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LEVELS OF GALECTIN-3, ADVANCED GLYCATED END-PRODUCTS IN SERUM, ENDOTHELIAL FUNCTION AND CARDIAC HEMODYNAMICS IN POST INFARCTION HEART FAILURE IN PATIENTS WITH REDUCED AND PRESERVED EJECTION FRACTION

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Ключові слова: *постінфарктна хронічна серцева недостатність, галектин-3, AGEs, ендотеліальна дисфункція, серцева гемодинаміка*

Abstract. Galectin-3, advanced glycated end-products serum levels, endothelial function and cardiac hemodynamics in post infarction heart failure patients with reduced and preserved ejection fraction. Kuryata O., Zabida A., Sirenko O. *Epidemiological studies have reported that the rate of signs and symptoms of heart failure after myocardial infarction is approximately 25%. In addition, approximately 40% of myocardial infarctions are accompanied by left ventricular systolic dysfunction. Aim.. Aim of the study is to evaluate serum levels of galactin-3, AGEs and endothelial function, cardiac hemodynamics in post infarction chronic heart failure patients with different ejection fraction. Materials and methods. All patients are divided into two main groups according to ejection fraction:1st group-20 patients with chronic heart failure with preserved ejection fraction, 2nd group-15 patients with chronic heart failure and reduced ejection fraction. Standard laboratory blood tests for erythrocyte sedimentation rate, haematological parameters, lipid profile, glucose, renal function, echocardiographic examination, endothelial function determine were performed for all patients. AGEs and galectin-3 serum levels were determined. Results. Patients with chronic heart failure and reduced ejection fraction and myocardial infarction in anamnesis had significantly increased left ventricle diastolic volume, left ventricle systolic volume,left ventricle diastolic dimension and left ventricle systolic dimension ($p<0.05$).AGEs serum level mildly increased in both groups.Galectin-3 level was significantly higher in pts with chronic heart failure and reduced ejection fraction($p < 0.05$)and was correlated with age($R=0.74$, $p<0.05$), left ventricle end diastolic volume ($R=0.57$, $p<0.05$), left ventricle end diastolic dimension ($R=0.48$, $p<0.05$), triglycerides level ($R=0.45$, $p < 0.05$). Most of the patients with chronic heart failure with myocardial infarction in anamnesis had endothelial dysfunction, the FMD% level was significantly higher in patients with preserved ejection fraction($p<0.05$). Conclusions. Patients with chronic heart failure and reduced ejection fraction are characterized by significantly higher levels of galectin-3, endothelial dysfunction frequency, cardiac hemodynamics abnormalities.*

Реферат. Рівні галектину-3, продуктів кінцевої глікації в сироватці крові, функціональний стан ендотелію та серцева гемодинаміка у хворих на серцеву недостатність після перенесеного інфаркту міокарда зі зниженою та збереженою фракцією викиду. Курята О., Забіда А., Сіренко О. *Епідеміологічні дослідження свідчать, що симптоми серцевої недостатності після перенесеного інфаркту міокарда мають місце приблизно в 25% хворих. Крім того, приблизно 40% інфарктів міокарда супроводжуються систолічною дисфункцією лівого шлуночка. Мета дослідження – оцінити рівень галектину-3, AGE в сироватці крові та ендотеліальну функцію, серцеву гемодинаміку в пацієнтів із хронічною серцевою недостатністю після інфаркту з різною фракцією викиду. Матеріали та методи. 35 хворих з хронічною серцевою недостатністю на тлі перенесеного інфаркту міокарда віком від 40 до 80 років були включені в дослідження. Пацієнти були розподілені на дві основні групи: 1-а група - 20 пацієнтів із хронічною серцевою недостатністю зі збереженою фракцією викиду, 2-а група - 15 пацієнтів із хронічною серцевою недостатністю зі зниженою фракцією викиду. Виконано стандартні лабораторні аналізи крові з визначенням гематологічних параметрів, ліпідного профілю, глюкози, функції нирок, ехокардіографічне обстеження, визначення функціонального стану ендотелію. Визначено рівні AGEs та галектину-3 у сироватці крові. Результати. Пацієнти із хронічною серцевою недостатністю та зниженою фракцією викиду на тлі перенесеного інфаркту міокарда в анамнезі мали достовірно вищі показники кінцевого діастолічного об'єму лівого шлуночка, кінцевого систолічного об'єму*

лівого шлуночка, кінцевого діастолічного розміру лівого шлуночка та кінцевого систолічного розміру лівого шлуночка (p<0,05). Рівень AGE у сироватці крові був помірно збільшеним в обох групах. Встановлено достовірно вищий рівень галектину-3 у хворих з хронічною серцевою недостатністю зі зниженою фракцією викиду (p<0,05), що корелює з віком (R=0,74, p<0,05), кінцевим діастолічним об'ємом лівого шлуночка (R=0,57, p<0,05)), кінцевим діастолічним розміром лівого шлуночка (R=0,48, p<0,05), рівнем тригліцеридів (R=0,45, p<0,05). Більшість пацієнтів з хронічною серцевою недостатністю з інфарктом міокарда в анамнезі мали ендотеліальну дисфункцію, рівень ендотелійзалежної вазодилятації був достовірно вищим у пацієнтів зі збереженою фракцією викиду (p<0,05). Висновки. Хворі із хронічною серцевою недостатністю та зниженою фракцією викиду характеризуються достовірно вищим рівнем галектину-3, підвищеною частотою ендотеліальної дисфункції, порушень серцевої гемодинаміки.

Epidemiological studies have reported that the rate of signs and symptoms of heart failure (HF) after myocardial infarction (MI) is approximately 25%. Importantly, this finding appears to be in agreement with the registries of several clinical trials. In addition, approximately 40% of myocardial infarctions are accompanied by left ventricular systolic dysfunction. Therefore, the available data suggest that HF after MI is a very frequent event [2]. Considering the type of cardiac dysfunction following MI, most patients present systolic dysfunction. Recent meta-analysis showed that restrictive mitral filling pattern, the most severe form of diastolic dysfunction, was presented in approximately 10% of the patients with preserved ejection fraction. In addition, restrictive pattern was associated with poor outcome [8]. However, the true prevalence and relevance of diastolic dysfunction after MI remains to be elucidated. Another important issue is that the consequences of cardiac dysfunction after MI are well established, and its presence increases the risk of death by at least 3- to 4-fold 6. Compared with patients without heart failure and left ventricular systolic dysfunction after myocardial infarction, patients who have heart failure and left ventricular systolic dysfunction are at higher risk for adverse outcomes, including cardiac rupture, cardiac arrest, stroke, longer hospitalizations, ventricular arrhythmias, recurrent myocardial infarction, and death, including sudden death [2].

Increasing HF severity is associated with NO imbalance and endothelial dysfunction that manifests in different forms [5]. Besides increasing afterload due to systemic [8] and pulmonary vascular constriction, altered endothelial function underlies regional vasomotor dysregulation in the renal and coronary circulation [14].

Decreased coronary of capacity vasodilator endothelium-dependent impairs myocardial perfusion, reduces coronary flow [7, 12], and worsens ventricular function [5]. The dysfunctional endothelium contributes to increased vascular stiffness and impaired arterial distensibility, augmenting myocardial damage [9, 10, 11]. NO imbalances also alter matrix metalloproteinases, which affect cell migration, cardiac hypertrophy, and atherosclerotic plaque stability [14].

Increased endothelin-1 in HF causes increased vascular resistance, smooth muscle cell growth, and matrix production, resulting in vascular remodeling, endothelial dysfunction, and HF progression. Reduced NO in HF affects endothelial progenitor cells, disabling endothelial repair and regeneration.

Advanced glycated end-products (AGEs) are end-products formed by oxidative and non-oxidative reactions between sugars and proteins [11]. AGEs form cross-links with long-living tissue proteins, which cause them to accumulate in the body over time. AGEs can bindto the receptor of AGE (RAGE) and thereby induce cardiovascular dysfunction [1] RAGE has a C-truncatedsecretory isoform, soluble RAGE (sRAGE), that circulates in plasma [17]. sRAGE has been proposed to have an atherosclerotic-protective function [4, 13]. However, AGE-RAGE interaction can also cause inflammation and increased AGE-accumulation.AGE-accumulation in turn can cause up regulation of RAGE [16]. Through decreased compliance of the heart and the vasculature, AGE accumulation is considered to be related to the onset and progression of HF [1].

Galectin-3 is a member of the family of soluble b-galactoside-binding lectins and it plays a crucial role in several diverse biological processes and diseases [12]. At the same time it is also associated with increased age, diabetic nephropathy, fibrotic conditions such as liver fibrosis [7], renal fibrosis, idiopathic lung fibrosis and chronic pancreatitis [15]. Recently it has drawn greater attention to its contribution in the pathophysiology of HF since it has been shown that galectin-3 promotes cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction.

Aim of the study is to evaluate serum levels of galectin-3, AGEs and endothelial function, cardiac hemodynamics in post infarction chronic heart failure patients with different ejection fraction.

MATERIALS AND METHODS

Baseline Study

The study was conducted with the approval from the Ethics committee at State Establishment “Dnipropetrovsk medical academy of Health Ministry of

Ukraine" according to principles outlined in the Helsinki declaration.

Inclusion criteria: patients with myocardial infarction in anamnesis(>6 months) and chronic heart failure (HF) (ESC, 2016) aged from 40 to 80 years. Patients with acute myocardial infarction (<6 months), 2nd and 3rd degree heart block, diabetes mellitus (DM), renal failure (glomerular filtration rate: GFR≤30 ml/min/1.73m²), hepatic failure, and cancer were excluded. All patients got standard treatment for HF according to ESC guidelines 2016 [6].

Standard laboratory blood tests for erythrocyte sedimentation rate, haematological parameters, lipid profile, glucose, renal and liver function tests were performed and body mass index (BMI) for all patients were calculated.

Echocardiographic examination was made by «VIVID 3», GE Medical Systems - USA in B, M, 2D, CFM, PW - mode pulse sensor 3S (3,5 MHz). Brachial artery measurement: brachial artery (BA) diameter, determining flow mediated dilatation (FMD)% and obtaining baseline and hyperemic BA flow velocities and deriving the respective flow volumes.

The fluorescent(f) AGEs in plasma were analysed by quantitative autofluorescence (fluorimeter Hoefer DQ 2000,USA) with fixed spectrum of excitation at 460 nm with 20% quinine solution as a standard with results expressed with conversion to glycated albumin.

Galectin-3 blood levels were measured by immunoassay analysis using the "Human Galectin-3 Platinum ELISA" kit (GmbH, Austria) on the Stat Fax 2100 (USA) immunoassay plate analyser.

Statistical analysis

In order to accomplish the analysis of data, we used statistical program V.6.1 (StatSoft inc), and "Excel 2013" Microsoft. Data are shown as number of subjects (%) or median[interquartile range(IQR) because data are not normal distribution.

The Mann-Whitney U-test and Wilcoxon test were used to analyze differences between two independent and dependent groups respectively. Correlation coefficient Spearman (R) was calculated. A p value <0.05 was considered statistically significant.

Study design

First group (n=20) pts with HF and preserved ejection fraction (EF)>45% (HFpEF), second group (n=15) - pts with HF and reduced ejection fraction (EF)≤45% (HFrEF).

RESULTS AND DISCUSSION

Clinical characteristics of patients were summarized in table 1.

Arterial Hypertension (AH) was estimated in 24 (69%) points, 1st degree – in 8 (23%), 2nd degree – in 16 (45%). Increased body mass index – in 22 (63%) pts, increased waist circumference – in 12 (34%).

Table 1

Baseline characteristics of the study population

Characterstics		1st group Post infarction CHFpEF (n=20)	2ndgroup Post infarction CHFrEF (n=15)	P value
Gender	Males(%)	17(85%)	13(87%)	-
	Females(%)	3(15%)	2(13%)	-
Heartfailurefunctional class (NYHA), %	2nd FC	12(60%)	4(27%)	-
	3rd FC	8(40%)	11(73%)	-
Age (years)	M±m	59 [53;77]	66 [62;71]	0.023
Body mass index (BMI)	M±m	28.4 [27.5;29.8]	27.7 [27;29.9]	0.145
Heart rate (beat/minute)	M±m	72 [68;78]	76 [68;89.5]	0.312
Atrial fibrillation (%)		5(25%)	6(40%)	-
Arterial hypertension (%)		17(85%)	8(51%)	-
Glomerular filtration rate (GFR)	M±m	84.4 [65.7;92.5]	86.6 [78.0;88.6]	0.153
Blood glucose mmol/l	M±m	5.2 [4.9;5.4]	5.5 [5.3;7.4]	0.098
Cholesterol mmol/l	M±m	4.9 [4.4;5.8]	4 [3.3;4.9]	0.031
Triglycerides mmol/l	M±m	1.7 [1.2;2.4]	0.9 [0.8;1.2]	0.027

Postinfarction HFpEF patients had significantly higher cholesterol level and triglycerides ($p<0.05$). In the same time post infarction HFrEF patients were significantly older in age ($p<0.05$). There were no significant differences between the other indicators.

It was established significant differences between echocardiographic indicators (table 2). Particularly, HFrEF patients with MI in anamnesis had significantly increasing levels of left ventricle end diastolic volume (LVEDV), left ventricle end systolic volume (LVESV), left ventricle end diastolic dimension (LVEDD), left ventricle end systolic dimension (LVESD) on 37.6%, 62.3%, 18.5% and 33.3% respectively ($p<0.05$). The EF level was correlated with age ($R=-0.72$, $p<0.05$), the LVEDV level ($R=-0.67$, $p<0.05$), total cholesterol level ($R=0.48$, $p<0.05$), triglycerides level ($R=0.42$, $p<0.05$). There was significant correlation between LVEDD and age ($R=0.68$, $p<0.05$),GFR ($R=-0.57$, $p<0.05$).

Table 2

Echocardiographic parameters in both groups

	1st group Post infarction CHFpEF (n=20)	2ndgroup Post infarction CHFrEF (n=15)	p
Left ventricle ejection fraction (EF) ,% M±m	57 [51.5;65]	40 [31;40.5]	0.003
Left ventricle end diastolic volume (LVEDV) ml M±m	133.5 [116.3;143.3]	214 [183;224.7]	0.006
Left ventricle end systolic volume (LVESV) ml M±m	53 [39.5;73]	140.5 [103;153.7]	0.021
Left ventricle end diastolic dimension (LVEDD) cm M±m	5.3 [5.0;5.4]	6.5 [6;6.7]	0.015
Left ventricle end systolic dimension (LVESD) cm M±m	3.6 [3.4;4.1]	5.4 [4.7;5.6]	0.024
Left atrium size (LAS) cm M±m	4 [3.9;4.2]	4.6 [4.3;5.0]	0.141

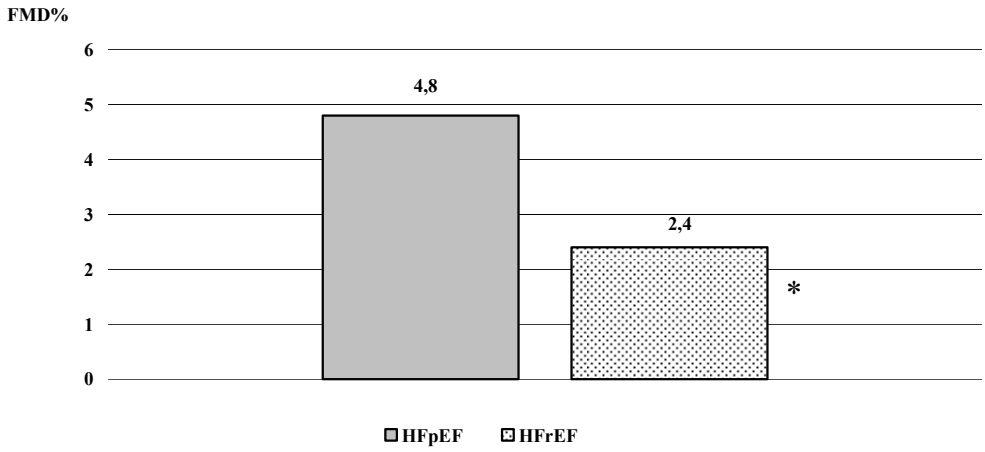
The median AGEs level was 1.6 [1.1;1.9]. There were no significant differences between AGEs level between study groups. The AGEs level correlated with GFR ($R=-0.62$, $p<0.05$), LVEDV ($R=0.63$, $p<0.05$). The median galectin-3 level was 6.9 [6.3;10.6], significant difference in galectin-3 level was established depending on EF level in pts with HF ($p<0.05$) (table 3). The galectin-3 level was significantly higher by 12.5% ($p<0.05$) in pts with HFrEF and correlated with age ($R=0.74$, $p<0.05$), LVEDV ($R=0.57$, $p<0.05$), LVEDD ($R=0.48$, $p<0.05$), triglycerides level ($R=0.45$, $p<0.05$).

Table 3

Serum levels of AGEs and galectin-3 differences

	1st group Post infarction CHFpEF	2nd group Post infarction CHFrEF	p
Advanced glycated end products (AGE)mg/ml	1.6 [1.4;1.9]	1.6 [1.2;1.8]	0.204
Galectin-3ng/ml	6.3 [5.8;9.1]	7.2 [6.9;10.8]	0.041

The FMD% level was significantly higher in 1st group pts. (fig.). The majority of patients with HFpEF, HFrEF and myocardial infarction in the anamnesis had endothelial dysfunction – 15 (75%) and 15 (100%). The FMD% level correlated with age ($R=-0.64$, $p<0.05$), GFR ($R=0.52$, $p<0.05$), LVEDV ($R=-0.63$, $p<0.05$), galactin-3 level ($R=-0.72$, $p<0.05$).



FMD% level in pts with HF with different EF

CONCLUSION

1. HFrEF patients with MI in anamnesis had significantly increased left ventricle diastolic volume, left ventricle systolic volume, left ventricle diastolic dimension, left ventricle end systolic dimension.
2. AGEs serum level was mildly increased in patients with HFpEF and HFrEF.
3. Galectin-3 level was significantly higher in pts with HFrEF and correlated with age.
4. Most of the patients with HFpEF, HFrEF had endothelial dysfunction but the FMD % level was significantly higher in HFpEF pts.

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