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

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

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

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Липокалин, ассоциированный с нейтрофильной желатиназой (NGAL), считаются одним из самых информативных биомаркеров хронической сердечной недостаточности (ХСН). 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 с ХСН ишемического генеза.

Материалы и методы. В исследование включили 51 больного ХСН ишемического генеза, II–IV стадий 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; S lat 6,90 ± 2,85 см/с против 7,67 ± 2,83 см/с; S lat 6,90 ± 2,85 см/с против 7,67 ± 2,83 см/с). СЕТ 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 с 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, но и предиктор изменений систолической функции сердца.
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 | Group of CHF patients with elevated serum NGAL level | 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  |

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

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)).

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).

In elderly patients (mean age 80 years) with acute HF, serum NGAL remained a sensitive 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. Chiolfi 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 cardiac-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-acetylated-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 urinary NGAL was weakly correlated with renal function in patients with acute decompensated HF.

Siassos 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 (r = -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. Siassos 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].

Siassos 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.

Conflicts of interest: authors have no conflict of interest to declare.

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