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The relationship between systolic function and serum NGAL levels in patients with chronic heart failure of ischemic origin

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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 the article

Key words: serum NGAL, left ventricular systolic function, chronic heart failure of ischemic origin, renal dysfunction, biomarker of tubulo-interstitial injury.

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Neutrophil gelatinase-associated lipocalin (NGAL) is considered one of the most informative biomarkers of chronic kidney disease (CKD). NGAL can also serve as a biomarker of cardiovascular disease and heart failure (HF). However, the relationship between systolic function and serum NGAL concentrations in patients with chronic HF (CHF) of ischemic origin remains insufficiently studied.

The aim. To study the influence of tubulo-interstitial injury marker NGAL on systolic function in patients with CHF of ischemic origin.

Materials and methods. The study included 51 patients with CHF, stage II AB, NYHA II-IV FC. Doppler echocardiographic examination was performed on the device Esaote MyLab Eight (Italy) according to standard methods. NGAL levels were analyzed using an ELISA kit (E-EL-H0096, Elabscience, USA). Depending to the concentration of serum NGAL, the patients were divided into 2 subgroups. In the first group (n = 37), the NGAL level was higher than 168 ng/ml, in the second (n = 14) – less than 168 ng/ml.

Results. The mean serum NGAL concentration in the first subgroup was 192 (183; 200) ng/ml, in the second subgroup – 154 (134; 160) ng/ml. The patients with CHF of ischemic origin with tubulo-interstitial injury (according to the serum concentration of NGAL) did not differ significantly from the patients with CHF of ischemic origin without tubulo-interstitial injury in age (P = 0.950), height (P = 0.983), weight (P = 0.681), body surface area (P = 0.975). Most of left ventricular systolic function indicators showed a downward tendency (S 6.90 ± 2.85 cm/s vs. 7.67 ± 2.83 cm/s (P = 0.536); S lat 7.33 ± 2.08 cm/s vs. 11.00 ± 4.00 cm/s (P = 0.467); TEI LV 0.56 ± 0.26 c.u. vs. 0.49 ± 0.14 c.u. (P = 0.747)) in the patients with CHF of ischemic origin with elevated serum levels of NGAL compared to similar indicators in the patients with CHF of ischemic origin without tubulo-interstitial injury. The index of LVEF was significantly lower in the patients with CHF with elevated serum NGAL compared to that in the patients with CHF with normal serum NGAL (50.43 ± 17.85 % vs. 63.29 ± 13.24 % (P = 0.021)).

Conclusions. Serum NGAL was not only the sensitive marker of tubulo-interstitial injury in patients with CHF of ischemic origin, but also appeared to be a predictor of changes in systolic heart function.

Ключові слова: сироватковий NGAL, систолічна функція лівого шлуночка, хронічна серцева недостатність ішемічного ґенезу, ниркова дисфункція, біомаркер ураження тубулоінтерстицію.

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Зв'язок систолічної функції серця та рівня NGAL у сироватці крові хворих на хронічну серцеву недостатність ішемічного ґенезу

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Ліпокалін, асоційований із нейтрофільною желатиназою (NGAL), вважають одним із найінформативніших біомаркерів хронічної хвороби нирок (ХХН). NGAL може бути біомаркером серцево-судинних захворювань і серцевої недостатності. Недостатньо вивчено питання щодо зв'язку систолічної функції у хворих на хронічну серцеву недостатність (ХСН) ішемічного ґенезу з вмістом NGAL у сироватці крові.

Мета роботи – дослідити зв'язок маркера ураження тубулоінтерстицію NGAL із систолічною функцією у хворих на ХСН ішемічного ґенезу.

Матеріали та методи. У дослідження залучили 51 особу, яка хвора на ХСН ішемічного ґенезу, II А–Б стадії, II–IV ФК за NYHA. Доплер-ехокардіографічне дослідження виконали на апараті Esaote MyLab Eight (Італія) за стандартною методикою. Рівень NGAL аналізували за допомогою набору ELISA kit (імуноферментний аналіз) (E-EL-H0096, Elabscience, США). За показниками вмісту сироваткового NGAL хворих на ХСН поділили на 2 групи: у першій (n = 37) цей показник становив понад 168 нг/мл, у другій (n = 14) – менше ніж 168 нг/мл.

Результати. Середній уміст NGAL у сироватці в першій групі становив 192 (183; 200) нг/мл, у другій – 154 (134; 160) нг/мл. Хворі на ХСН ішемічного ґенезу з ураженням тубулоінтерстицію (за вмістом NGAL у сироватці) вірогідно не відрізнялися від пацієнтів із ХСН ішемічного ґенезу без ураження тубулоінтерстицію за віком (p = 0,950), зростом (p = 0,983), вагою (p = 0,681), площею поверхні тіла (p = 0,975). Більшість показників систолічної функції лівого шлуночка свідчила про тенденцію до її зниження (S 6,90 ± 2,85 см/с проти 7,67 ± 2,83 см/с (p = 0,536); S lat 7,33 ± 2,08 см/с проти 11,00 ± 4,00 см/с (p = 0,467); TEI LV 0,56 ± 0,26 ум. од. проти 0,49 ± 0,14 ум. од. (p = 0,747)) у хворих на ХСН ішемічного ґенезу з підвищеним рівнем NGAL у сироватці порівняно з відповідними показниками у хворих на ХСН ішемічного ґенезу без ураження тубулоінтерстицію. Показник ФВ ЛШ вірогідно менший у хворих на ХСН із підвищеним рівнем NGAL у сироватці порівняно з показником пацієнтів із ХСН і нормальним вмістом NGAL у сироватці (50,43 ± 17,85 % проти 63,29 ± 13,24 % (p = 0,021)).

Висновки. Сироватковий NGAL – не тільки чутливий маркер ураження тубулоінтерстицію нирок у хворих на ХСН ішемічного ґенезу, але і предиктор змін систолічної функції серця.

Взаимосвязь систолической функции сердца и уровня NGAL в сыворотке крови у больных хронической сердечной недостаточностью ишемического генеза

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Ключевые слова: сывороточный NGAL, систолическая функция левого желудочка, хроническая сердечная недостаточность ишемического генеза, почечная дисфункция, биомаркер поражения тубулоинтерстиция.

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Липокалин, ассоциированный с нейтрофильной желатиназой (NGAL), считают одним из самых информативных биомаркеров хронической болезни почек (ХБП). NGAL может быть биомаркером сердечно-сосудистых заболеваний и сердечной недостаточности. Недостаточно изучен вопрос о взаимосвязи систолической функции у больных хронической сердечной недостаточностью (ХСН) ишемического генеза с содержанием NGAL в сыворотке крови.

Цель работы – исследовать взаимосвязь маркера поражения тубулоинтерстиция NGAL с систолической функцией у больных ХСН ишемического генеза.

Материалы и методы. В исследование включили 51 больного ХСН ишемического генеза, II А–Б стадии, II–IV ФК по NYHA. Допплер-эхокардиографическое исследование проведено на аппарате Esaote MyLab Eight (Италия) по стандартной методике. Уровень NGAL анализировали с помощью набора ELISA kit (иммуноферментный анализ) (E-EL-H0096, Elabscience, США). По содержанию сывороточного NGAL больных ХСН разделили на 2 группы: в первой (n = 37) этот показатель был выше 168 нг/мл, во второй (n = 14) – меньше 168 нг/мл.

Результаты. Среднее содержание NGAL в сыворотке в первой группе составило 192 (183; 200) нг/мл, во второй – 154 (134; 160) нг/мл. Больные с ХСН ишемического генеза с поражением тубулоинтерстиция (по содержанию NGAL в сыворотке) достоверно не отличались от пациентов с ХСН ишемического генеза без поражения тубулоинтерстиция по возрасту (p = 0,950), росту (p = 0,983), весу (p = 0,681), площади поверхности тела (p = 0,975). Большинство показателей систолической функции левого желудочка свидетельствовало о тенденции к ее снижению (S 6,90 ± 2,85 см/с против 7,67 ± 2,83 см/с (p = 0,536); S lat 7,33 ± 2,08 см/с против 11,00 ± 4,00 см/с (p = 0,467); TEI LV 0,56 ± 0,26 у. е. против 0,49 ± 0,14 у. е., (p = 0,747)) у больных ХСН ишемического генеза с повышенным уровнем NGAL в сыворотке по сравнению с соответствующими показателями пациентов с ХСН ишемического генеза без поражения тубулоинтерстиция. Показатель ФВ ЛЖ существенно ниже у больных ХСН с повышенным уровнем NGAL в сыворотке по сравнению с показателем пациентов с ХСН и нормальным содержанием NGAL в сыворотке (50,43 ± 17,85 % против 63,29 ± 13,24 % (p = 0,021)).

Выводы. Сывороточный NGAL – не только чувствительный маркер поражения тубулоинтерстиция почек у больных ХСН ишемического генеза, но и предиктор изменений систолической функции сердца.

Renal dysfunction is one of the most common and important comorbidities in chronic heart failure (CHF) and is associated with unfavorable outcome, including mortality [1].

Neutrophilic gelatinase-associated lipocalin (NGAL) is considered one of the most informative biomarkers of acute renal failure (ARF) and chronic kidney disease (CKD) [2]. It is a low molecular weight glycosylated protein (25 kDa) of the lipocalin family, and is encoded by a gene that is expressed in constantly low amounts in neutrophils, hepatocytes, renal proximal and distal tubular epithelial cells. In healthy humans, its serum and urine concentrations are less than 20 ng/ml [3].

NGAL has been shown to be involved in inflammatory, atherosclerotic processes and may serve as a biomarker of cardiovascular disease and CHF [2,4].

In patients with CHF, an increase in all-cause mortality and hospitalization have been associated with NGAL activation in cardiomyocytes and an increase in its level [5].

Elevated plasma NGAL level in ARF and CKD is correlated with an increase in its urine concentration, but does not reflect genuine kidney damage, since extrarenal NGAL production rather contributes to these results [3].

Serum NGAL levels may be elevated in patients with coronary heart disease and CHF, including patients without renal dysfunction and are correlated with the severity of heart disease. Besides, NGAL has proven its prognostic significance in the elderly patients without kidney disease in a study on morbidity and cardiovascular mortality [6].

However, the relationship between systolic function in patients with CHF of ischemic origin and serum NGAL concentration remains insufficiently studied.

Aim

To study the influence of tubulo-interstitial injury marker NGAL on systolic function in patients with CHF of ischemic origin.

Materials and methods

The study was conducted on the clinical base of the Department of Propaedeutics of Internal Medicine, Radiation Diagnostics and Radiation Therapy (Zaporizhzhia State Medical University) in the Cardiology Department of City Hospital No. 6 (Zaporizhzhia), in accordance with the Good Clinical Practice guidelines and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Zaporizhzhia State Medical University.

After obtaining written informed consents, the study included 51 patients with CHF of ischemic origin, stage II AB, New York Heart Association (NYHA) II–IV functional class (FC). The diagnosis of CHF of ischemic origin was made in accordance with the Recommendations for the diagnosis and treatment of CHF (2017) of the Association of Cardiologists of Ukraine and the Ukrainian Association of Heart Failure [7]. Doppler echocardiographic examination was performed on a device Esaote MyLab Eight (Italy) according to standard methods [8].

Blood samples were taken in the morning on an empty stomach and placed into chilled EDTA (ethylenediaminetetraacetic acid) vacuum tubes immediately after collection. Then, the samples were centrifuged for 10 minutes in a refrigerated centrifuge, and the plasma and serum were stored at -80 °C. NGAL levels were analyzed using an ELISA kit (E-EL-H0096, Elabscience, USA) in a diagnostic center Medlife-Bio (Director – O. S. Ostashinskaya). Sensitivity 0.10

Table 1. Types of LV geometry in CHF patients with normal or elevated serum NGAL levels

Type of LV geometry	Group of CHF patients with normal serum NGAL level, n = 14	Group of CHF patients with elevated serum NGAL level, n = 37	P
Normal	0 % (0)	14 % (5)	0.1461
Eccentric hypertrophy	58 % (8)	70 % (26)	0.3846
Concentric hypertrophy	21 % (3)	16 % (6)	0.6759
Eccentric remodeling	21 % (3)	0 % (0)	0.0060
Concentric remodeling	0 % (0)	0 % (0)	1.0000

ng/ml. The measurement range of the kit is 0.16–10.00 ng/ml with a variation of the internal analysis coefficient <10 %. NGAL levels were expressed in ng/ml.

The patients were divided into 2 subgroups based on the concentration of serum NGAL. The cut-off values of NGAL (168 ng/ml) was obtained by ROC analysis depending on the composite endpoint (death, acute coronary syndrome (ACS), stroke, decompensated HF).

In the first group (n = 37), the NGAL level was higher than 168 ng/ml, in the second (n = 14) – less than 168 ng/ml. The mean serum NGAL level in the first group was 192 (183; 200) ng/ml, in the second group – 154 (134; 160) ng/ml. The patients with CHF of ischemic origin with tubulo-interstitial injury (according to the serum NGAL concentration) didn't differ significantly from the patients with CHF of ischemic origin without tubulo-interstitial injury in age (P = 0.950), height (P = 0.983), weight (P = 0.681), body surface area (P = 0.975).

Statistical processing of the material was performed using the software package Statistica 13.0 (StatSoft, USA), license number JPZ8041382130ARCN10-J. The Shapiro–Wilk test was used to ascertain the normality of the quantitative data. The parameters with normal distribution were given as the arithmetic mean and standard deviation (M ± SD). The results without normal distribution were demonstrated by descriptive statistics as median, lower and upper quartiles – Me (Q25; Q75). The normal and non-normal distributed quantitative variables in the groups were compared by T-test or Mann-Whitney test, respectively, after ascertaining the normality of distribution. The difference was considered statistically significant at a P-value <0.05. All the tests were two-tailed.

Results

There was no significant difference between the main parameters of LVDD (P = 0.858), right ventricle (P = 0.423), left atrium (P = 0.916) in the groups of patients with CHF with and without an increase in serum NGAL. Nevertheless, the patients with CHF with elevated serum NGAL levels were likely to have a greater EDV LV (185.64 ± 68.80 ml vs. 178.80 ± 58.74 ml, P = 0.042), LVDS (4.46 ± 1.25 cm vs. 3.86 ± 0.82 cm, P = 0.024) than those in the patients with CHF with normal serum NGAL levels. On the absolute wall thickness and left ventricular myocardial mass index side, the groups of patients with CHF with elevated or normal serum NGAL levels did not differ statistically, although there was an upward trend with an increase in serum NGAL concentration. The relative left ventricular posterior wall thickness was significantly increased in the patients with CHF and elevated serum NGAL levels (0.35 ± 0.09 cm vs. 0.34 ± 0.14 cm, P = 0.029).

Differences in types of left ventricular (LV) geometry were an increase in the percentage of eccentric hypertrophy to 70 % with a reduction in eccentric remodeling in the HF patients with high serum NGAL concentrations (P = 0.006). Most of the patients in both groups had eccentric hypertrophy (70 % vs. 58 %, P = 0.3846), but this difference did not reach statistical significance (*Table 1*).

The vast majority of the left ventricular systolic function indicators trended downward (S 6.90 ± 2.85 cm/s vs. 7.67 ± 2.83 cm/s (P = 0.536); S lat 7.33 ± 2.08 cm/s vs. 11.00 ± 4.00 cm/s (P = 0.467); TEI LV 0.56 ± 0.26 ppm vs. 0.49 ± 0.14 ppm (P = 0.747)) in the patients with CHF of ischemic origin and elevated levels of serum NGAL compared with those in the patients with CHF of ischemic origin without tubulo-interstitial injury. LV ejection fraction (LV EF) was significantly reduced in the CHF patients with elevated serum NGAL compared to the CHF patients with normal serum NGAL (50.43 ±17.85 % vs. 63.29 ±13.24 % (P = 0.021)).

The vast majority of CHF patients regardless of serum NGAL levels had diastolic dysfunction of "relaxation disorder" type (57 % vs. 49 %, P = 0.6123) with a slight predominance of "pseudonormal" diastolic filling pattern of the LV (35 % vs. 14 %) P = 0.1476) in the CHF patients with elevated serum NGAL levels. The serum NGAL involvement in pathological heart remodeling in the CHF patients was evident by correlations between its concentration and LVDS (r = 0.31; P = 0.02), LV EF (r = -0.40; P = 0.007), lateral mitral valve annulus diastolic velocity e' (r = -0.32; P = 0.02).

Discussion

In physiological conditions, NGAL is expressed at a low level in the epithelium of a variety of human tissues and organs including kidney, heart, stomach, lung and colon. Recent studies have shown an increase in serum NGAL levels in patients with acute and CHF. Poniatowski B. et al. (2009) identified serum and urine NGAL as a sensitive early marker of renal dysfunction in patients with CHF [9].

The GALLANT prospective trial showed that plasma NGAL level at the time of hospital discharge is a powerful prognostic indicator of 30 days outcomes in patients with acute HF. In addition, NGAL was not only a risk predictor for kidney injury, but it was an overall risk biomarker for cardiovascular events in patients with acute HF. NGAL is regarded as one of the earliest markers synthesized in the kidney following acute ischemic or nephrotoxic injury [10].

The study results of K. Damman et al. (2008) have brought out clearly that structural tubular damage is commonly associated with increased urinary NGAL concentrations in patients with CHF [11].

NGAL is an early marker of cardio-renal syndrome in patients with CHF. Alvelos M. et al. (2011) have estimated a cut-off value of serum NGAL above 170 ng/ml (AUC = 0.93, P < 0.001), which was associated with renal function worsening in patients with CHF [12].

In elderly patients (mean age 80 years) with acute decompensated HF, serum NGAL remained a sensitive marker of renal injury, although it had only moderate diagnostic accuracy [13]. According to M. Chioffi and co-authors (2013), serial measurements of NGAL in patients with acute

decompensated HF can accurately predict ARF in the first days of hospital admission [14].

Our findings on the cut-off value of NGAL (168 ng/ml) in patients with CHF of ischemic origin were very close to the cut-off values obtained in the study of M. Alvelos et al. (2011), which is the best evidence of the NGAL prognostic potential as the early marker of cardio-renal syndrome.

As regards the relationship between serum NGAL and LV systolic function in CHF patients, all kinds of opinions on this issue are worth mentioning here. For instance, K. Damman (2014) in his study showed that serum NGAL did not significantly correlate with LVEF or NYHA FC, as well as with other biomarkers such as kidney injury molecule-1 (KIM-1) and N-acetyl-β-D-glucosaminidase (NAG) [15].

At the same time, K. Shrestha et al. (2012) [16] found a significant correlation between serum NGAL levels and blood creatinine ($r = 0.68$, $P < 0.0001$) and glomerular filtration rate ($r = -0.69$, $P < 0.0001$), whereas urine NGAL was weakly correlated with renal function in patients with acute decompensated HF.

Siasos G. et al. (2014) reported a significantly higher level of NGAL in patients with CHF ($P = 0.007$) compared with healthy individuals. NGAL levels were inversely correlated with LVEF in the group of HF patients ($r = -0.23$, $P = 0.045$) [17].

According to our study, LVEF was significantly reduced in the CHF patients with elevated serum NGAL compared with that in the CHF patients with normal serum NGAL (50.43 ± 17.85 % vs. 63.29 ± 13.24 %, $P = 0.021$).

In a study of E. Martínez-Martínez et al. (2017), a greater increase in serum NGAL levels were significantly associated with lower 6-month LVEF recovery in patients after myocardial infarction (MI). The authors demonstrated that cardiac NGAL expression was increased at 7 days after MI and this effect was dependent on mineralocorticoid receptors activation. The researchers found elevated plasma NGAL levels in coronary heart disease patients even without renal dysfunction and correlated with the severity of the heart disease [18].

In the OPTIMAAL trial, higher serum NGAL levels were also associated with poor LV recovery in HF patients after myocardial infarction [19].

Evangelos Oikonomou et al. (2018) analyzed the relationship between NGAL levels and systolic parameters, loading condition and biomarkers of myocardial fibrosis in patients with stable HF of ischemic origin. The mean age in the CHF group was 67 ± 13 years, 53 % had diabetes mellitus and most of them had NYHA II FC. The median NGAL level was 159 (107; 207) ng/ml. No correlation was found between NGAL and age, body mass index, sex, blood pressure, and blood glucose. At the same time, in the CHF group, the NGAL level was inversely correlated with LV EF (rho = -0.31; $P = 0.02$), but there was no association of NGAL with the NYHA functional classification (NYHA II: 143 (106; 224) ng/ml vs. NYHA III: 167 (112; 241) ng/ml; $P = 0.13$) [5].

We have revealed only the downward trend in some indicators of LV systolic function (S 6.90 ± 2.85 cm/s vs. 7.67 ± 2.83 cm/s ($P = 0.536$); S lat 7.33 ± 2.08 cm/s vs. 11.00 ± 4.00 cm/s ($P = 0.467$); TEI LV 0.56 ± 0.26 ppm vs. 0.49 ± 0.14 ppm ($P = 0,747$)) with the increase in serum NGAL levels in the patients with CHF of ischemic origin.

An association between serum NGAL levels and remodeling in LV geometry was found. According to the results of echocardiography in the study of G. Siasos et al. (2014), 53.3 % and 37.2 % of ACS patients demonstrated LV concentric hypertrophy and concentric remodeling, respectively. Eccentric LV hypertrophy was detected in 5.7 % of patients, and only 3.8 % of ACS patients had normal LV geometry. The inverse correlation between serum NGAL and LVEF ($r = -0.23$, $P = 0.045$) was obtained [17].

We obtained evidence suggesting a shift in the distribution of LV geometry types towards increased percentage of eccentric hypertrophy to 70 % with reduced eccentric remodeling in the HF patients with high serum NGAL concentrations ($P = 0.006$).

Shalenkova M. A. (2018) reported a positive correlation between both serum and urine NGAL levels and echocardiographic parameters related to systolic function, size and geometry of the LV reporting that NGAL may serve as an additional biomarker not only of acute renal damage, CKD, but also of the cardiovascular pathology severity and heart remodeling in patients after exacerbation of coronary heart disease [21].

In patients with ischemic CHF, elevated serum NGAL levels were significantly correlated with the clinical stage of HF [19] and HF FC by the NYHA classification [22].

Numerous studies have supported the prognostic value of NGAL in patients with cardiovascular disease. Sahinarslan A. et al. (2011) have found a 12 times higher incidence of MI in coronary heart disease patients with serum NGAL levels greater than 127 ng/ml [20].

Siasos G. et al. (2014) found a higher serum NGAL level (266.00 (144.39; 508.20) ng/ml) in a complicated course of ACS compared to that without complications (172.61 (132.30; 262.68) ng/ml, $P = 0.023$) [17].

NGAL may also predict worsening of renal function and the evolution of cardiorenal syndrome earlier than monitoring serum creatinine levels in patients hospitalized for CHF.

Conclusions

In patients with CHF of ischemic origin, the serum level of NGAL was not only the sensitive marker of renal tubulo-interstitial injury, but also appeared to be a marker of cardiac remodeling. An increase in serum NGAL above 168 ng/ml in patients with CHF of ischemic origin was associated with the decrease in LVEF by 20 % ($P = 0.021$).

Prospects for further research are to study the relationship between markers of tubulo-interstitial injury (KIM-1 and NAG) and cardiac structural and geometric changes in patients with CHF of ischemic origin.

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