The Utility of Galectin-3 as a Diagnostics and Pharmacotherapy Monitoring Biomarker in Heart Failure

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Abstract

Aim: Development of new biomarkers, which can be used as instruments for early detection of diseases to select drug therapy and monitor its efficacy, is of great importance. The aim of this work is to assess the serum galectin-3 and N-terminal-pro brain natriuretic peptide (NT-proBNP) changes after 3 weeks of standard heart failure pharmacotherapy.

Materials and Methods: The study included 65 patients (38 women and 27 men) with New York Heart Association II-III chronic heart failure. Mean age of patients was 71.2 ± 10.4 years. According to echocardiographic study, the patients were divided into two groups: the first group (HFpEF) included patients with ejection fraction < 55% and the second group (HFrEF) consisted of patients with ejection fraction > 55%. Median baseline NT-proBNP levels were 47.5 [IQR, 27.2; 76.4] and 99.0 [IQR, 45.6; 160.2] pmol/l in HFpEF and HFrEF groups, respectively. Median baseline galectin-3 levels were 8.0 [5.4; 10.8] ng/ml in HFpEF group, and 9.7 [7.7; 16.1] ng/ml in HFrEF group.

Results: The correlation between the increased galectin-3 level and ejection fraction (r = -0.3; p = 0.04), creatinine (r = 0.3, p = 0.04), and increased plasma NT-proBNP (r = 0.3; p = 0.02) was found. By the end of the third week of the treatment period, galectin-3 levels decreased from 8.0 [IQR 5.4; 10.8] ng/ml to 6.3 [IQR 3.4; 8.7] ng/ml in HFpEF group, and from 9.7 [7.7; 16.1] ng/ml to 7.1 [5.3; 12.8] ng/ml in HFrEF group.

Conclusion: Galectin-3 can be considered as a useful biomarker for heart failure diagnostics and pharmacotherapy monitoring.

Keywords: Heart Failure; Biomarkers; Aldosterone; Galectin-3; NT-ProBNP

Introduction

Heart failure is one the major public health problems. Despite significant progress in new therapeutic methods in past decade, it remains one of the most frequent causes of mortality and morbidity. After HF diagnosis, nearly 60% of men and 45% of women will die within 5 years [1]. Thus, development of new diagnostics and treatment methods remains relevant and actual task.

Currently, BNP and NT-proBNP are the only biomarkers recommended for heart failure diagnostics and pharmacotherapy monitoring and optimization. It is known that BNP synthesis and secretion is triggered by myocardial wall stretch caused by volume and pressure

overload. Along with the myocardial wall stretch, other processes like fibrosis and inflammation play the significant role in the pathophysiology of chronic heart failure.

According to results of DEAL-HF and COACH studies, galectin-3 (Gal-3) induces the processes of cardiac fibrosis and inflammation and promotes left ventricular remodeling in patients with heart failure [2-4]. Gal-3 belongs to a family of β-galactoside binding lectins. Gal-3 binds to a number of extracellular matrix proteins, such as tenascin, fibronectin, and laminin, due to their collagen-like protein domains. Multiple cell types express Gal-3 including neutrophils, macrophages, mast cells, fibroblasts, and osteoclasts. Animal studies demonstrate that Gal-3 is secreted by activated macrophages and plays a key role in the mediation of aldosterone-dependent cardiac fibrosis [5,6].

According to several cohort studies, Gal-3 can predict the risk of major cardiovascular events, hospitalization, and mortality in patients with heart failure [7-9].

Aim of the Study

The aim of our study was to assess plasma Gal-3 levels in patients with HF NYHA II-III patients, to evaluate its correlations with clinical and echocardiographic parameters and to compare NT-proBNP and galectin-3 changes before and after pharmacotherapy.

Methods

The initial screening of our single-center, prospective, cohort clinical trial included 78 patients with chronic decompensated heart failure. A total of 79 patients with chronic decompensated heart failure underwent preliminary screening. All patients were hospitalized in I.V. Davydovsky State Clinical Hospital (Moscow). Among them, 65 patients with a diagnosed ischemic heart failure of New York Heart Association (NYHA) class II-III that matched the inclusion criteria were enrolled into the study. Among the included patients, 38 (58.5%) were women and 27 (41.5%) were men, with a mean age of 71.9 ± 9.5 years (Figure 1). All patients signed a written informed consent form. The study eligibility criteria included: age 18 years old or older with a history and clinical findings of heart failure for at least three months before screening, signed informed consent, confirmed diagnoses of HF NYHA II-III. The exclusion criteria were: history of cancer less than 5 year prior to the study, myocardial infarction, stroke, coronary revascularization (PCI or CABG) less than 4 month prior to the study, autoimmune and collagen tissue disorders, renal failure, liver failure, participation in other clinical study, current alcohol and drug abuse. The study protocol was approved by the Ethics Committee of I.M. Sechenov First Moscow State Medical University.
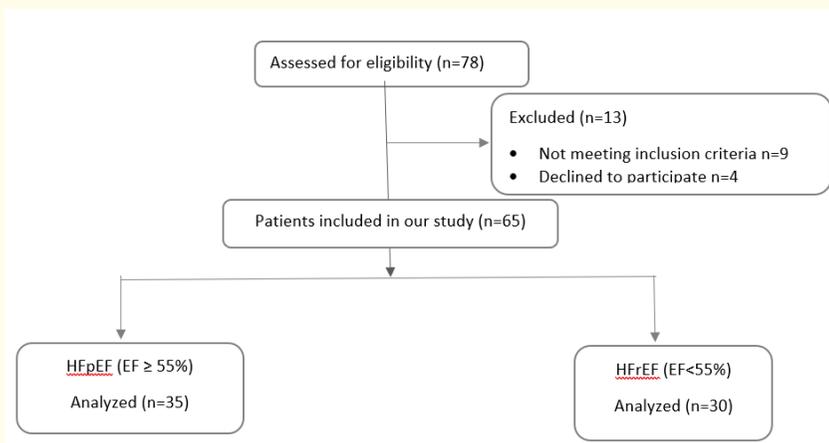
Figure 1: *Patient flow diagram.*

Physical, laboratory and echocardiographic examinations were performed before initiation of pharmacotherapy (excluding treatment on prehospital stage) at patient admission and after 3 weeks of treatment. In order to assess changes in galectin-3 and NT-proBNP plasma levels, blood tests were repeated by the end of week 3. All patients received standard HF treatment compliant with practice guidelines and consistent with best clinical practices and included angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, a mineralocorticoid receptor antagonist, and loop diuretics [10].

Echocardiography

Echocardiographic examinations were performed with HP Sonos-5500 cardiac ultrasound scanner (Hewlett-Packard, USA) using 2-4 MHz transducer. All patients were examined in the left lateral and supine position by precordial M-mode and 2-dimensional echocardiography. LV end-diastolic and end-systolic diameters, EF (%) and end-systolic left atrial (LA) diameters were measured from both M-mode in the parasternal long axis views and modified Simpson Method in the apical four chamber views. Left ventricular myocardial mass was calculated with R. Devereux formula [11].

Laboratory assessment

Blood samples were collected within 12 h of hospitalization in all patients. The follow-up galectin-3 and NT-proBNP plasma level tests were performed by the end of week 3 of therapy. Venous blood samples of all patients were obtained for tests of whole blood count, serum electrolyte levels, kidney and liver function tests, plasma aldosterone, NT-proBNP and Gal-3 levels. Venous fasting blood sample was collected into EDTA-containing Vacuette tubes (Greiner Bio-One) and centrifuged at 3,000g for 10 minutes. Plasma samples were separated and stored at -30°C until usage within 3 months. Assessment of aldosterone plasma levels was performed using human aldosterone ELISA Kit (DBC, Canada). The concentrations of the Gal-3 level were measured using human galectin-3 ELISA Kit (Bender MedSystems, USA). Plasma NT-proBNP levels were assessed by a sandwich enzyme immunoassay for determination of human NT-proBNP in human serum or EDTA plasma (Biomedica Gruppe, Austria).

A 6-minute walking test and clinical state evaluation

A 6-minute walking test was carried out in all patients included in the study prior to treatment and evaluation of their clinical state by Scale of Clinical State (SCS) (Mareev V.Y. modification, 2000). The same walking test and clinical state evaluation with SCS were repeated at week 3 of the treatment period in all patients [12].

Statistical analysis

All analyses were performed using STATISTICA 10 statistical software package (Dell Software Company). Categorical analyses were expressed as numbers (n) and percentages (%), while continuous analysis was reported as mean, standard deviation, median, minimum and maximum as required. Not-normally distributed data were expressed as median (interquartile range, IQR) and compared using the Kruskal-Wallis ANOVA and Median test (for more than 2 independent groups) or Mann–Whitney test (for 2 independent groups). Wilcoxon signed-rank test was used for related samples. Correlations were performed by using Spearman's rank correlation method.

To evaluate the changes in the measurements obtained before and after treatment, the paired sample t-test or Wilcoxon test was used depending on whether the statistical hypothesis was fulfilled.

We compared baseline characteristics using Fisher exact test and χ^2 test for categorical data. The level of statistical significance for all tests was determined as 0.05. Correlations were performed using Pearson's or Spearman's rank (for non-parametric data analysis) correlation method.

Results

The baseline patients' characteristics are presented in table 1. We enrolled 65 consecutive patients with chronic heart failure. In both groups, patients were comparable by age, sex, and comorbidities (previous myocardial infarction, arterial fibrillation, diabetes). Median

plasma galectin-3 level was 8.1 [IQR 5.4; 10.9] ng/ml in HFpEF patients, and 9.7 [7.6; 16.7] ng/ml in HFrEF patients (p > 0.05). NT-proBNP plasma levels were significantly increased in HFrEF patients (107.3 [IQR 54,1; 172,9] pmol/l) compared to HFpEF group (47.2 [23.6; 76.9], pmol/l, p < 0.01). Patients with HFpEF were more frequently female. The other baselines characteristics are shown in table 1.

Parameters	HFpEF (n=35)	HFrEF (n=30)	p
Age, years	72.7 ± 8.6	71.0 ± 10.5	> 0.05
Gender Male Female	10 (28.6%) 25 (71.4%)	17 (57.7%) 13 (43.3%)	
BMI, kg/m^2	131.7 ± 21.9	27.3 ± 8.1	> 0.05
Systolic blood pressure, mm Hg,	131.7 ± 21.9	134.5 ± 19.9	> 0.05
Diastolic blood pressure, mm Hg	80.4 ± 9.9	77.5 ± 11.1	> 0.05
Heart Rate, bpm	82.7 ± 16.04	88.6 ± 20.8	> 0.05
Scale of Clinical State, points	6.3± 2.1	7.0 ± 1.4	> 0.05
6-min walk distance, m	267.9 ±113.8	195.0 ± 102.0	< 0.01
RA, mm	44 [37;46]	46.5[39.5; 53.25]	> 0.05
LA, mm	46.5 ± 7.4	48.0 ± 5.4	> 0.05
LV End Diastolic Diameter, mm	47.8 ± 5.5	56.9 ± 6.7	< 0.00001
LV End Diastolic Volume, ml	109.3 ± 24.5	158.3 ± 37.5	< 0.00001
Interventricular Septum Thickness, mm	12.4 ± 3.2	13.3 ± 2.2	> 0.05
Left ventricular posterior wall thickness, mm	11.1 ± 2.0	10.0 ± 2.1	> 0.05
LV MM, mm	215 ± 63.2	258.7 ± 104.1	< 0.05
LV EF, %	64.1 ± 7.3	36.6 ± 8.2	< 0.00001
LV MMI, g/m^2	109.7 ± 27.1	116.9 ± 39.4	> 0.05
Total Cholesterole, mmol/l	4.6 ± 1.2	4.2 ± 1.3	> 0.05
Glucose, mmol/l	6.4 ± 3.3	6.2 ± 2.3	> 0.05
Creatinine, mcmol/l	95 [82;116]	125 [96.5;154]	< 0.01
GFR, ml/min	56.5 ± 19.1	49.0 ± 15.2	> 0.05
Galectin-3, ng/ml	8.0 [5.4;10.8]	9.7 [7.7;16.1]	> 0.05
NT-proBNP, pmol/l	47.5 [27.2;76.4]	99.0 [45.6;160.2]	< 0.01
Aldosterone, pg/ml	286.8 ± 7.9	329.4 ± 12.4	p < 0.001
Antiplatelet therapy	26 (74%)	26 (87%)	> 0.05
Statins	22 (63%)	22 (74%)	> 0.05
B-blockers	20 (57%)	21 (70%)	> 0.05
ACEI/ARB	31 (89%)	27 (90%)	> 0.05
MR Antagonist	8 (23%)	11 (37%)	> 0.05
Loop diuretics	27 (77%)	27 (90%)	> 0.05

Table 1: *Baseline Patient Characteristics.*

Note: *Continuous variables are presented as mean value ± standard deviation [SD], p value or median [interquartile range, IQR], p value, categorical variables are presented as absolute number (%), p value.*

Bold means p value < 0.05.

Both galectin-3 and NT-proBNP levels inversely correlated with LV EF (r = -0.5, **p < 0.001**, and r = -0.3, **p < 0.0001**, respectively). Correlations or tendency to correlations were also revealed between NT-proBNP plasma levels and right ventricle (RA), left atrium (LA), left ventricle end diastolic diameter, Pulmonary Artery Wedge, that can be explained with the pathophysiology of NT-proBNP secretion. No correlation between galectin-3 and other echocardiographic parameters were found. Higher NT-proBNP levels in patients with lower LVEF are associated with significant myocardial wall tension and LV volume overload, whereas elevated galectin-3 in patients with reduced EF patients marks fibrosis processes underlying myocardial remodeling.

It was detected that galectin-3 plasma levels significantly correlate with aldosterone levels (r = 0.4, p < 0.001) (Figure 2). This finding supports the hypothesis that aldosterone plays an important role in galectin-3 production by macrophages, which may further cause myocardial fibrosis.
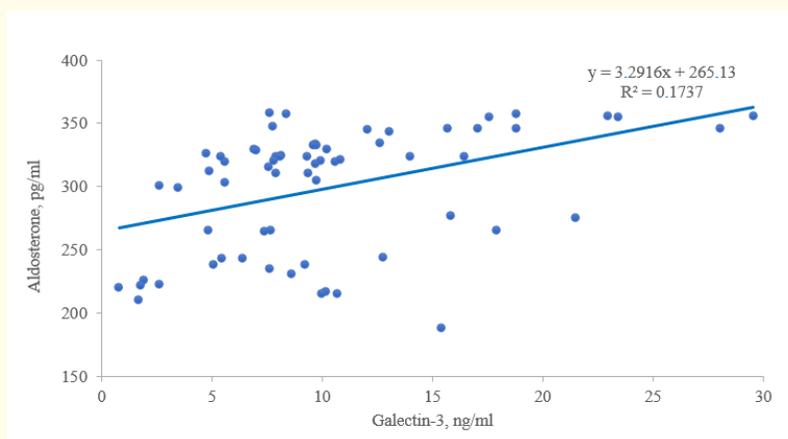
Figure 2: Correlation between plasma Galectin-3 and aldosterone levels (Spearman's Correlation Coefficient, r = 0.4, p < 0.001).

Galectin-3 and NT-proBNP changes after standard HF therapy

The follow-up galectin-3 and NT-proBNP plasma level tests were performed in all patients by the end of week 3 of therapy. A significant decrease was observed in both galectin-3 (p < 0.001) and NT-proBNP (p < 0,01) levels after 3 weeks of standard HF treatment which included ACEI/ARB, beta-blocker, loop diuretic and spironolactone (Table 2) (Figure 3-6). Galectin-3 level decreased in 84.3% of patients, whereas NT-proBNP - in 84.2% of patients.

Parameters	NT-proBNP, pmol/l		p	Galectin-3, ng/ml		p
	Before treatment	After treatment		Before treatment	After treatment	
HFpEF (n = 35)	47.5 [27.2; 76.4]	23.4 [14.2; 48.9]	p < 0.01	8.0 [5.4; 10.8]	6.3 [3.4; 8.7]	< 0.01
HFrEF (n = 30)	99.0 [45.6; 160.2]	47.7 [22.8; 110.9]	p < 0.01	9.7 [7.7; 16.1]	7.1 [5.3; 12.8]	< 0.05

Table 2: Biomarkers changes after 3 weeks of standard HF treatment. Variables are presented as median [interquartile range, IQR], p value.
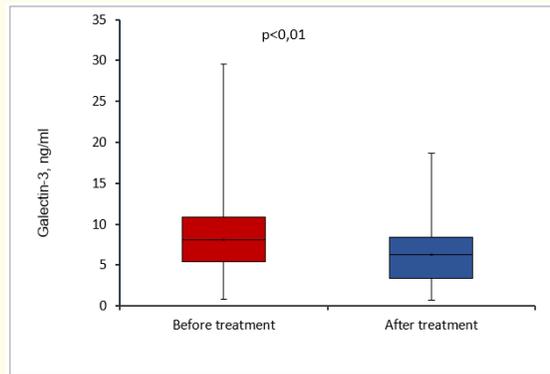
Figure 3: Changes of galectin-3 levels in patients HFpEF after 3 weeks of standard HF therapy
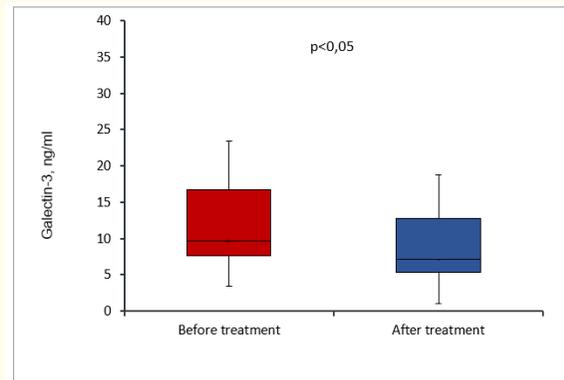
Figure 4: Changes of galectin-3 levels in patients with HFrEF after 3 weeks of standard HF therapy.
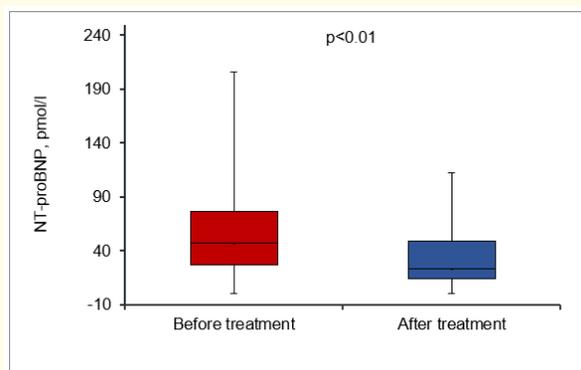
Figure 5: Changes of NT-proBNP levels in HFpEF patients after 3 weeks of standard HF therapy.
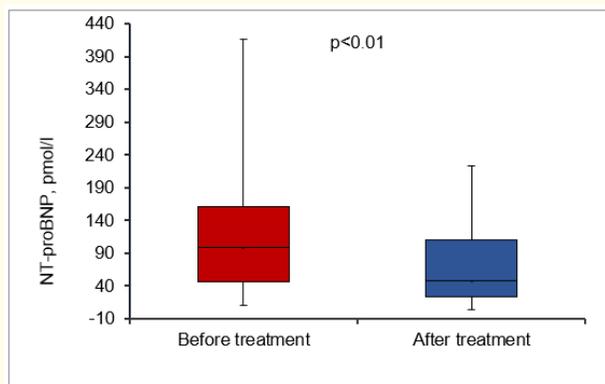
Figure 6: Changes of NT-proBNP levels in HFrEF patients after 3 weeks of standard HF therapy.

Discussion

The relationship between elevated NT-proBNP levels and poor HF prognosis is demonstrated in multiple studies [13,14]. Thus, the correlation between NT-proBNP and novel biomarkers is a subject of interest. To the best of our knowledge, changes of galectin-3 levels after short-term HF treatment comparing to changes of NT-proBNP were not investigated in any other studies before. The correlation between galectin-3 and plasma aldosterone levels (r = 0.4, p < 0.001) suggests that the biomarker may serve as a mediator of aldosterone-induced cardiac fibrosis.

In this work, we demonstrated the association between plasma NT-proBNP and galectin-3 levels (r = 0.3, p = 0.02) (Table 2). This finding is consistent with the results of a multicenter randomized study HF-ACTION [15].

In several studies, the prognostic value of repeated galectin-3 measurement in HF patients was illustrated. [16,17] Galectin-3 elevation by ≥ 15% increased the risk of cardiovascular events after 3 months (RR 2.85; 95% CI 1.13 - 7.15, p = 0.03), and after 6 months (RR 2.68; 95% CI 1.14 - 6.32, p = 0.02). According to DEAL-HF study results, HF patients with galectin-3>17.8 ng/ml and NT-proBNP>100.1 pmol/l had 42.7% increased the risk of hospitalizations and mortality [2]. Van Kimmenade RR., *et al.* demonstrated the correlation of increased galectin-3 levels with age, renal failure, and HF severity. [18] In our work median galectin-3 level was associated with HF NYHA class (p < 0.05). Galectin-3 was also significantly correlated with plasma creatinine (r = 0.3, p < 0.05).

The median plasma NT-proBNP level in patients with HF NYHA III class (91.6 [43.7; 137.7] pmol/l) was higher than in patients with HF NYHA II (45.8 [21.0; 74.8] pmol/l, p < 0,0005). This observation is well correlated to results of PRIDE study were higher NT-proBNP concentrations were associated with greater NYHA class [20].

Galectin-3 is a novel biomarker that was shown to mediate fibrosis in the heart failure. It was demonstrated that galectin-3 myocardial macrophages synthesis is stimulated by aldosterone. Galectin-3 mediates paracrine signal to fibroblasts that lead to proliferation and pro-collagen I deposition [21]. Recent studies demonstrated the role of galectin-3 as myocardial fibrosis mediator, stimulated by aldosterone. In our study, we observed a significant correlation between galectin-3 and aldosterone plasma levels. These findings support hypothesis on the important role of aldosterone in galectin-3 synthesis stimulation and its further contribution to myocardial fibrosis. However, further studies with larger sample size are needed to confirm these results.

In a study by Calvier., *et al.* hypertension, inflammation, fibrosis, and increased aortic galectin-3 expression levels were found in rats treated with aldosterone, whereas no changes occurred in Galectin-3 knock-out mice. Spironolactone or modified citrus pectin treatment

reversed all the above effects [22]. In a cohort study by Deveci., *et al.* spironolactone use was associated with regression of galectin-3 along with clinical improvement in HF symptoms [23]. In a study analyzing effects of cardio rehabilitation programme on plasma cardiac biomarkers in patients with chronic heart failure and reduced LV EF cardio rehabilitation was shown to decrease galectin-3 levels [24,25]. The TRIUMPH study demonstrated that repeated measurements of galectin-3 are a strong and independent predictor of adverse outcome in patients following admission for acute HF [26"ISSN" : "07351097", "PMID" : "29096809", "abstract" : "![Figure][1]</img> Background Several clinical studies have evaluated the association between ST2 and outcome in patients with heart failure (HF]. In this study during hospitalization, the average galectin-3 level remained steady for patients who remained free of the primary endpoint. For patients who reached the primary endpoint during follow-up, the average estimated galectin-3 level decreased slightly after the initial hospitalization [26]"ISSN" : "07351097", "PMID" : "29096809", "abstract" : "![Figure][1]</img> Background Several clinical studies have evaluated the association between ST2 and outcome in patients with heart failure (HF.

Tang., *et al.* found that galectin-3 levels were significantly lower in patients who received a β-blocker (13.4 ng/mL vs 14.9 ng/mL; p = 0.02) and spironolactone (13.1 ng/mL vs 14.3 ng/mL; p = 0.043) therapies as compared to patients without treatment [7]. In our study median galectin-3 level decreased from baseline 8.5 [5.2; 15.7] ng/ml to 6.5 [3.3; 12.8] ng/ml (p < 0.001) after 3 weeks of HF treatment with ACEI/BRA, beta-blocker, loop diuretic, spironolactone. NT-proBNP median level decreased from baseline 121.5 [43.3; 177.9] pmol/l to 82.7 [31.9; 132.7] after 3 weeks of HF pharmacotherapy. In a randomized DEAL-HF study conducted on the patients with chronic heart failure, high concentrations of galectin-3 were associated with increased hospitalization and mortality rates [21].

The most important limitations of our study are the relatively small number of patients and a single-center type. Since levels of galectin-3 are affected by renal failure, liver failure, and collagen tissue disorders, the patients with these disorders were excluded from the study, and this limitation also decreased the number of patients. Finally, more accurate could be obtained if the reduction of the fibrotic adverse process in myocardium would be confirmed by the examination of a myocardial biopsy.

Conclusions

The obtained clinical and experimental data suggest that galectin-3 is not only a diagnostic biomarker of HF but can also be useful as a marker for monitoring of pharmacotherapy efficacy. Findings on galectin-3 and aldosterone levels correlation support the hypothesis that the synthesis of this novel biomarker can be mediated by aldosterone. Galectin-3 inhibition may reduce myocardial fibrosis and remodeling processes and thus improve HF prognosis. Therefore, galectin-3 may serve as an additional biomarker in HF diagnostics as an indicator of myocardial fibrosis. The combination of two biomarkers (galectin-3 and NT-proBNP) gives us independent information on HF prognosis. Use of galectin-3 in clinical practice may broaden HF diagnostics and risk evaluation possibilities. However, taking into account some limitations of this study discussed above, additional experimental work is needed to better evaluate opportunities associated with the use of galectin-3 for pharmacotherapy efficacy monitoring.

Clinical Significance

- Few studies have investigated plasma galectin-3 changes in response to HF pharmacotherapy.
- Our study shows galectin-3 plasma levels decrease after 3 weeks of standard HF therapy. Galectin-3 levels decrease was associated with general improvement of the clinical state of HF patients. This finding may allow considering galectin-3 as an additional biomarker of HF therapy monitoring.
- Further studies are needed to assess the utility of Gal-3 as a response-to-treatment biomarker.

Declaration of Interest

All authors contributed to the conception and design of the study and the interpretation of data, and also had full access to all of the study data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

Ethical Conduct of Research

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study protocol was approved by the Ethics Committee of I.M. Sechenov First Moscow State Medical University (the approval protocol №11-16).

Informed Consent

All patients who participated in the study gave written informed consent.

Conflict of Interests

The authors declare that they have no conflicts of interests.

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