

ЛАБОРАТОРНЫЙ БИОМАРКЕР ГАЛЕКТИН-3 В ДИАГНОСТИКЕ ВОСПАЛИТЕЛЬНЫХ ИЗМЕНЕНИЙ МИОКАРДА У ПАЦИЕНТОВ С ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ

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Резюме. В настоящее время фибрилляция предсердий (ФП) является одним из наиболее распространенных нарушений сердечного ритма. Многочисленные данные свидетельствуют о значительном вкладе воспалительных изменений миокарда в развитии и прогрессировании ФП. Поиск новых лабораторных биомаркеров, позволяющих оценить активность воспалительных процессов в миокарде, а также изучение их диагностической значимости для неинвазивной диагностики у пациентов с ФП представляется актуальным. В этой связи целью работы явилось изучить особенности сывороточного содержания биомаркера Гал-3 и выявить его взаимосвязь с воспалительными изменениями миокарда у пациентов с ФП. В зависимости от результатов гистологических исследований пациенты были разделены на 2 группы: 1-я группа – с морфологически верифицированным активным лимфоцитарным миокардитом (АЛМ), 2-я – с признаками лимфоцитарной инфильтрации (ЛИ). Анализ частоты выявления и степени выраженности воспалительного процесса в миокарде показал, что активность 4-5 баллов обнаружена только в группе 1, большинство пациентов в группе 2 имели степень активности воспалительного процесса 1 балл. У всех пациентов с ЛИ показано слабое интерстициальное воспаление. В группе с АЛМ регистрировали умеренное и выраженное интерстициальное воспаление, по результатам ИГХ исследования обнаружено высокое количество клеток CD3⁺ и CD45⁺ в сравнении с группой 2 ($p < 0,001$). Не выявлено значимых межгрупповых отличий сывороточного уровня Гал-3. При этом в группе 1 показано значимое снижение Гал-3 через 6 месяцев после аблации ($p = 0,028$). У пациентов с АЛМ выявлены положительные корреляции Гал-3 с такими критериями миокардита, как степень выраженности воспалительного процесса, вовлеченность эндокарда. У пациентов группы 1 показана ассоциация сывороточного содержания Гал-3 с уровнем CD68⁺ ($R = 0,48$ $p = 0,030$). В группе 2 выявлена корреляция между уровнем Гал-3 через 6 месяцев после РЧА с инфильтрацией CD45⁺ клетками ($R = 0,69$ $p = 0,003$). Таким образом, у пациентов с ФП и признаками активного

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лимфоцитарного миокардита установлены значимые ассоциации между биомаркером Гал-3 и показателями воспалительных изменений в миокарде, что подтверждает важную роль Гал-3 в качестве участника воспалительного процесса.

Ключевые слова: фибрилляция предсердий, воспалительные изменения, миокардит, инфильтрация, лабораторная диагностика, галектин-3

LABORATORY BIOMARKER GALECTIN-3 IN THE DIAGNOSTICS OF MYOCARDIAL INFLAMMATORY CHANGES IN PATIENTS WITH ATRIAL FIBRILLATION

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Abstract. Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. Numerous data indicate a significant contribution of myocardial inflammatory changes in the development and progression of AF. The search for new laboratory biomarkers to assess the activity of myocardial inflammatory processes, and the study of their diagnostic significance for noninvasive diagnosis in patients with AF is relevant. Therefore, the aim was to study the features of the serum level of the biomarker Gal-3 and to identify its relationship with inflammatory changes in the myocardium in patients with AF. Depending on the results of histological studies, the patients were divided into 2 groups: group 1 – with morphologically verified active lymphocytic myocarditis (ALM), group 2 – with lymphocytic infiltration (LI). Analysis of the frequency of detection and severity of the inflammatory process in the myocardium showed that activity of 4-5 scores was detected only in group 1. In 2nd group, activity of the inflammatory process in most patients was 1 score. All patients with LI mild interstitial inflammation were showed. In the ALM group moderate and severe interstitial inflammation was detected. A high number of CD3⁺ and CD45⁺ cells were found in 1st group compared to group 2 ($p < 0.001$).

There were no significant intergroup differences in the serum level of Gal-3. At the same time, in 1st group showed a significant decrease in Gal-3 in 6 months after treatment ($p = 0.028$). Positive correlations of Gal-3 with the severity of the inflammatory process and endocardial involvement were revealed in patients with ALM. The association of serum Gal-3 levels with CD68⁺ levels in 1st group was detected ($R = 0.48$, $p = 0.030$). In 2nd group, a correlation between the level of Gal-3 in 6 months after ablation with infiltration of CD45⁺ cells was found ($R = 0.69$, $p = 0.003$). Thus, in patients with AF and active lymphocytic myocarditis, significant associations were established between biomarkers of Gal-3 and inflammatory changes in the myocardium. This confirms the important role of Gal-3 as a participant in the inflammatory process.

Keywords: atrial fibrillation, inflammation changes, myocarditis, infiltration, laboratory diagnostics, galectin-3

Introduction

Atrial fibrillation (AF) is one of the most common and clinically significant cardiac arrhythmias. Currently, the prevalence of AF in the adult population ranges from 2 to 4% and increases with age [11]. Despite the rapid development of interventional and pharmacological treatment, the number of arrhythmias is steadily increasing. This increases cardiac mortality, morbidity, duration of hospitalization and overall health system costs.

Currently in population cohort studies have been identified many independent risk factors for

AF. Among them, diabetes, arterial hypertension, coronary heart disease, hypertrophic and dilated cardiomyopathy, congestive heart failure and valve defects [15]. However in 3-11% of cases, the etiology of AF cannot be established. In such patients, AF develops in the absence of concomitant diseases, clinical- instrumental, functional and laboratory research methods do not reveal the causes of AF. In these cases they talk about an idiopathic form of AF. The absence of an obvious cause of idiopathic AF can complicate the choice of medical and surgical treatment tactics, reduce the effectiveness

of radiofrequency ablation, and have unpredictable effects on drug therapy [3].

It is known that various pathological processes underlie the occurrence of AF. Numerous clinical and experimental data indicate a significant contribution of inflammatory changes in the myocardium to the initiation, maintenance and progression of AF [7, 10].

Currently various research methods are widely used to diagnose inflammatory changes in the myocardium. Among them instrumental methods of radionuclide imaging and single-photon emission computed tomography with ^{99m}Tc -pyrophosphate, laboratory studies of nonspecific markers of inflammation. However, the diagnostic capabilities of these methods in determining signs of myocardial inflammation are limited by insufficient specificity and sensitivity, high cost, and therefore cannot be widely used in everyday clinical practice.

The most accurate diagnostic method is to perform a lifetime endomyocardial biopsy (EMB) [2]. EMB is a reliable method for determining inflammatory myocardial disease based on histological and immunohistochemical studies (IHC) [1]. Despite the obvious advantages of EMB, this method is associated with a number of significant disadvantages, such as limited indications for the procedure and a high risk of complications. In this regard, the search for new methods of noninvasive diagnosis of inflammatory changes in the myocardium is relevant.

An analysis of literature data over the past decade has shown the widespread use of laboratory biomarkers, reflecting various aspects and pathogenetic mechanisms of the development and progression of AF [4, 8]. Recently the role and prognostic value of the biomarker galectin-3 (Gal-3) has been actively studied in AF. Gal-3 is known to induce myocardial fibrosis, enhancing myofibroblast proliferation, extracellular matrix accumulation and macrophage infiltration, stimulating the signaling pathway of transforming growth factor β [13]. Along with this, there is no data on the role of Gal-3 in the diagnosis of myocardial inflammatory changes.

Thus, the search for new laboratory biomarkers for the noninvasive diagnosis of myocardial inflammatory processes and the determination of their diagnostic significance in patients with AF is relevant and necessary for understanding the pathogenetic mechanisms of the development and progression of AF.

Objective: to study the features of the serum level of the Gal-3 and to identify its relationship with myocardial inflammatory changes in patients with idiopathic AF.

Materials and methods

A total of 39 patients with idiopathic AF (41.0 ± 9.2 y. o.) were recruited in the prospective single-center

study. All patients underwent radiofrequency ablation (RFA) of the pulmonary veins. Endomyocardial biopsy from the right ventricle with histologic and IHC studies was performed. Histological studies were performed at the light-optical level using an AxioImager M2 Zeiss microscope. Morphological verification of myocarditis was performed in accordance with the modified Dallas criteria. The degree of inflammation activity and the severity of fibrosis were assessed using semi-quantitative histological criteria proposed for assessing morphological changes in inflammatory cardiomyopathy, taking into account the consensus of the European Society of Cardiology for the diagnosis and treatment of myocarditis [10]. An IHC study to determine the immunophenotype of infiltrate cells was performed on paraffin sections. The polyvalent detection system HRP DAB (Spring BioScience) was used to visualize the studied antigens. The calculation of CD3^+ , CD45^+ and CD68^+ cells of the infiltrate was carried out taking into account the area of sections in each fragment of the endomyocardium; the number of these cells per 1 mm^2 was calculated.

Venous blood was drawn into sterile vacutainers before surgery (T1) and 6 months after RFA (T2). Obtained blood samples have been stored at room temperature for 30 min and were centrifuged at 3000 rpm for 15 min. The serum samples have been collected and stored at -40°C until the quantitative analysis was performed. The serum levels of Gal-3 were evaluated using enzyme-linked immunosorbent assay and Human Galectin-3 Platinum ELISA test system (eBioscience, Austria).

The analysis of the obtained data was performed using the STATISTICA 10.0 software. The type of the distribution of the data was evaluated by Kolmogorov–Smirnov test. Results were presented as the median value (Me) and the interquartile range ($Q_{0.25}$ – $Q_{0.75}$) in the case of non-normal distribution. The Kruskal–Wallis rank criterion was used for pairwise comparison. Wilcoxon test was used to estimate the significance of differences in the values of the dependent parameters. The Pearson's χ^2 -criterion with the Yates correction was used to comparison of results measured in score scales. The Spearman's rank correlation coefficient (R) was calculated to assess the relationship between the parameters. A value of $p < 0.05$ was considered statistically significant in all statistical evaluations.

All patients signed an informed consent forms prior to participation in the study. The protocol of the study was approved by the local ethics committee and it was developed in compliance with the Medical Association Declaration of Helsinki “Ethical principles for medical research involving human subjects” and the “Rules of Clinical Practice in the Russian Federation”.

Results and discussion

According to the results of laboratory and instrumental studies, there are no data for organic pathology of the cardiovascular system, as well as inflammatory diseases and conditions that would cause the development of arrhythmia in patients in both groups. Depending on the results of histological and IHC studies the patients were divided into 2 groups: 1 – with active lymphocytic myocarditis (ALM) (n = 22); 2 – with lymphocytic infiltration (IL) (n = 18). Clinical and functional characteristics of the groups were comparable (Table 1). A comparative analysis of the frequency of detection and severity of the inflammatory process in the myocardium showed that the number of patients with inflammation activity 0-1 significantly differed between groups (p = 0.035, p = 0.006, respectively). In the 2nd group, activity of the inflammatory process in most patients was 1 score (55.6%). Activity 4-5 scores were detected only in group 1. An equal number of patients in 1st group had a degree of activity of 2 and 3 points (Table 2).

Analysis of the data revealed intergroup differences in the level of interstitial inflammation. All patients with LI mild interstitial inflammation (< 7 T lymphocytes/mm²) were showed. In the patients with ALM moderate and severe interstitial inflammation was detected. A high number of CD3⁺ and CD45⁺ cells were found in the 1st group compared to group 2 (p < 0.001). In the 1st group severe (> 14 T lymphocytes/mm²) interstitial inflammation was recorded in 6 patients (28.6%). In both groups, endocardial involvement was absent in most cases. Also, focal necrosis was registered in most patients: in 9 patients (42.9%) in the 1st group and 11 (61.1%) – in the 2nd group. There were no significant intergroup differences in the level of cardiomyocyte degeneration were not revealed (Table 2).

The results of the IHC study showed significant intergroup differences in infiltration by immunocompetent cells. According to the data obtained, a higher level of CD3⁺ and CD45⁺ was detected in the 1st group compared to group 2 (p < 0.001) (Table 2).

TABLE 1. CLINICAL AND INSTRUMENTAL CHARACTERISTICS OF PATIENTS DEPENDING ON THE RESULTS OF ENDOMYOCARDIAL BIOPSY

	Group 1 (n = 21)	Group 2 (n = 18)
Age, years	41 (35-49)	41.5 (38-46)
Arrhythmic history, years	4 (2-6)	4.5 (2-9)
Male, n (%)	18 (85.7%)	15 (83.3%)
Female, n (%)	3 (14.3%)	3 (16.7%)
Arrhythmia form, n (%)		
paroxysmal	5 (23.8%)	9 (50%)
persistent	7 (33.3%)	5 (27.8%)
long-standing persistent	9 (42.9%)	4 (22.2%)
Left atrium, mm	41 (36-43)	37.5 (34-44)
Right ventricle, mm	25 (21-26)	21.5 (20-26)
End diastolic size, mm	49 (46-54)	50 (48-53)
End systolic size, mm	31 (29-36)	33 (30-37)
Ejection fraction, %	65 (59-67)	65.5 (57-67)
Interventricular septum, mm	10 (9-11)	9 (8-10)
Thickness of the posterior wall of the left ventricle, mm	10 (9-10)	9 (8-10)
End diastolic volume, mL	116 (93-128)	118 (101-128)
End systolic volume, mL	37 (33-50)	42.5 (35-55)
Myocardial mass, g	182 (157-194)	171.5 (135-212)
Myocardial mass index	82 (77-97)	79.5 (69-93)
Stroke volume, mL	70 (61-79)	72 (61-81)
Mean pressure in the right ventricle, mmHg	28 (23.5-31.5)	28.5 (24-31)

TABLE 2. RESULTS OF HISTOLOGICAL, IMMUNOHISTOCHEMICAL AND LABORATORY STUDIES

	Group 1	Group 2	p
Inflammatory process activity, score	n (%)	n (%)	
0	–	5 (27.8)	0.035
1	2 (9.5)	10 (55.6)	0.006
2	5 (23.8)	2 (11.1)	0.541
3	7 (33.3)	1 (5.5)	0.081
4	5 (23.8)	–	0.082
5	2 (9.5)	–	0.538
Interstitial inflammation	n (%)	n (%)	
Weak < 7 T lymphocytes (cells/mm²)	–	18 (100)	0.000
Moderate 7 ≤ 14 T lymphocytes	15 (71.4)	–	0.000
Severe > 14 T lymphocytes	6 (28.6)	–	0.043
Endocardial involvement	n (%)	n (%)	
No detected	13 (61.9)	16 (88.9)	0.119
Availability	8 (38.1)	2 (11.1)	0.119
Necrosis	n (%)	n (%)	
No detected	3 (14.2)	5 (27.8)	0.521
Focal	9 (42.9)	11 (61.1)	0.415
Multifocal	9 (42.9)	2 (11.1)	0.066
CD3⁺	8.0 (5-11)	2.5 (0-5)	< 0.000
CD45⁺	21.0 (14-25)	10.0 (8-14)	0.008
CD68⁺	15.0 (11-22)	14.0 (10-16)	0.496
Galectin-3, ng/mL			
T1	16.8 (14.3-25.7)	17.5 (13.5-22.1)	0.686
T2	15.4 (11.7-18.0)	12.0 (10.1-16.2)	0.141

No intergroup differences were found in infiltration by CD68⁺.

There were no statistically significant intergroup differences in the serum level of Gal-3 at stages T1 and T2. In the 1st group showed a significant decrease of the Gal-3 level in 6 months after RFA ($p = 0.028$). In the 2nd group the Gal-3 level did not differ between stages.

In patients with ALM Gal-3 levels was associated with the severity of myocardial inflammatory processes ($R_{T1} = 0.52$, $p = 0.016$; $R_{T2} = 0.48$, $p = 0.031$) and interstitial inflammation ($R_{T1} = -0.53$, $p = 0.015$). In 1st group Gal-3 levels were significantly higher in patients with the identified criterion of endocardial involvement compared with patients without sign ($p_{T1} = 0.022$, $p_{T2} = 0.049$, respectively). The association of serum levels of Gal-3 with CD68⁺ levels in 1st group was shown ($R = 0.48$, $p = 0.030$). In patients with LI, a correlation between the level of Gal-3 in 6 months after RFA and the CD45⁺ cells level was found ($R = 0.69$, $p = 0.003$). There were no correlations between Gal-3 expression and histological criteria in 2nd group. However, positive correlations of infiltration by CD3⁺ and CD45⁺ cells with the activity of the inflammatory process and necrosis were revealed ($R = 0.55$, $p = 0.018$). In patients with ALM, there

were no correlations between IHC and histological criteria of inflammatory processes in the myocardium.

Numerous clinical and fundamental studies have been devoted to the study of the role of inflammation in the initiation, maintenance and progression of AF. It is believed that the presence of inflammation in the atrial tissue is crucial in the mechanisms of electrical remodeling and structural adjustment, such as a decrease in the conduction velocity, a reduction in the duration of the action potential, as well as an increase in the size of the atrium [8].

It is known that the frequency of myocarditis is from 20 to 30% of all non-coronary heart diseases [1]. Analysis of the literature data showed that, despite the small number of EMB results in patients with AF, all of them indicate a high prevalence of myocarditis. A number of studies have revealed infiltration by immunocompetent cells in the atrial myocardium of patients with isolated AF was detected, and the number of patients with active lymphocytic myocarditis reached 80% [10]. According to our results, histological signs of ALM were detected in 21 patients (53.8%) with idiopathic AF, in other cases LI was detected.

It is known that activation of T lymphocytes in peripheral blood can play an important role in the

pathogenesis of AF. In patients with AF, endocardial infiltrates containing CD45⁺, CD3⁺T lymphocytes, CD68⁺ macrophages were detected [9]. According to the authors, the T cell response mediated by a chronic inflammatory process may be part of the pathogenetic process leading to the development of cardiac arrhythmias. In our study, patients with ALM showed moderate (≥ 7 and < 14 T lymphocytes/mm²) and severe interstitial inflammation (≥ 14 T lymphocytes/mm²). In addition, according to the results of IHC studies, it was revealed that the expression of the membrane protein CD3, which is one of the main components of the T cell receptor, was significantly higher in ALM. The expression level of CD45, which is a common leukocyte antigen, was also significantly higher than in the group with LI.

According to our results, in patients with AF, infiltration of a large number of CD68⁺ macrophages into the atrial tissue was observed without significant intergroup differences. It is known that macrophages (CD68⁺ cells) regulate the development of inflammatory response and fibrosis, and can support chronic subclinical inflammation, and are involved in the development of autoimmune reactions. CD45 is a common leukocyte antigen. The expression level CD45⁺ was also significantly higher than in the group with LI. According to our results, patients with AF had infiltration of a large number of CD68⁺ macrophages into the atrial tissue without significant intergroup differences. As is known, macrophages (CD68⁺ cells) regulate the development of inflammatory response and fibrosis, can support chronic subclinical inflammation, and are involved in the development of autoimmune reactions.

The histological criterion of endocardial involvement characterizes how deep the infiltration of immunocompetent cells occurs outside the myocardium. In our study, in the group with ALM, signs of endocardial involvement, as well as multifocal necrosis, were detected more often. The presence of individual signs of myocarditis in the 2nd group may be due to the fact that AF itself is a factor provoking the development of inflammation in the atrial myocardium.

It is likely that the identified myocardial inflammatory changes are signs of an ongoing inflammatory process associated with infiltration by immunocompetent cells, and can further lead to structural restructuring, fibrosis, and the formation of new multiple diffusely located arrhythmogenic foci in the left atrium.

The possibilities of diagnosing inflammatory changes in the myocardium are currently limited. Therefore, the search for new laboratory biomarkers that will allow indirectly assess the activity of myocardial inflammatory processes, as well as the

study of their clinical and diagnostic significance in patients with AF seems relevant.

To date, there is no information on randomized trials to assess the significance and informativeness of determining biomarkers for myocarditis. According to the clinical guidelines for the diagnosis and treatment of myocarditis [1], in the absence of specific biomarkers, it is recommended to study of C-reactive protein, troponin T and I, the N-terminal fragment of the natriuretic propeptide, cardiac autoantibodies specific to myocardial tissue in the blood serum.

Gal-3 plays an important role in immune and inflammatory responses, regulating homeostasis and immune cells function. Depending on the intracellular or extracellular localization, Gal-3 can play a damaging or protective role. As a regulator of the immune response and T cell activity, Gal-3 participates in the development of autoimmunity mediated T cell [12]. Gal-3 is a well-studied biomarker associated with cardiac remodeling and unfavorable prognosis in heart failure of various etiologies. Ho et al. (2014) have demonstrated that a high level of circulating Gal-3 is associated with an increased risk of AF [6]. Along with this, there are no data on the role of Gal-3 in the diagnosis of inflammatory changes in the myocardium in patients with various forms of rhythm and conduction disturbances.

A number of studies have shown that the level of the Gal-3 in patients with AF is higher than in healthy volunteers [5, 14]. The results of our study did not reveal any differences in the Gal-3 level between patients with ALM and LI. At the same time, only in 1st group a significant decrease in Gal-3 in 6 months after RFA was shown.

According to the literature, there is information about the relationship between the level of Gal-3 in patients with AF and the severity of left atrial fibrosis, established by magnetic resonance imaging [14]. In our work in patients with ALM, positive correlations of Gal-3 with criteria of myocarditis (as the degree of severity of the inflammatory process and interstitial inflammation) were revealed. For the first time in patients with ALM was established a relationship between the serum levels of Gal-3 and the criterion of endocardial involvement.

In an experimental mouse model of acute and chronic myocarditis induced by Coxsackievirus B3, high expression of Gal-3 in macrophages, T cells and fibroblasts was shown using flow cytometry analysis [12]. The positive correlations between the level of Gal-3 and infiltration by immunocompetent cells revealed in our work and confirm the important role of Gal-3 as an active participant in the inflammatory process.

The comparatively small number of the recruited patients may be regarded as the major limitation of

our study. However, all the patients included in our study, underwent rigorous screening to correspond to the strict inclusion and exclusion criteria.

Conclusion

Thus, in patients with AF and signs of active lymphocytic myocarditis, significant associations were established between the galectin-3 biomarker and indicators of inflammatory changes in the myo-

cardium. Further studies are needed to assess the prognostic value of the level of circulating galectin-3 in the diagnosis of myocardial inflammatory changes in AF.

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