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SERUM MATRIX METALLOPROTEINASE (MMP)-2,9 ACTIVITY, GALECTIN-3 AND SYSTEMIC INFLAMMATION IN PATIENTS WITH POSTINFARCTION HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Abstract. Serum matrix metalloproteinase-2,9 activity, galectin-3 and systemic inflammation in patients with postinfarction heart failure with preserved ejection fraction. Kuryata O., Zabida A., Sirenko O. *The available data suggest that heart failure (HF) after myocardial infarction (MI) is a very frequent event. 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. However, the true prevalence and relevance of diastolic dysfunction after MI remains to be elucidated. Objective: study was designed to evaluate the serum level of MMP-2,9, galactin-3 and C-reactive protein (C-RP) in postinfarction heart failure with preserved ejection fraction (HFpEF) patients. Methods: We divided all included patients into two main groups: 1st group – 20 patients with HFpEF and history of myocardial infarction. 2nd group – 18 patients with HFpEF and stable angina. Standard laboratory blood tests for erythrocyte sedimentation rate (ESR), C-RP, haematological parameters, lipid profile, glucose, renal and liver function tests were performed and calculated body mass index (BMI) for all patients. MMP activity assay and galectin-3 serum level was detected for all patients. Results: It was established significant differences between study groups in MMP-2, MMP-9 levels. Particularly, patients with HFpEF with MI in anamnesis had significantly higher MMP-2, MMP-9 levels on 21.8% and 20.7% respectively. The C-RP and leucocytes levels were significantly higher in 1st group pts. Significant differences in MMP-2, MMP-9 were established in 1st group patients in different age groups (p<0.05) (tab. 3). The MMP 2 level was positively correlated with MMP 9 level (R=0.73, p<0.05), the MMP 9 level – with age (R=0.68, p<0.05). There were no significant differences between galectin-3 level in study group. But we estimated significant differences in galectin-3 level between 1st and 2nd subgroups (p<0.05). Conclusion: Serum MMP-2, MMP-9, CRP and galactin-3 were significantly increased in pts with postinfarction heart failure with preserved ejection fraction compare to pts without myocardial infarction in anamnesis.*

Реферат. Рівень матричних металопротеїназ-2,9, галектину-3 та системне запалення у хворих з постінфарктною серцевою недостатністю зі збереженою фракцією викиду. Курята О.В., Забіда А., Сіренко О.Ю. *Літературні дані свідчать, що серцева недостатність (СН) після перенесенго інфаркту міокарда (ІМ) є частою подією. Однак поширеність і фактори виникнення діастолічної дисфункції лівого шлуночка після перенесеного ІМ залишаються маловивченими. Мета: оцінити рівні сироваткових ММР-2,9, галактину-3 та С-реактивного білка (СРП) при постінфарктній серцевій недостатності зі збереженою фракцією викиду. Матеріали та методи: у дослідження включено 38 пацієнтів з СН зі збереженою фракцією викиду віком від 40 до 80 років: 1 група (n=20) з перенесеним інфарктом міокарда в анамнезі, 2-а група (n=18) пацієнтів зі стабільною стенокардією. Виконано стандартні лабораторні аналізи крові, визначення СРП, гематологічних параметрів, ліпідного профілю, глюкози, креатиніну. Визначення активності ММР та рівня галактину-3 в сироватці крові проводилось усім пацієнтам. Результати: пацієнти з ХСН з ІМ в анамнезі мали достовірно вищий рівень ММР-2, ММР-9 на 21,8% та 20,7% відповідно (p<0,05). Рівні СРП та лейкоцитів були достовірно вищими в пацієнтів 1-ї групи (p<0,05). Достовірні відмінності рівней ММП-2, ММР-9 встановлені в пацієнтів з перенесеним ІМ у різних вікових групах (p<0,05). Рівень ММР-2 позитивно корелював з рівнем ММР-9 (R=0,73, p<0,05), рівень ММР-9 – з віком (R=0,68, p<0,05). Встановлені достовірні відмінності між рівнем галектину-3 серед пацієнтів різного віку (p<0,05). Висновок: сироваткові рівні ММР-2, ММР-9, СРП та галектину-3 були достовірно вищі у хворих з постінфарктною серцевою недостатністю зі збереженою фракцією викиду порівняно з пацієнтами без інфаркту міокарда в анамнезі.*

The available data suggest that heart failure (HF) after myocardial infarction (MI) is a very frequent event [10]. 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 [9, 10]. 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 [9].

The endothelium may also be central to the pathophysiology of heart failure, with endothelial cell damage or dysfunction that is probably more evident than that from vascular disease alone [1, 2, 3]. Certainly, heart failure is associated with abnormalities of thrombogenesis, leading to an increase in thrombosis related complications in this condition [10]. In HF, myocardial ischaemia features prominently (even in dilated cardiomyopathy) and severely depressed myocardial blood flow is a predictor of poor prognosis [15].

Left ventricular (LV) regional remodelling is a continuous process that last for months to years after the acute injury and which will eventually lead to the development of HF. Matrix metalloproteinases (MMPs) and tissue inhibitor metalloproteinase (TIMPs) continue to have an important role in the process of chronic LV remodelling [12, 15].

A region specific portfolio of MMPs is induced after MI and is accompanied by a decline in TIMP levels, indicative of a loss of MMP-inhibitory control. MMP-1 and MMP-9 levels are significantly reduced within the border and MI regions at 8 weeks post-MI, whereas MMP-2 levels increases substantially within the border and MI regions [15], suggesting that MMP-9 mainly is associated with early post-MI events [12, 16]. In contrast to the acute MI setting, a different set of MMPs emerges at 8 weeks after MI. Interestingly, MMP-8, localized to neutrophils, is increased by over 6-fold within the border and MI regions at 8 weeks after MI, suggesting that MMP-8 is associated with a more chronic inflammatory response [6, 12, 16]. The levels of the collagenase MMP-13, and MT1-MMP are increased by nearly 3-fold in both border and MI region 8 weeks post-MI [15]. MMP-3 is reduced within the MI region and MMP-7 falls within the border and MI regions 8 weeks post-MI. TIMP abundance decreases significantly in the border region after MI, and TIMP-1, -2 and -3 fall to undetectable levels within the MI region. Similar results are obtained by the use of a pig model of MI [12]. These data clearly demonstrate that targeting of the regional imbalance between specific MMPs and TIMPs within the post-MI myocardium holds a therapeutic potential.

Galectin-3 is a β-galactoside–binding lectin secreted by activated macrophages, which has gained interest as at least a marker of, or possibly even a potential mediator in inflammation and fibrosis, processes that are central to the pathophysiology of LV remodeling [6, 14, 16]. Tsai et al. suggested few important clinical implications of galectine-3: 1) circulating galectine-3 was significantly higher in MI patients than in normal controls; 2) there were significant positive correlations of high circulating galectine-3 to an advanced Killip score, unstable haemodynamics requiring inotropic support, advanced HF and a high CADILLAC risk score; 3) elevated galectin-3 was proven to be a strong independent predictor of 30-day MACO (major adverse clinical outcome) among patients with STEMI undergoing primary percutaneous interventions [16]. Though, Weir et al. had demonstrated that higher galectin-3 concentrations at baseline were significantly associated with lower left ventricle ejection fraction (LVEF) at 24-week follow-up, although there was no significant relationship between galectin-3 and remodeling per se [6].

Zile et al. had demonstrated in one small series that galectin-3 levels were significantly elevated in cohort of patients with HF with HFpEF [14]. Galectin-3 might provide an early warning marker for patients who are at risk for development of HF symptoms and may allow medical intervention. According to other animal and human studies, galectin-3 in addition to clinical and some studies have shown that galectin-3 had independent prognostic value, even after correction for established risk factor such as age, sex, BNP level, renal function, and diabetes mellitus [7].

Prognostic value of galectin-3 levels in plasma appears to be much stronger in the subset of patients with HFpEF in comparison with HF with reduced ejection fraction (HFrEF) [8, 11, 13]. Also, base line levels of galectin-3 seem to be sufficient to predict outcome, because serial measurement did not increase the prognostic yield [4, 7].

Aim of our study to evaluate the serum level of MMP-2, -9, galactin-3 and C-reactive protein (CRP) in postinfarction heart failure with preserved ejection fraction patients.

MATERIALS AND METHODS

Baseline study

The study was conducted with approval from the Ethics committee at State Establishment «Dnipropetrovsk Medical Academy of Health Ministry of Ukraine» according to principles outlined in the Helsinki declaration.

Patients (n=38) included aged 40 to 80 years, 29 males and 9 females were diagnosed with (HFpEF), according to ESC guidelines (2016) [5], and their functional class according to NYHA classification for HF. All patients got standard treatment for chronic heart failure (CHF) according to ESC guidelines 2016 [10].

Patients with acute myocardial infarction (<6 months), ejection fraction (EF) ≤40%, 2nd and 3rd degree heart block, diabetes mellitus (DM), kidney insufficiency (glomerular filtration rate: GFR≤30 ml/min/1.73m²), hepatic failure, and cancer were excluded.

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

Gelatin zymography (mmp activity assay)

The gelatinolytic activity was analyzed by separating serum proteins (100 µg/track) on 7.5% SDS-PAGE gels copolymerized with gelatin (3 mg/ml). After electrophoresis, the gels were washed twice for 30 min in gold 2.5% (v/v) Triton X-100 to remove SDS, and then 5 times for 5 min in cold bi-distilled water. After washing, gels were incubated overnight at 37 °C in developing 50 mM tris-HCl buffer (pH 7.6), containing 0.15 M NaCl, 5 mM $CaCl_2$, 1 mM ZnCl2, and 0.02% Tween-80. Zymograms were stained with 0.11% Coomassie Briliant Blue R-250 solution in 30% methanol and 10% acetic acid and destained in the same solution lack of Coomassie Blue. The final gel had a uniform blue background except in those regions to which MMPs had migrated and cleaved the substrate. The gelatinolytic activity was identified as transparent bands against the background of Coomassie Blue-stained gelatine. The zymograms were visualized and analyzed densitometrically.

All patients were assessed with galectin-3 blood levels by immunoassay analysis using the "Human Galectin-3 Platinum ELISA" kit (GmbH, Austria) on the Stat Fax 2100 (USA) immunoassay plate analyser. The base level was taken as 0 ng/ml.

Study design

We divided all included patients into two main groups:

1st group: 20 patients with HFpEF and history of myocardial infarction.

2nd group: 18 patients with HFpEF and stable angina.

Table 1

Baseline characteristics of the study population

Characteristics		Patients with CHF+MI in anamnesis (n=20)	Patients with CHF+stable angina (control group) (n=18)	p
Gender	Males (%)	16 (80%)	13 (72%)	
	Females (%)	4 (20%)	5 (28%)	
Age, years M±m		66±9	70±4	0,2106
CHFClass according to NYHA	2nd FC	10 (50%)	11 (61%)	
	3rd FC	10 (50%)	7 (39%)	
Heart rate, beat/minute M±m		74±5	77±4	0.137
Body mass index (BMI) M±m		28,00±2.10	30,00±2.50	0.202
Blood glucose, mmol/L M±m		5.45±0.20	5.15±0.25	0.337
Cholesterol, mmol/L M±m		5.50±1.60	4.95±0.25	0.048
Triglycerides, mmol/L M±m		1.60±0.40	1.20±0.25	0.101
ECHOCARDIOGRAPHY				
Left ventricle ejection fraction (EF), % M±m		56.00±10.00	61.00±11.00	0.136
Left ventricle end diastolic volume (LVEDV), ml M±m		137.50±45.50	116.00±35.00	0.028
Estimated Pulmonary artery pressure sPAP, mmHg M±m		30.01±9.12	28.24±7.14	0.547
Treatment history, no, (%)				
Beta-blockers		16 (80%)	13 (72%)	
Renin angiotensin aldosterone system (RAAS) inhibitors		15 (75%)	14 (78%)	
Statins		17 (85%)	15 (83%)	
Acetylsalicylic acid (ASA)		19 (95%)	16 (88%)	

RESULTS AND DISCUSSION

Clinical characteristics of patients were summarized in table 1. HFpEF patients with MI in anamnesis had significantly higher cholesterol level and left ventricle end diastolic volume (LVEDV) ($p<0.05$). There were no significant differences between the other indicators and treatment characteristics.

Table 2

The level of MMP-2, MMP-9, galectin-3 in patients with HFpEF depending on MI anamnesis

	1st group	2nd group	p
MMP-2 (ng/ml) M±m	78.00±18.00	61,00±16.00	0.002
MMP-9 (ng/ml) M±m	217.50±21.50	172.50±6.50	0.003
Galectin-3 (ng/ml) M±m	8.10±4.23	7.04±3.12	0.347

It was established significant differences between study groups in MMP - 2, MMP-9 levels. Particularly, HFpEF patients with MI in anamnesis had significantly higher MMP-2, MMP-9 levels on 21.8% and 20.7% respectively.

The CRP and leucocytes levels were significantly higher in 1st group pts. (fig.).

Significant differences in MMP-2, MMP-9 were established in 1st group patients in different age groups ($p<0.05$) (tab. 3). The MMP-2 level was positively correlated with MMP 9 level ($R=0.73$, $p<0.05$), the MMP-9 level – with age ($R=0.68$, $p<0.05$).

There were no significant differences between galectin-3 level in study group. But we estimated significant differences in galectin-3 level between 1st and 2nd subgroups ($p<0.05$) (tab. 3).

While cytokines and MMPs have independent effects on the myocardium, past in vitro and animal studies have identified the ability of cytokines to regulate the transcription and synthesis of various MMPs. For example, TNF over-expression in mice led to increased protein levels of MMP-2 and -9 and TIMP-1 [4, 8, 11, 17]. Regulation of MMP synthesis includes several transcription factors that are downstream of cytokine signaling. Specifically, in fibroblasts, IL-1β stimulation has been reported to increase protein levels of MMP-2 and -9, which were attenuated with the inhibition of the transcription factor NF-κB [11]. Similarly, IL-6 can induce the expression of MMP-1 in macrophages mediated through transcriptional regulation of activator protein-1 and NF-κB [8]. By contrast, the anti-inflammatory cytokine IL-10 suppressed MMP-2 synthesis by signaling through the activating transcription factor 3 and binding to the cAMP-responsive element of the MMP-2 gene [4].

Table 3

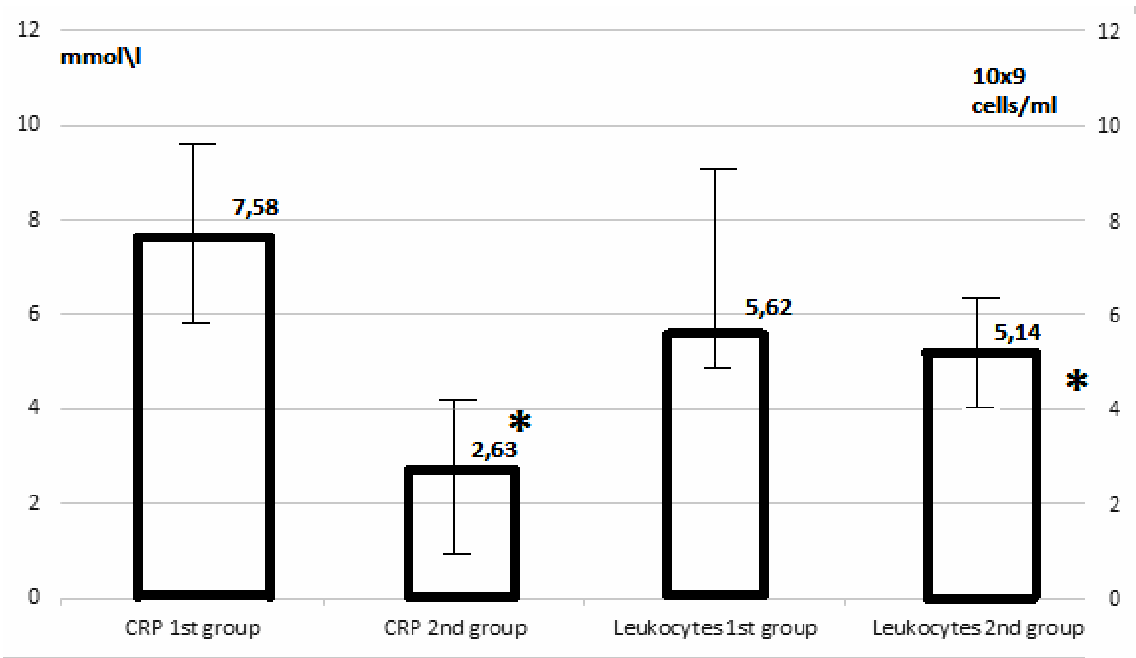
The level of MMP-2, MMP-9, galectin-3 in patients with HFpEF in different age groups

	1st group		2nd group	
	40-59 y.o.	≥ 65 y.o.	40-59 y.o.	≥ 65 y.o.
MMP-2 (ng/ml) M±m	81.50±14.50*	85.50±8.50*	72.00±5.00	78.00±13.00
MM-9 (ng/ml) M±m	212.50±16.50*	219.50±19.50*	172.5±6.50	175.00±4.00
Galectin-3 (ng/ml) M±m	6.78±2.91	11.31±1.01#	6.21±2.29	9.95±0.22#

N o t e s : * – p< 0.05 between 1 and 2 groups, # – p<0.05 between 40-59 y.o. and ≥65 y.o. groups.

Galectin-3 overexpression is also a characteristic feature of “profibrotic” M2 macrophages: naïve macrophages stimulated with interleukin-4 (IL-4) and IL-13 express higher levels of galectin-3, together with pathophysiology of diabetes mellitus type 1 by inducing β-cell apoptosis: mice β-cells from galectin-3 were resistant to inflammation-induced cell death by counteracting mitochondrial apoptotic pathways [6]. This is in contrast to previous research that demonstrated that intracellular galectin-3 supresses mitochondrial apoptotic pathways by preserving mitochondrial integrity [14].

In summary, the final outcome of the fibro-inflammatory response is determined by a dynamic balance between neutrophil apoptosis, macrophage and T-cell responses, fibroblast activation and myofibroblast persistence, and intracellular galectin-3 seems to be involved in many of these responses. However, our current understanding of galectin-3-mediated apoptotic mechanisms is limited and further studies are warranted to characterize the role of intracellular galectin-3 in apoptosis of different cell types, especially in immune-cells and collagen-producing cells.



Note. * – p<0.05

CRP, leucocytes levels in patients with HFpEF depending on MI in anamnesis

Limitation

In addition to the few number of patients included in this study, we excluded from our study patients with acute coronary artery diseases and acute heart failure, because of this our results apply only to the patients with chronic coronary artery diseases and chronic heart failure.

There are many matrix metalloproteinases which involved in all cardiovascular diseases, but in our study we measured levels and activity of only MMP-2 and MMP-9.

CONCLUSION

1. Serum MMP-2, MMP-9, CRP and galactin-3 were significantly increased in pts with postinfarction heart failure with preserved ejection fraction comparing to pts without myocardial infarction in anamnesis.
2. Increased level of serum MMP-2, MMP-9, CRP were positively correlated with age reaching maximal concentration with age ≥65 years old in pts with postinfarction heart failure with preserved ejection fraction.

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ФУНКЦІЯ ЗОВНІШНЬОГО ДИХАННЯ У ХВОРИХ ПІСЛЯ ТРАНСПЛАНТАЦІЇ НИРКИ В УМОВАХ ІМУНОСУПРЕСИВНОЇ ТЕРАПІЇ

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