-АР). Это способствует усугублению сократительной дисфункции миокарда и развитию аритмий, в том числе фибрилляции предсердий (ФП). Косвенным показателем состоятельности β1-АР является β-адренореактивность мембран эритроцитов (β-АРМ).

Цель: оценка β-АРМ у пациентов с разными формами ФП, в том числе с дилатацией левого (ДЛП) или правого (ДПП) предсердия.

Материалы и методы. В выборку включены 38 пациентов, из них 65,8% с пароксизмальной, 21% с персистирующей, 13,2% с длительно персистирующей формами ФП. Всем пациентам проведено оперативное лечение ФП методом радиочастотной или криоаблации. ДЛП выявлена у 39,4% пациентов, ДПП – у 34,2% пациентов. В-АРМ определяли до лечения, через 3 сут, 3 и 12 мес после аблации.

Результаты. Группы пациентов с разными формами ФП, а также пациенты с ДЛП/ДПП и без нее показали сопоставимые значения β-АРМ на разных сроках измерения. В группе без ДЛП/ДПП β-АРМ повышалась через 3 сут после аблации по сравнению с β-АРМ до лечения (p = 0,002/p = 0,004) и через 3 мес вернулась к уровню до лечения. В то же время в группе пациентов с ДЛП/ДПП β-АРМ значимо не менялась до и в разные периоды после аблации.

Заключение. У пациентов с ФП без ДЛП/ДПП выявлено повышение β-АРМ через 3 сут после аблации по сравнению с уровнем до лечения и снижение напряженности САС через 3 мес. При наличии ДЛП/ДПП динамика в β-АРМ отсутствовала.

Ключевые слова: β-адренореактивность мембран эритроцитов, фибрилляция предсердий, дилатация предсердий

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Cardiac rhythm disturbances are some of the most common problems in cardiology practice. Arrhythmias are associated with an increased risk of cardiovascular complications, lead to a decline in the quality of life, disability, and high mortality [1]. Currently, atrial fibrillation (AF) is one of the most common cardiac rhythm disturbances. Patients with AF experience an observable decline in the quality of life, exercise

tolerance; at the same time, left ventricular dysfunction appears and / or progresses with the development of heart failure in patients with AF [2].

It is known that the development of cardiovascular diseases, including cardiac rhythm disturbances, is accompanied by a persistent increase in the activity of the sympathoadrenal system (SAS). The level of catecholamines (adrenaline and norepinephrine) increases in the blood and myocardium, and it can affect the number and functional state of β1-adrenergic receptors (β1-AR) in cardiomyocytes [3].

Hyperactivation of the SAS leads to desensitization of β1-AR and a decrease in the number of receptors on the membrane of cardiomyocytes, which contributes to aggravation of myocardial contractile dysfunction [4]. This, in turn, can lead to a further increase in sympathetic activation, thereby forming a vicious cycle [5].

Evaluation of the functionality of β1-AR and the SAS activity is important for predicting the severity of the course of cardiovascular diseases, including cardiac rhythm disturbances. In particular, based on this approach, a method for predicting ventricular tachycardia in patients with coronary heart disease has been developed [6]. The β-adrenergic receptor reactivity of erythrocyte membranes (β-ARM) is an indirect indicator of the SAS activity. It is determined by the distribution density of β-AR on cell membranes, the degree of their affinity with plasma catecholamines, and the concentration of catecholamines. The method for evaluating β-ARM is based on studying the effect of various adrenergic agents on osmotic resistance of erythrocytes. A β-blocker, which binds to β-AR of the cell membrane and reduces the degree of hemolysis, is used [4].

Thus, the **aim** of this study was to evaluate β-ARM in patients with different types of AF, including those with left or right atrial dilation.

MATERIALS AND METHODS

The study sample included 38 patients (25 (65.8%) men and 13 (34.2%) women) admitted to the Department of Cardiac Pacing and Heart Arrhythmia Surgical Treatment of Cardiology Research Institute, Tomsk National Research Medical Center (NRMC) of the Russian Academy of Sciences. The age in the sample was 49 (26; 77) years. All clinical and laboratory studies were conducted in accordance with the ethical standards of the Biomedical Ethics Committee and the 1964 Declaration of Helsinki and its subsequent amendments.

All patients were diagnosed with atrial fibrillation (AF) based on the results of ECG and daily monitoring [7]. All patients underwent surgical treatment for AF using radiofrequency ablation (RFA) or cryoballoon ablation (CBA) according to the generally accepted method. The intervention included pulmonary vein antrum isolation with a circular electrode and a complete block of atrio – venous electrical conduction.

The clinical characteristics of the patients are presented in Table 1. Before surgical treatment of AF, the patients underwent an echocardiography during the examination. Echocardiography was performed using a Philips HD15 device (Netherlands) from standard positions with an evaluation of the size of the heart chambers and the left ventricular (LV) ejection fraction using the Simpson method. Some patients, in addition to AF, had other cardiac rhythm disturbances: 3 (7.9%) patients – ventricular extrasystole, 1 (2.6%) patient – supraventricular extrasystole, 2 (5.3%) patients – first-degree atrioventricular block.

Table 1

Clinical characteristics of patients, *n* (%)

Parameter	Value
Paroxysmal/persistent/long-standing persistent AF, *n* (%)	25 (65.8) / 8 (21) / 5 (13.2)
RFA / CBA, *n* (%)	31 (81.6) / 7 (18.4)
AF rhythm at admission, *n* (%)	18 (47.4)
Chronic heart failure, NYHA class I/II/III, *n* (%)	11 (28.9) / 3 (7.9) / 3 (7.9)
Coronary heart disease, *n* (%)	7 (18.4)
Essential hypertension, *n* (%)	22 (57.9)
Diabetes mellitus, *n* (%)	1 (2.6)
Obesity, *n* (%)	13 (34.2)
Left ventricular ejection fraction, %, *Me* (Q_1–Q_3)	65.5 (59.0; 69.0)
End-systolic volume, ml, *Me* (Q_1–Q_3)	34 (29; 46)
End-diastolic volume, ml, *Me* (Q_1–Q_3)	104 (89; 119)
Left ventricular sphericity index, *Me* (Q_1–Q_3)	0.54 (0.51; 0.56)
Left atrial dilation, *n* (%)	15 (39.4)
Right atrial dilation, *n* (%)	13 (34.2)
Left ventricular dilation, *n* (%)	3 (7.9)

Note: FC – functional class.

In order to determine β-ARM, venous blood samples were taken from patients in a vacutainer with EDTA before ablation and 3 days, 3 months, and 12 months after it. We used the commercial kit "B-ARM-Agat" (Agat-Med LLC, Russia) in accordance with the manufacturer's protocol. The method is based on the fact that the hemolysis of erythrocytes placed in a hypoosmotic medium is inhibited in the presence of a β-blocker. The value of β-ARM was calculated using the formula: (Eo1 + Eo2)/(Ek1 + Ek2) x 100%, where β-ARM is the value

of the adrenergic receptor reactivity; Eo1 and Eo2 are optical densities of experimental samples; Ek1 and Ek2 are optical densities of control samples.

Statistical analysis was carried out using the SPSS, version 13 software (IBM, USA). Quantitative data were previously checked for normality of distribution using the Shapiro – Wilk test. Further analysis of quantitative variables was performed using the Mann – Whitney test or the Kruskal – Wallis test. The analysis of dependent data was performed using the Wilcoxon test. The results were presented as the median and the interquartile range Me (Q_1–Q_3). The strength of the linear relationship between quantitative parameters was assessed using the Spearman's rank correlation coefficient r. The relationship between qualitative data was determined using the Pearson's $\chi 2$ test or the two-tailed Fisher's exact test. The differences were statistically significant at $p < 0.05$.

RESULTS

The changes in β-ARM were evaluated before ablation in 37 patients, 3 days after ablation – in 35 patients, 3 months after ablation – in 17 patients, and 12 months after ablation – in 4 patients. Beta-ARM was 19.7% (12.9; 27.5), 24.1% (15.1; 32.1), 20.3% (9.3; 29.3), and 32.5% (20.0; 43.2), respectively. There was a slight β-ARM increase 3 days after ablation compared to β-ARM before the treatment (Figure), but the significance level was $p = 0.060$. After 3 months, the β-ARM value was similar to the level before ablation ($p = 0.758$). After 12 months, the level of β-ARM increased by 1.5 times compared to the value before the treatment, however, due to the small sample of patients at this point, the differences did not show statistical significance ($p = 0.465$). We did not include the 12-month point in the further analysis due to a small sample size.

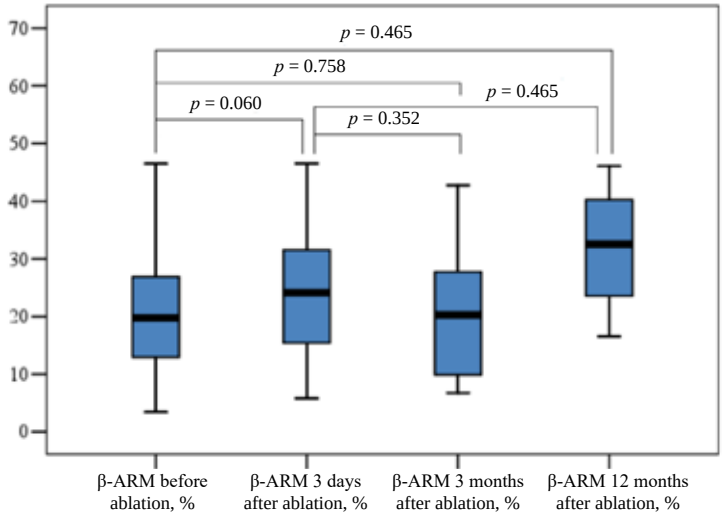

Figure. Changes in β-ARM before and after ablation

In the study sample, a direct linear correlation was found between β-ARM before ablation and end-systolic volume ($r = 0.331$, $p = 0.046$), as well as left ventricular sphericity index ($r = 0.436$, $p = 0.007$). However, there was no significant linear relationship between β-ARM before ablation and left ventricular ejection fraction (LVEF) in patients with AF ($r = –0.169$, $p = 0.316$).

Beta-ARM before ablation, 3 days and 3 months after ablation was comparable between the groups of patients with different types of AF. In addition, β-ARM did not change significantly after ablation compared to the point before therapy in groups with different types of AF. Patients with persistent and long-standing persistent AF compared to patients with paroxysmal AF showed an expected decrease in LVEF and an increase in end-systolic volume (ESV) and end-diastolic volume (EDV). The results are presented in Table 2.

In the studied sample, left atrium dilation (LAD) was detected in 5 (20%) of 25 patients with paroxysmal AF, in 6 (75%) of 8 patients with persistent AF, and in 4 (80%) of 5 patients with long-standing persistent AF ($p = 0.003$). Patients with LAD had higher ESV, EDV, and LVSI (Table 3).

There were no significant differences in β-ARM both before ablation and at different periods after the treatment between the groups of patients with and without LAD (Table 3). In the group without LAD, a significant increase in β-ARM was detected

3 days after ablation compared to β-ARM before the treatment (p = 0.002), and 3 months after ablation, β-ARM was similar to the level before the treatment (p = 0.678). At the same time, in the group of patients with LAD, β-ARM did not change significantly before and in different periods after ablation.

Table 2

Echocardiography parameters and β-adrenergic receptor reactivity of erythrocyte membranes in patients with different types of atrial fibrillation, *Me* (Q_1; Q_3)

Parameter	Paroxysmal AF	Persistent AF	Long-standing persistent AF	p
LVEF, %	67 (64; 70)	64 (47; 67)	62 (44; 63)	0.045
ESV, ml	32 (27; 38)	38 (31; 71)	48 (46; 76)	0.007
EDV, ml	96 (86; 108)	112 (96; 127)	126 (121; 131)	0.007
LV SI	0.54 (0.52; 0.56)	0.57 (0.52; 0.59)	0.56 (0.56; 0.58)	0.394
β-ARM before ablation, %	24.1 (14.2; 27.5)	15.1 (11.0; 26.3)	17.1 (16.2; 17.8)	0.476
β-ARM 3 days after ablation, %	24.6 (17.4; 36.6)	16.0 (11.3; 31.5)	21.6 (15.1; 23.3)	0.438
β-ARM 3 months after ablation, %	18.9 (8.5; 26.7)	21.3 (15.1; 40.9)	26.1 (11.9; 40.4)	0.664

Note: LVSI – left ventricular sphericity index.

Table 3

Echocardiography parameters and β-adrenergic receptor reactivity of erythrocyte membranes during left atrial dilation, *Me* (Q_1; Q_3)

Parameter	With LA dilation	Without LA dilation	p
LVEF, %	64 (47; 67)	67 (64; 70)	0.064
ESV, ml	39 (32; 77)	32 (28; 38)	0.024
EDV, ml	118 (97; 140)	98 (86; 112)	0.013
LVSI	0.57 (0.55; 0.60)	0.54 (0.52; 0.56)	0.048
β-ARM before ablation, %	18.7 (15.7; 33.0)	17.2 (12.0; 24.6)	0.171
β-ARM 3 days after ablation, %	20.8 (13.5; 32.1)	24.4 (16.7; 33.8)	0.474
β-ARM 3 months after ablation, %	21.3 (10.9; 34.0)	18.9 (8.8; 25.8)	0.606

Among all patients included in the study, right atrium dilation (RAD) was detected in 5 (20%) patients with paroxysmal AF, in 4 (50%) patients with persistent AF, and in 4 (80%) patients with long-standing persistent AF (p = 0.020). Patients with RAD had lower LVEF, higher ESV, EDV, and LVSI (Table 4). Also, β-ARM before ablation was 1.4 times higher in the patients with RAD than in those without dilation before ablation, but the difference did not reach statistical significance (p = 0.07). With RAD, β-ARM values remained at the same level both before ablation and after therapy at different times.

At the same time, in the group without RAD, a statistically significant increase in β-ARM at 3-days point was detected compared to β-ARM before ablation (p = 0.004), and then a return of β-ARM to the pre-ablation level after 3 months was noted (p = 0.959).

Table 4

Echocardiography parameters and β-adrenergic receptor reactivity of erythrocyte membranes during RA dilation

Parameter	With RA dilation	Without RA dilation	p
LVEF, %	62 (46; 66)	67 (64; 70)	0.030
ESV, ml	46 (31; 77)	32 (28; 38)	0.022
EDV, ml	121 (96; 145)	98 (86; 109)	0.018
LVSI	0.57 (0.56; 0.60)	0.54 (0.51; 0.56)	0.012
β-ARM before ablation, %	23.6 (15.9; 36.1)	17.2 (12.0; 24.6)	0.070
β-ARM 3 days after ablation, %	22.9 (14.3; 37.1)	23.8 (15.6; 30.9)	0.945
β-ARM 3 months after ablation, %	22.4 (10.9; 34.0)	19.6 (8.8; 25.8)	0.601

DISCUSSION

It is well known that SAS hyperactivation is a risk factor for cardiac rhythm disturbances. Elevated levels of catecholamines stimulate β1-AR of cardiomyocytes, which leads to activation of adenylate cyclase, an increase in the content of intracellular cAMP, and activation of protein kinase A. Hyperphosphorylation of ryanodine receptors promotes leakage of Ca^{2+} from

the sarcoplasmic reticulum, resulting in a decrease in the cardiac contractile function and an increased risk of arrhythmia [8].

Hyperactivation of the SAS also leads to pathological remodeling of β-AR. There is a dissociation of the receptor from G-proteins and a decrease in the density of receptors on the cell membrane up to cessation of receptor synthesis, which leads to progression of myocardial contractile dysfunction. An increased load on the left ventricle inevitably leads to an increase in pressure and overload of the atria, causing their subsequent dilation [3, 5].

Beta-ARM makes it possible to indirectly evaluate the functional state of β-AR. In most healthy individuals, this parameter is within the range of 2.0–20.0%, which indicates an increase in the osmotic resistance of erythrocytes as a result of blocking β-AR with an adrenergic blocker. An increase in β-ARM indicates receptor desensitization [4].

In our sample of patients with AF, β-ARM did not exceed the conditional norm before ablation. On day 3 after ablation, a slight increase in β-ARM values was observed compared to the level before ablation (although the significance level was not reached), which can be regarded as a response of the SAS to surgical intervention. After 3 months, β-ARM returned to the values before ablation. It can be assumed that, in general, there was no significant desensitization of β-AR in the study sample. However, in the studied sample, a direct linear correlation was found between β-ARM before ablation and ESV, as well as LVSI. In the group of patients with a long-standing persistent AF, the ESV values exceeded the limits of the reference values (> 43 ml / m^2) [9], which, together with an increase in β-ARM, indicates a deterioration in the LV systolic function.

It has been shown that the values of β-ARM significantly exceed the limits of the conditional norm in patients with myocardial infarction (46.8%), and the values turned out to be even higher in patients with advanced heart failure (58.8%) [10]. However, in the case of cardiac rhythm disturbances, lower levels of β-ARM also cannot be considered as an absolutely favorable indicator. Beta-ARM less than 51.26% and lower in patients with coronary heart disease is an independent predictor of ventricular tachycardia [6].

In our sample of patients with AF, the values of β-ARM in groups with different types of AF were comparable before ablation, as well as 3 days and 3 months after ablation. In addition, there were no significant changes in β-ARM in each group of patients with different types of AF.

At the same time, patients with persistent and long-standing persistent AF had reduced LVEF and higher ESV and EDV compared to these parameters in patients with paroxysmal AF, which indicates a deterioration in the LV systolic function. In addition, the group of patients with paroxysmal AF had the lowest prevalence of LAD and RAD.

It is well known that atrial dilation can create a substrate for electrophysiological myocardial remodeling, which, together with progressive structural remodeling, forms the basis for the onset of AF. The presence of this rhythm disturbance, in turn, contributes to further atrial remodeling [11].

In the studied sample, in groups of patients without atrial dilation, an increase in β-ARM above the conditional norm was detected 3 days after ablation. This can be explained by the normal response of the SAS to stress. After 3 months, the level of β-ARM again returned to the level before ablation, while not exceeding the limits of the conditional norm, which makes it possible to assess the restoration of the functional activity of β-AR.

However, in groups of patients with LAD / RAD, β-ARM values remained at the same level both before ablation and after the therapy at different times, while the values were at the upper limit or above the conditional norm. According to the feedback mechanism, which accounts for desensitization, the smaller the number of receptors on cell membranes, the higher the level of catecholamines in the blood [4]. The values of β-ARM in patients with atrial dilation may be due to increased activity of the SAS and indicate protective desensitization that maintains myocardial contractile reserve within the conditions of its structural changes.

Thus, the evaluation of the functioning of β1-AR and the SAS activity is of great importance for predicting the severity of the course of cardiovascular diseases.

CONCLUSION

Thus, higher values of β-ARM before ablation directly correlated with higher values of ESV and LVSI, which indicates a deterioration in LV systolic function. However, there was no correlation between β-ARM before ablation and LVEF. Patients with different types of AF had comparable levels of β-ARM. Patients with AF without left / right atrial dilation

showed an increase in β-ARM 3 days after ablation compared to the level of β-ARM before the treatment and a decrease in SAS tension after 3 months. In the presence of left / right atrial dilation in patients with AF, there were no changes in β-ARM.

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Authors' contribution

Muslimova E.F. – analysis and interpretation of the data, critical revision of the manuscript for important intellectual content. Popova V.O. – analysis and interpretation of the data, justification of the manuscript. Rebrova T.Yu. – analysis and interpretation of the data. Archakov E.A. – analysis and interpretation of the data, critical revision of the manuscript for important intellectual content. Batalov R.E., Afanasiev S.A. – conception and design, final approval of the manuscript for publication.

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