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Grażyna Sygitowicz[1, A–F], Mariusz Tomaniak[2, A–F], Krzysztof J. Filipiak[2, A, C, E, F], Łukasz Kołtowski[2, B, C, E], Dariusz Sitkiewicz[3, A, C, E, F]

Galectin-3 in Patients with Acute Heart Failure: Preliminary Report on First Polish Experience

[1] Department of Laboratory Medical Diagnostics, Medical University of Warsaw, Poland
[2] 1st Chair and Department of Cardiology, Medical University of Warsaw, Poland
[3] Department of Laboratory Medical Diagnostics, Medical University of Warsaw, Poland

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Galectin-3 (Gal-3) as a biomarker of fibrosis and inflammation has been implicated in the development and progression of heart failure (HF) and may predict increased morbidity and mortality in society.
Objectives. In this preliminary report we investigated the utility of a novel serum marker for the diagnosis of acute HF (AHF).
Material and Methods. The study involved 14 AHF patients aged 67.0 ± 14.6 yrs. with left ventricular ejection fraction (LVEF) 29.29 ± 10.73%, hospitalized at the Intensive Coronary Care Unit, where the research took place. In addition, a control group consisting of 19 volunteers who were age, gender and ethnically matched to the HF group was recruited. In the study group, the concentrations of Gal-3, NT-proBNP, hsCRP and basic clinical parameters, such as prevalence of dyspnea and LVEF were determined. The concentration of Gal-3 in serum was examined by an automated quantitative test (VIDAS® Galectin-3, bioMerieux SA, France) using the ELFA technique. The survival rate was assessed after a 12-month follow-up.
Results. The median (IQR) Gal-3 concentrations in patients with AHF were higher (nearly 2.1-times) than in the control group – 17.8 (10.3–27.8) ng/mL vs. 8.4 (6.5–11.0) ng/mL; p = 0.0007. In our study group, the median (IQR) of concentrations of NT-proBNP 4723 (1415–29725) pg/mL and hsCRP 10.0 (4.9–13.9) mg/L were observed. In those patients, the statistically significant correlation (Spearman's rank-correlation coefficient) between the concentrations of Gal-3 and NT-proBNP (Rs = 0.565; p = 0.035) as well as the value of LVEF and the concentration of hsCRP (Rs = –0.663; p = 0.020) were stated. The serum Gal-3 concentrations were significantly higher among the 4 HF patients (28.6%) who had died than among the HF patients who were alive after this time (n = 10) (55.6 ± 37.6 ng/mL vs. 15.0 ± 7.04 ng/mL; p = 0.005).
Conclusions. Higher expression of Gal-3 is an indicator of myocardial fibrosis and remodeling in decompensated HF. Therefore, galectin-3 seems to be an interesting and valuable marker of AHF (**Adv Clin Exp Med 2016, 25, 4, 617–623**).

Key words: biomarkers, NT-proBNP, acute heart failure, galectin-3, left ventricle ejection fraction.

Heart failure (HF) is a disease with high mortality regardless of treatment [1]. HF is a common health problem with a multitude of causes that affects more than 20 million people worldwide and that number is expected to grow [2].

Apart from the identification of subjects with advanced HF, it is desirable to be able to detect patients at highest risk for adverse cardiac remodeling. Hence, the role of biomarkers for the risk evaluation in acute heart failure (AHF) has recently increased.

Brain natriuretic peptide (BNP) and its cleavage equivalent – amino-terminal proBNP (NT-proBNP) have been validated for confirming the diagnosis of AHF in breathless subjects and assessing the prognosis in these patients [3]. The production of these substances is rapidly upregulated as a response to the increased heart wall stress in the setting of HF exacerbation. Aside from volume overload, other processes including inflammation may play an important role in HF progression, and

these pathomechanisms may not be reflected in BNP or NT-proBNP concentrations [1, 3–5].

Recent experimental and clinical studies suggest that galectin-3 (Gal-3) may be involved in the regulatory pathways responsible for immune response and fibrosis. Its elevated serum levels were measured not only in such fibrotic conditions as pancreatitis, cirrhosis, idiopathic lung fibrosis and renal failure, but also in adverse cardiac remodeling. As a consequence, it constitutes an attractive biomarker in HF patients [6–11].

Galectins: Structure, Functions and Classifications

Galectins (Gals) constitute a family of evolutionary conserved β-galactoside binding lectins that play many important regulatory roles in immunity, inflammation, atherosclerosis, diabetes, embryogenesis, and also neoangiogenesis [12]. Members of the galectin family are categorized by their characteristic amino acid sequences. Galectins contain conserved carbohydrate recognition domains (CRDs) (around 130 amino acids). On the basis of their molecular architecture, galectins have been classified into three main types: (a) "proto-type" galectins, comprising a single polypeptide chain that is able to dimerize (nine types of galectins); (b) "tandem repeat-type" galectins, composed of a single polypeptide chain presenting two CRDs connected by a linker peptide (five types of galectins) and (c) the "chimera-type" galectin-3, which consists of one C-terminal CRD linked to an N-terminal peptide [12, 13]. Galectin-3 (Gal-3) is characterized by the presence of 100–150 additional amino acids – proline, tyrosine and glutamine – N-terminal rich domain, non-carbohydrate binding compounds. This gives the molecule the unique property of forming multivalent oligomeric structures, enabling it to mediate the complex interactions at the intracellular and intercellular level [14]. High levels of Gal-3 are expressed on activated macrophages, basophils, and mast cells. Many authors suggest a significant role of galectin in the pathogenesis and pathophysiology of cardiovascular diseases, in particular atherosclerosis, stroke, myocardial infarction, and heart failure [5, 7, 15]. Gal-3 is a member of the β-galactoside-binding animal lectin family, and its interaction with several ligands at the extracardiac matrix (ECM), including laminin, synexin, integrins, and collagens, could modulate inflammation and immunity [8]. A previous study demonstrated that cardiac macrophages could produce Gal-3 after activation, but subsequent studies have found the Gal-3-binding sites in cardiac fibroblasts and the ECM [9]. As a result of the interaction of integrin β-1, galectin is transported into the cytoplasm of other cells, particularly cardiac fibroblasts, which are activated with subsequent proliferation. Stimulated fibroblasts synthesize extracellular matrix proteins, particularly collagen type 1, leading to fibrosis and adverse cardiac remodeling [12]. Of greater importance is the effect of Gal-3 on myocardial fibrosis development and progression of heart failure. Numerous studies have shown the significant prognostic value of serum Gal-3 as a predictor of adverse outcomes in patients with heart failure [5, 16]. In this preliminary report, we investigated the utility of a novel serum marker for the diagnosis of acute heart failure.

Material and Methods

Study Population

In this prospective, single center registry, 14 patients hospitalized at the Department of Cardiology, Medical University of Warsaw, between October 2013 and January 2014 due to acute heart failure (HF), or exacerbation of chronic HF, were enrolled. A diagnosis of HF in this study conformed to the Framingham criteria and was confirmed by clinical history, physical examination, biochemical tests, electrocardiogram, chest radiography and echocardiography.

The study included patients presenting within 24 h from the onset of a dyspnea (at rest or with minimal exertion) with pulmonary congestion confirmed radiologically and left ventricular ejection fraction (LVEF) below 50%, computed according to the Simpson's method.

Patients with acute coronary syndrome, active infection, Cushing's syndrome, primary hyperaldosteronism, Addison's disease, liver cirrhosis, acute renal failure, paraneoplastic syndromes, subarachnoid hemorrhage, chronic lung diseases, acute and chronic pulmonary embolism and myopathies were excluded from the study.

Patients were divided into three-subgroups according to the New York Heart Association (NYHA) functional class (II–IV). Data regarding time of chronic HF diagnosis, risk factors, cardiovascular comorbidities, family history and previously used medications was collected.

All enrolled patients underwent physical examination, with special emphasis on the clinical features of heart failure, ECG, and laboratory tests. In addition, a control group comprising 19 subjects who were age, gender, BMI and ethnically matched to the HF group was recruited.

The study protocol was approved by the Bioethics Committee of Warsaw Medical Universi-

ty and all enrolled patients gave written informed consent before inclusion.

Biochemical Analysis

Venous blood samples were collected after overnight fasting into plastic tubes with a clot activator. After centrifugation, the serum concentrations of hsCRP, NT-proBNP, glucose, creatinine and lipid parameters were immediately determined. The rest of the serum was immediately frozen at –70ºC for later measurement of galectin-3.

Serum galectin-3 concentrations were measured using instruments of the VIDAS family. The assay principle combines a one-step immunoassay sandwich method with a final fluorescent detection (ELFA technique, Enzyme-Linked Fluorescent Assay) (VIDAS® Galectin-3, bioMerieux SA, Marcy-l`Etoile, France). VIDAS® Galectin-3 set contains the Solid Phase Receptacle (SPR®) which is used as the solid phase as well as pipetting device. The sample is transferred into the well containing anti-galectin-3 antibody (conjugate) labeled with alkaline phosphatase. The sample/conjugate mixture is cycled in and out of the SPR® several times. This operation enables the galectin-3 to bind with the immunoglobulins fixed to the interior wall of the SPR® and to the conjugate to form a sandwich. Unbound compounds are eliminated during the washing steps. Calibration of the assay was done according to the manufacture's protocol. Values were normalized to a standard curve. The intra-assay and inter-assay variances for Gal-3 were 1.25% and 5.5%, respectively.

Serum lipids (total cholesterol, triglycerides and HDL cholesterol), creatinine and glucose were determined by automated analyzer (Roche Diagnostics, Cobas). LDL-cholesterol was estimated by the Friedewald formula unless triglyceride levels were > 300 mg/dL, in which case direct LDL-cholesterol determinations were performed. The estimated glomerular filtration rate (eGFR), as an indicator of renal function, was estimated from serum creatinine using a formula that accounts for the influence of age on creatinine production, which has been validated in patients with HF, and was described in detail elsewhere (MDRD) [17]. The concentrations of high sensitivity C-reactive protein (hsCRP) and N-terminal pro-brain natriuretic peptide (NT-proB -NP) in the serum were measured using a Flex® Reagent Cartridge and Dimension®EXL™ integrated chemistry system with a LOCI® Module (Siemens HealthCare Diagnostics Ltd., Camberley, UK).

Echocardiography

Left ventricular ejection fraction (LVEF) was determined using biplane modified Simpson's measurements. Echocardiography was performed with the Philips iE Ultrasound System [18].

Statistical Analysis

Statistical analysis was performed using the data analysis software system StatSoft. Inc. STATISTICA v. 10. P-values < 0.05 were considered as statistically significant. Continuous variables were tested for normal distribution using the Shapiro--Wilk test. Results for normally distributed continuous variables are expressed as mean ± standard deviation and we used the unpaired Student's t-test to compare mean values. Continuous variables with non-normal distribution are presented as the median value and interquartile range (IQR, range from the 25th to the 75th percentile). Between-group comparisons of medians were performed with the Mann-Whitney U test. Correlations among continuous variables were assessed with the use of the Spearman's rank correlation coefficient. Categorical variables are expressed as numbers (percentages) and analyzed using Fisher's exact test.

Results

Fourteen consecutive patients (11 male, 3 female, mean ages 67.0 ± 14.6 yrs) with LVEF 29.29 ± 10.73%, hospitalized for AHF in the Intensive Coronary Care Unit, were enrolled. Patients with ischemic systolic HF comprised over 90% of analyzed cases. The baseline demographic characteristics of the study group are presented in Table 1. The control group included 19 subjects without HF at the age of 59.6 ± 10.1 yrs (14 male, 5 female). There were no statistical differences in the age, gender and body mass index compared to the HF group. Of the 19 patients without HF, 13 had hypertension (68.4%), 3 had coronary heart disease (15.8%) and 8 had diabetes mellitus (42.1%).

The median serum concentrations of Gal-3 were significantly higher in patients with acute HF vs. those without HF – 17.8 (10.3–27.8) ng/mL vs. 8.4 (6.5–11.0) ng/mL; p = 0.0007, respectively (Fig. 1). In our study group, the median (IQR) NT-proBNP concentrations of 4723 (1415–29725) pg/mL and hsCRP 10.0 (4.9–13.9) mg/L were observed (Table 1).

In the AHF group, a significant correlation (Spearman's rank-correlation coefficient) between concentrations of Gal-3 and NT-proBNP (Rs = 0.565; p = 0.035) as well as the value of LVEF and the concentration of hsCRP (Rs = –0.663; p = 0.020) were stated (Fig. 3 and Fig. 2C, respectively).

Table 1. Baseline characteristics of patients with acute heart failure (n = 14) and control group (n = 19)

	AHF (n = 14)	**Control (n = 19)**	**p-value**
Personal factors			
Age, yrs*	67.0 ± 14.6	59.6 ± 10.1	0.094
Male gender, % (n)	78.6 (11)	73.7 (14)	0.312
BMI, kg/m^2*	25.5 ± 3.4	24.8 ± 2.2	0.473
Overweight, BMI > 25, % (n)	57.1 (8)	42.1 (8)	0.381
Last year hospitalization, % (n)	57.1 (8)	–	–
Risk factors			
LVEF, %*	29.2 ± 10.7	61.9 ± 5.6	< 0.0001
Current smoking, % (n)	35.7 (5)	52.6 (10)	0.413
Hypertension, % (n)	71.4 (10)	68.4 (13)	0.327
IV NYHA functional class, % (n)	28.6 (4)	–	–
Hypercholesterolemia, % (n)	28.6 (4)	21.1 (4)	0.479
Creatinine, mg/dL*	1.46 ± 0.94	0.89 ± 0.11	0.014
Chronic kidney disease, % (n)	28.6 (4)	–	–
Stage 3 (Egfr < 60 mL/min/1.73 m^2), % (n)	14.3 (2)	–	–
Stage 4 (eGFR < 30 mL/min/1.73 m^2), % (n)	28.6 (4)	–	–
Diabetes mellitus	42.9 (6)	42.1 (8)	0.403
hsCRP, mg/L**	10.0 (4.9–13.9)	1.1 (0.9–1.3)	< 0.0001
NT-proBNP, pg/mL**	4723 (1415–29725)	na	–
Previous cardiovascular disease			
Coronary artery disease, % (n)	92.9 (13)	15.8 (3)	0.453
Peripheral artery disease, % (n)	21.4 (3)	–	–
Atrial fibrillation, % (n)	42.9 (6)	–	–
Stroke, % (n)	21.4 (3)	–	–
Treatment before admission			
ACE inhibitor, % (n)	42.9 (6)	42.1 (8)	0.403
β-blocker, % (n)	50.0 (7)	47.4 (9)	0.379
Aldosterone antagonist, % (n)	7.1 (1)	–	–
Digoxin, % (n)	7.1 (1)	5.3 (1)	0.692
Loop diuretic, % (n)	50.0 (7)	47.4 (9)	0.379
Risk markers at baseline			
Dyspnea, % (n)	100 (14)	–	–
Heart rate, bpm*	108.1 ± 23.7	74.1 ± 5.03	< 0.0001
Systolic blood pressure, mm Hg*	129.6 ± 16.6	115.3 ± 10.2	0.004

* – mean ± standard deviation; ** – median (IQR, range from the 25th to the 75th percentile); na – not assessed;
ACE – angiotensin-converting enzyme.

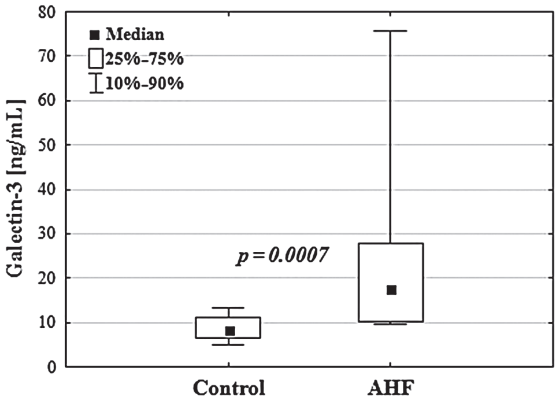

Fig. 1. Serum galectin-3 levels in patients with acute HF (n = 14) and control group (n = 19). Box-whisker plots of Gal-3 levels are shown. Boxes encompass the 25th (Q1) to 75th (Q3) quartiles. Points within boxes represent median values

Nevertheless, no significant correlations between Gal-3 serum levels and the NYHA function class nor between Gal-3 serum levels and the LVEF value were found. Likewise, in our group, the serum concentrations of NT-proBNP were not associated with the LVEF measurements (Fig. 2A and Fig. 2B, respectively).

In the 12-month follow-up, 4 patients in the AHF group had died. Of note, the serum Gal-3 concentrations during the index hospitalization were significantly higher than among HF patients who were alive after this time (n = 10) (55.6 ± 37.6 ng/mL vs. 15.0 ± 7.04 ng/mL; p = 0.005) (Fig. 4).

Discussion

Our preliminary study demonstrated that, among patients with AHF hospitalized in the tertiary care center, the plasma levels of Gal-3 were significantly elevated in comparison with controls without AHF, which is in line with some experimental and clinical studies [3–6, 19].

Of note, we found a significant positive correlation between Gal-3 and NT-proBNP plasma concentrations, which is a well-established and the most validated diagnostic and prognostic marker of HF [20, 21]. Such an association of a novel particle's serum concentration with the levels of a biomarker already recommended for risk stratifications and HF diagnosis in patients presenting with acute dyspnea, suggests that Gal-3 constitutes a promising new diagnostic modality in this clinical condition.

NT-proBNP is released into the blood as a direct response of the heart muscle to volume overload. By contrast, no upregulation of Gal-3 has been observed when the cardiomyocytes were stretched, suggesting that this novel serum biomarker might be present in the sera of HF patients in more stable concentrations.

One may assume that by the employment of a multimarker strategy, including neurohormonal

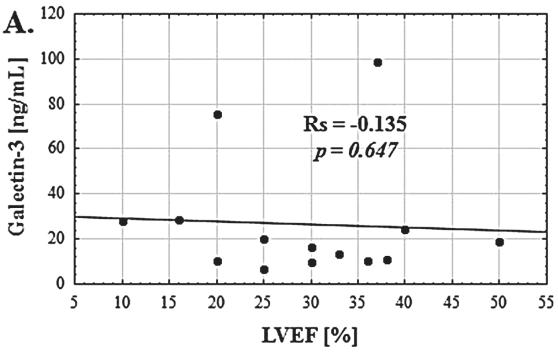

Fig. 2A. Correlations between concentrations of serum galectin-3 and value of left ventricular ejection fraction in patients with AHF. Spearman's rank correlations: Rs = –0.135, p = 0.647

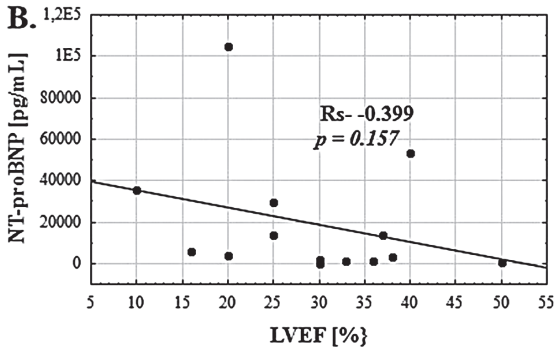

Fig. 2B. Correlations between concentrations of serum NT-proBNP and value of left ventricular ejection fraction in patients with AHF. Spearman's rank correlations: Rs = –0.399, p = 0.157

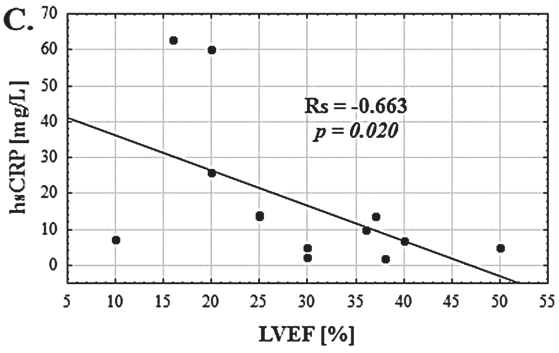

Fig. 2C. Correlations between concentrations of serum hsCRP and value of left ventricular ejection fraction in patients with AHF. Spearman's rank correlations: Rs = –0.633, p = 0.020

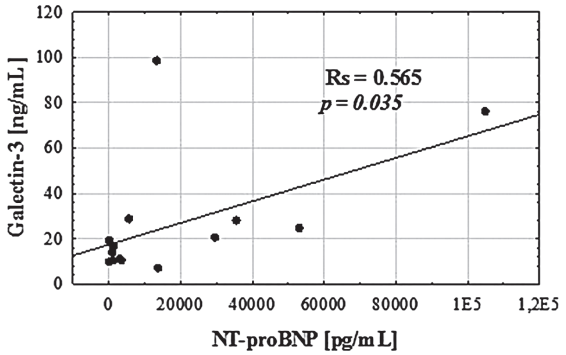

Fig. 3. Correlations between concentrations of serum galectin-3 and NT-proBNP in patients with acute HF. Spearman's rank correlation Rs = 0.565, p = 0.035

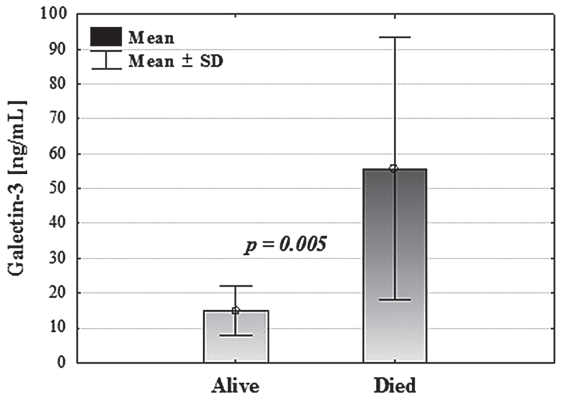

Fig. 4. Serum galectin-3 levels in patients with acute HF who were alive (n = 10) and who died (n = 4). Results are expressed as mean ± standard deviation (SD)

(NT-proBNP) and inflammation-related markers, we could improve diagnostic efficacy and prognostication in AHF. Additionally, as fibrosis and inflammatory processes substantially precede the onset of HF, the future potential application of Gal-3 assessments may involve the identification of asymptomatic patients with active cardiac fibrosis and earlier use of targeted therapies to delay the clinical manifestation of the disease [22].

It should be noted that the Gal-3 levels were not dependent on LVEF, which is in line with some previous reports [20, 21]. According to some authors, in patients with chronic HF the elevated serum levels of galectin-3 were associated with higher NYHA functional class and worse treatment outcome [5, 14]. By contrast, we found no correlation between Gal-3 and NYHA class in patients with AHF, which is consistent with the study by Januzzi et al. [19]. Nevertheless, our pilot study was not focused on detecting such differences.

Recent studies have revealed that Gal-3 appears to be a promising prognostic biomarker in HF patients [3, 6, 7, 21, 23, 24]. In our study, patients who died during the follow-up period presented significantly higher baseline Gal-3 levels than the survivors, which is in line with some previous reports [3, 6, 7, 21, 23, 24]. Nevertheless, the clinical utility of this particle in the diagnostics as well as monitoring of therapy still needs to be addressed in large, prospective trials.

Limitations

There are several limitations to this study. This is a preliminary study and the size of the analyzed group is small. Secondly, unlike in the control group, there were several co-morbidities in the HF groups that might have influenced the plasma concentration of Gal-3 in these patients. Nevertheless, it appears that the data available from preclinical as well as previous clinical studies allows for association of the elevated levels of Gal-3 with the condition of decompensated HF. Another limitation is the fact that Gal-3 is not a heart-specific enzyme. Finally, larger prospective studies are necessary to assess whether Gal-3 assessments may add independently-valuable data to the currently-used biomarkers in AHF.

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Address for correspondence:

Grażyna Sygitowicz
Department of Laboratory Medical Diagnostics
Medical University of Warsaw
ul. Banacha 1
02-097 Warszawa
Poland
Tel.: +48 22 57 20 765
E-mail: gsygitowicz@poczta.onet.pl

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