Neutrophil gelatinase-associated lipocalin levels in right and left heart failure: an observational study

Sağ ve sol kalp yetersizliğinde nötrofil jelatinaz-birleşik lipokalin seviyeleri: Gözlemsel bir çalışma

Fatih Koca, İbrahim Halil Tanboğa, Mehmet Mustafa Can, Alper Özkan, Nurşen Keleş, Hacer Ceren Tokgöz, Tahir Bezgin, Cihangir Kaymaz

Clinic of Cardiology, Kartal Koşuyolu Yüksek İhtisas Education and Research Hospital, İstanbul-*Turkey*

ABSTRACT

Objective: Neutrophil gelatinase-associated lipocalin (NGAL) is a novel marker for early detection of renotubular deterioration. Despite the limited data concerning the NGAL in heart failure (HF), significance of NGAL in right-sided HF remains unknown. We assessed serum and urinary NGAL in left and right-sided HF due to non-ischemic cardiomyopathy (NICMP) and severe pulmonary arterial hypertension (PAH).

Methods: In this cross-sectional observational study, we compared three groups; 35 patients with NICMP, 28 patients with PAH and 27 healthy controls. None had a serum creatinine ≥1.5 mg/dL. Plasma brain natriuretic peptide (BNP) levels, estimated glomerular filtration rate (eGFR) by Cockroft-Gault (CG) and Modification of Diet in Renal Disease Study formulas, echocardiographic measures of left and right ventricles (LV, RV) and non-invasive measurement of cardiac index (CI) by echocardiography and impedance cardiography were assessed. Differences among the groups for continuous variables were evaluated by the ANOVA and the Kruskal-Wallis test as appropriate. The Chi-square test was used for comparison of categorical variables.

Results: Despite eGFR with CG formula was lower in NICMP and PAH subsets as compared to those in controls (102±27 and 99.4±29.4 vs 122.4±25.9 mL/min, $p<0.05$ and $p<0.005$ in order), serum NGAL [141 (113-151), 174 (130-192) and 132 (95-181) ng/mL] and urinary NGAL [15 (12-18), 15 (12-22) and 13 (8-18) ng/mL] levels were not different among groups ($p=0.15$ and $p=0.35$, respectively).

Conclusion: Despite the mildly impaired eGFR in left-sided HF due to NICMP and right-sided HF due to PAH, neither serum, nor urinary NGAL levels are elevated in these patients. *(Anadolu Kardiyol Derg 2011; 11: 498-503)*

Key words: Neutrophil gelatinase-associated lipocalin, renotubular, heart failure, glomerular filtration rate, echocardiography

ÖZET

Amaç: Nötrofil jelatinaz-birleşik lipokalin (NJBL) renotübüler kötüye gidişatın erken tespitinde kullanılan yeni bir belirteçtir. Kalp yetersizliğinde (KY) NJBL'ye dair sınırlı veri bulunmasına rağmen sağ KY'deki önemi bilinmemektedir. Biz serum ve idrar NJBL seviyelerini sol ve sağ kalp yetersizliğinde-non-iskemik kardiyomiyopati (NİKMP) ve ciddi pulmoner arteryel hipertansiyonda (PAH) araştırdık.

Yöntemler: Enine-kesitli gözlemsel olan bu çalışmada 3 grubu karşılaştırdık; NİKMP'li 35 hasta, PAH'lu 28 hasta ve 27 sağlıklı kontrol grubu. Hiçbirinin serum kreatinini ≥1.5 mg/dL değil idi. Plazma beyin natriüretik peptid (BNP) seviyeleri, Cockroft-Gault ve Modification of Diet in Renal Disease Study formülleri ile hesaplanan tahmini glomerüler filtrasyon hızı (tGFH), sağ ve sol ventrikül ekokardiyografik ölçümleri ve kardiyak indeksin (Kİ) eko ve impedans kardiyografi ile non-invaziv ölçümleri değerlendirildi. Devamlı değişkenlerin gruplar arası karşılaştırılması ANOVA ve Kruskal-Wallis testi ile yapıldı. Devamlı olmayan değişkenler ise Ki-kare testi ile değerlendirildi.

Bulgular: Cockroft-Gault formülü ile hesaplanan tGFH, NİKMP ve PAH alt gruplarında kontrol grubuna kıyasla daha düşük olmasına rağmen (102±27 ve 99.4±29.4'e karşı 122.4±25.9 mL/dak, $p<0.05$ ve $p<0.005$ sırası ile), serum NJBL [141 (113-151), 174 (130- 192) ve 132 (95-181) ng/mL] ve idrar NBJL [15 (12-18), 15 (12-22) ve 13 (8-18) ng/mL] seviyeleri NİKMP, PAH ve kontrol grubu arasında fark göstermedi ($p=0.15$, $p=0.35$ sırası ile).

Sonuç: NİKMP nedeniyle sol kalp yetersizliği ve PAH nedeniyle sağ kalp yetersizliği olan hastalarda; hafifçe azalmış tGFH'ye rağmen, ne serum ne de idrar NJBL seviyeleri artmıştır. *(Anadolu Kardiyol Derg 2011; 11: 498-503)*

Anahtar kelimeler: Nötrofil jelatinaz-birleşik lipokalin, renotübüler, kalp yetersizliği, glomerüler filtrasyon hızı, ekokardiyografi

Address for Correspondence/Yazışma Adresi: Dr. Cihangir Kaymaz, Clinic of Cardiology, Kartal Koşuyolu Yüksek İhtisas Education and Research Hospital, Denizer Cad. Cevizli Kavşağı, No:2 Cevizli/ Kartal, 34846, İstanbul-*Turkey* Phone: +90 216 459 44 40 Fax: +90 216 459 63 21 E-mail: cihangirkaymaz2002@yahoo.com

Accepted Date/Kabul Tarihi: 25.05.2011 **Available Online Date/Çevrimiçi Yayın Tarihi:** 25.07.2011

doi:10.5152/akd.2011.133

Introduction

Renal dysfunction as measured by reduced glomerular filtration rate (GFR) and /or increased urinary albumin excretion has been shown to be associated with increased morbidity and mortality in acute and chronic heart failure (HF) (1, 2). Because serum creatinine is insensitive to changes in GFR (3, 4), some novel markers were highlighted to detect early stages of renal dysfunction. One of these biomarkers is a neutrophil gelatinase-associated lipocalin (NGAL, 24p3, SIP24, lipocalin 2, or siderocalin), a 25 kDa protein of the lipocalin family, which is normally secreted in low amounts in lung, kidney, trachea, stomach and colon tissue (5). It increases massively in the cortical tubules, blood and urine within the hours after acute ischemic or nephrotoxic injury, and also very quickly decrease when the initiating trigger has vanished (6). Infections also stimulate NGAL release from neutrophils (7). Neutrophil gelatinase-associated lipocalin provides kidney-protective activity due to some pleiotropic actions including the upregulation of epithelial marker E-cadherin expression. Therefore, blood and/or urinary NGAL might serve as a real-time indicator representing the duration and severity of renotubular insult (8).

There are several studies about heart failure and NGAL levels. One of them showed that the presence of elevated admission serum NGAL levels is associated with heightened risk of subsequent development of worsening renal function in patients admitted with acute decompensated heart failure (9). In another study, increased plasma neutrophil gelatinase-associated lipocalin levels were found that predict mortality in elderly patients with chronic heart failure (10). A recent study revealed that tubular damage, as indicated by increased urinary concentrations of NGAL is common in patients with chronic HF and mildly reduced GFR (11).

Despite the limited data concerning the NGAL as a marker for worsening renotubular function in acute and chronic HF, significance of NGAL in right-sided HF resulting in increased venous pressures remains unknown. In addition, there are only several studies about NGAL levels and clinical indicators in literature.

We aimed to investigate serum and urinary NGAL levels in two settings of HF which may be associated with low renal arteriovenous perfusion gradients, in left-sided HF due to non-ischemic cardiomyopathy (NICMP) and in right-sided HF secondary to severe pulmonary arterial hypertension (PAH). Secondly, we assessed the echocardiographic, hemodynamic and neurohormonal correlates of NGAL levels in HF.

Methods

Patients and controls

Our study was designed as cross-sectional observational. The study group comprised three subgroups; 35 patients with NICMP (F: 15, M: 20, age: 47.6±13.4 years), 28 patients with PAH (F: 14, M: 14, age: 37.3±14.8 years) and 27 healthy controls (F: 13, M: 14, age 34.6±12.8 years). None had a serum creatinine ≥1.5 mg/dL.

All of the patients with NICMP but none with PAH were under angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy. PAH group consisted of 14 patients with idiopathic PAH, 12 patients with PAH related to congenital heart diseases that 6 of them were PAH due to ventricular septal defect, 3 of them were atrial septal defect (ASD) and 2 of them were patent ductus arteriosus (PDA) and 1 of them was combination of ASD-PDA and finally 2 patients with pulmonary hypertension related to chronic thrombo-embolic diseases. Twenty three of the patients with PAH were taking bosentan and/or sildenafil treatment.

All the patients and controls were informed about the aim of the study and gave their consent and the protocol was approved by the institutional ethics committee.

Clinical status was investigated with functional class by using the modified New York Heart Association (NYHA). No patients had worsening or decompensated heart failure when were included in the study.

Exclusion criteria

Exclusion criteria from study were as follows: preexisting acute or chronic renal disease (on the basis of elevated serum creatinine and/or history of kidney disease, e.g. proteinuria, erythrocyturia), a history of nephrotoxic drugs or contrast exposure at least 1 week before the study, anemia, infectious or systemic inflammatory disease associated with increased erythrocyte sedimentation rate, C-reactive protein and/or leucocytosis.

Glomerular filtration rate

Estimated glomerular filtration rate (eGFR) was calculated by two formulas; Cockcroft-Gault (CG) and Modification of Diet in Renal Disease Study (MDRD) (12, 13). The formula for eGFR calculation using the Cockroft-Gault formula was [140-age×Mass(in kilogram)/ [serum creatinine(in mg/dL)×72] [×0.85 if female] and MDRD formula was ($186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$) [×0.742 if female] ×[1.212 if black] as validated in congestive HF patients (3).

Serum-urinary NGAL and brain natriuretic peptide assays

Serum and urinary NGAL were assessed by ELISA method. Samples were collected simultaneously with echocardiographic assessment. Samples were stored at -80°C (14). To avoid microbial contamination, samples were treated with ε-aminocaproic acid and sodium azide, resulting in the final concentration of 0.03% and 0.1%, respectively. In the BioVendor (Modrice, CZECH REPUBLIC) Human Lipocalin-2/NGAL ELISA, the standards, quality controls and samples are incubated in microtiter wells pre-coated with polyclonal anti-human Lipocalin-2 antibody. After 60 min incubation and a washing, biotin-labelled polyclonal anti-human Lipocalin-2 antibody is added and incubated with captured Lipocalin-2 for 60 min. After another washing, the

streptavidin-HRP conjugate is added. Following the 30 min incubation and the last washing step, the remaining conjugate is allowed to react with the substrate solution. The reaction is stopped by addition of acidic solution, and absorbance of the resulting yellow product is measured spectrophotometrically at 450 nm. The absorbance is proportional to the concentration of Lipocalin-2. A standard curve was constructed by plotting absorbance values against concentrations of standards, and concentrations of unknown samples are determined using this standard curve. The measured concentration of samples calculated from the standard curve was multiplied by their respective dilution factor, because samples have been diluted prior to the assay; e.g. 1.75 ng/ml (from standard curve)x30 (dilution factor)=52.5 ng/ml.

Blood levels of brain natriuretic peptide (BNP) were assessed by Access İmmunoassay Method (Biosite, Fullerton, USA).

Echocardiography and impedance cardiography

Echocardiographic assessment was performed by GE Vingmed Vivid 5 (GE-Vingmed Ultrasound AS, Horten, Norway) echocardiography system and 3 MHz transthoracic echocardiography transducer. All of the echocardiographic parameters were measured appropriately to standards (15). Echocardiographic measures of left and right ventricle (LV, RV) were as follows: LV ejection fraction (EF %) with Teichholz and Simpson's methods, LV and RV eccentricity index (EI), myocardial performance index (MPI) of LV and RV, tissue velocities of mitral and tricuspid annulus (Em, Sm, Et, St), tricuspid annular plane systolic excursion (TAPSE), pulmonary arterial systolic pressure (PAPs) estimated from tricuspid regurgitation and respiratory variation of vena cava inferior diameter (VCIrv).

Non-invasive assessment of cardiac index (CI) was performed by echocardiography and transthoracic impedance cardiography (ICG) (Bioz, Cardiodynamics International Corporation, San Diego, CA).

Statistical analysis

Statistical analyses were performed using SPSS software version 14.0 (Chicago, IL, USA). Data were presented as mean±standard deviation if normally distributed. Non-normally distributed data were presented as median and interquartile range (IQR, 25^{th}-75^{th}). Normality was assessed by the Kolmogorov-Smirnov test. Differences between patients and controls were tested using ANOVA or Kruskal Wallis Test wherever appropriate. Bonferroni test was used for ANOVA posthoc analyses. For categorical variables, the Chi-square test was used. Correlations were performed using Spearman's correlation coefficients. A value of $p<0.05$ was considered statistically significant.

Results

Clinical and laboratory characteristics (Table 1)

The mean age of NICMP patients was higher than in PAH patients and control subjects (p=0.01). PAH patients had lower body weight (p=0.02) and tendency to lower systemic arterial pressures (p=0.05) as compared to NICMP patients and with controls.

However, study groups did not differ with respect to gender, NYHA class, blood urea nitrogen and creatinine levels (p>0.05).

Plasma BNP values were significantly higher in NICMP and PAH patients as compared to controls (p<0.0001).

Echocardiographic and impedance cardiographic parameters (Table 2)

Both subgroups of HF had a lower CI assessed by echocardiography and ICG than controls (p<0.05 for both). However, no difference was noted between NICMP and PAH with respect to CI (p>0.05). PAPs was higher in patients with PAH as compared to those in NICMP and control subgroups (p<0.0001). However, PAPs was not different between NICMP and controls (p>0.05). Patients with NICMP had lower LVEF than patients with PAH and controls (p<0.0001). However, measures of RV function as assessed by TAPSE, St, tricuspid E/E', MPI, and VCIrv were significantly impaired in PAH subgroup in comparison to those in patients with NICMP and controls (p<0.0001 for all). These measures of RV function were comparable between NICMP and control subsets (p>0.05).

NGAL levels

Glomerular filtration rate estimated by Cockroft-Gault formula was lower both in NICMP and PAH subgroups as compared to those in controls (p<0.05 and p<0.005 in order). However, neither serum NGAL nor urinary NGAL levels were different among NICMP, PAH and control subgroups (p=0.15, p=0.35 in order) (Table 1) (Fig. 1, 2).

Correlations of NGAL and clinical variables

A weak correlation was found between serum and urinary NGAL levels (r=0.47 p<0.0005). While controls showed a high correlation between serum and urine NGAL levels (r=0.83,

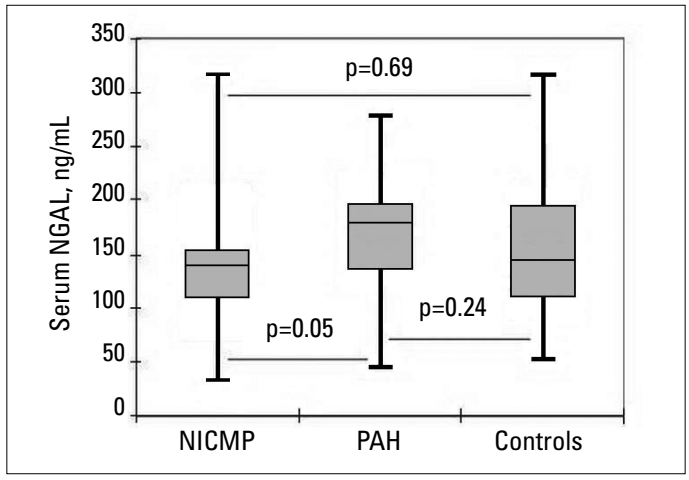

Figure 1. Serum NGAL levels in NICMP, PAH and control groups
NGAL - neutrophil gelatinase-associated lipocalin, NICMP - nonischemic cardiomyopathy, PAH - pulmonary hypertension

Table 1. Baseline characteristics

Variables	NICMP (n=35)	PAH (n=28)	Controls (n=27)	F/Chi-square	p*
Age, years	47.6±13.4	37.3±14.8	34.6±12.8	12.4	0.01
Male, %	57	50	51		0.7
Female, %	43	50	49		0.7
Weight	78±15.5	65.2±15.5	75.4±15.5	11.2	0.02
NYHA class, 1/ 2-3/ 4, %	14/86/0	10/90/0	NA		0.8
Systolic BP, mmHg	118.4±21.4	104.5±17.9	116.3±19	8.2	0.05
Diastolic BP, mmHg	77.6±16.2	67.9±13.9	76.3±11.2	7.4	0.06
BUN, mg/dL	13.7±4.1	13.7±5.3	11.7±3.4	1.1	0.27
Serum creatinine, mg/dL	0.93±0.2	0.88±0.21	0.84±0.18	1	0.3
eGFR, CG, mL/min	102±27	99.4±29.4	122.4±25.9	5.8	<0.05
eGFR, MDRD, mL/min	81.5±22	90.5±26.6	94.5±18	4.7	<0.05
Plasma BNP, pg/mL	165 (53-382)	139 (27-985)	17 (13-21)	28.2	<0.0001
Serum NGAL, ng/mL	141 (113-151)	174 (130- 192)	132 (95-181)	1.7	0.15
Urinary NGAL, ng/mL	15 (12-18)	15 (12-22)	13 (8-18)	1.2	0.35

Data are presented as mean±SD, median and inter-quartile range (25^{th}-75^{th}) and proportions/percentages
*ANOVA (posthoc Bonferroni) test, Kruskal-Wallis test, Chi-square test
BNP - brain natriuretic peptide, BP - blood pressure, BUN - blood urea nitrogen, CG - Cockroft-Gault Formula, eGFR - estimated glomerular filtration rate, MDRD - Modification Diet in Renal Disease study formula, NGAL - neutrophil gelatinase-associated lipocalin, NA - not assessed, NYHA- New York Heart Association

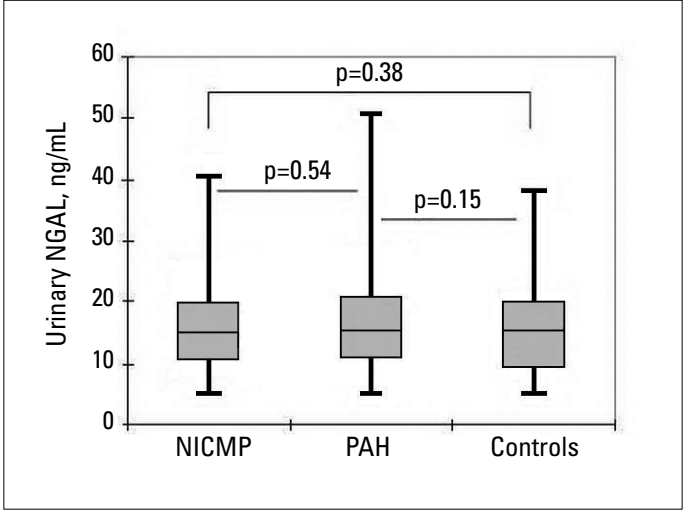

Figure 2. Urinary NGAL levels in NICMP, PAH, and control groups
NGAL - neutrophil gelatinase-associated lipocalin, NICMP - nonischemic cardiomyopathy, PAH - pulmonary hypertension

p<0.0001), this correlation was attenuated in PAH and NICMP subgroups (r=0.32 and r=0.41) respectively. When we looked at correlations between NGAL levels and NYHA class, neither serum NGAL (p=0.10 in PAH and p=0.55 in NICMP) nor urinary NGAL (p=0.18 in PAH and p=0.65 in NICMP) showed correlation in PAH and NICMP subgroups. Similarly there was no correlation between age and NGAL levels in these three subgroups (p>0.05). Plasma BNP showed no correlation with serum NGAL (r=-0.11) or urinary NGAL (r=0.028) levels in overall study population. The correlation coefficients between plasma BNP and serum NGAL were comparable among PAH, NICMP and control subgroups (r=-0.23, r=-0.14 and r=0.07). Similarly, three subgroups had comparable and low correlations between plasma BNP and urine NGAL levels (r=0.18, r=-0.21 and r=-0.04).

Table 2. Echocardiographic and impedance cardiographic data

Variables	NICMP (n=35)	PAH (n=28)	Controls (n=27)	F	p
LVEF, %	31.54±5.8 *	62±6.6	65.4±4.7	27.2	<0.0001
LV MPI	0.87±0.18 *	0.35±0.12	0.32±0.04	16.4	<0.0001
LV Sm, m/sn	0.05±0.016 *	0.078±0.014	0.095±0.027	15.2	<0.0001
LV E/E'	16±7.2 *	9.3±4.2	7.6±1.7	25.1	<0.0001
PAPs, mmHg	28±5.8	96.1±17.8 *	20±3	29.2	<0.0001
TAPSE, cm	2.3±1.8	1.45±0.37 *	2.32±0.24	15.3	<0.0001
RV MPI	0.36±0.1	0.55±0.22 *	0.27±0.02	13.4	<0.0001
RV St, m/sn	0.12±0.03	0.09±0.02 *	0.14±0.026	18.2	<0.0001
RV E/E'	9.4±4.6	10.7±3.8 *	4.8±1.3	11.2	<0.0001
VCI rv (%)	48±3	32±12 *	58 ± 7	28.7	<0.0001
ECHO CI, L/m^2	2.7±0.85 **	2.7±0.7 **	3.1±0.5	4.5	<0.05
ICG CI, L/m^2	2.9±0.6**	2.6±0.8 *	3.4±0.6	7.8	<0.05

Data are presented as mean±SD, median and interquartile range (25^{th}-75^{th}) and proportions/percentages
ANOVA and posthoc Bonferroni test: * p<0.0001 vs controls, ** p<0.05 vs controls
CI - cardiac index, E - early diastolic filling velocity, E'- early diastolic filling tissue Doppler velocity of septal annulus, ECHO - transthoracic echocardiography, ICG - impedance cardiography, LV - left ventricle, LVEF - left ventricular ejection fraction, MPI - myocardial performance index, PABs - pulmonary arterial systolic pressure, RV - right ventricle, St - tricuspid lateral annular systolic velocity, TAPSE - tricuspid annular plane systolic excursion, VCIrv - respiratory variation of vena cava inferior

Creatinine levels were not correlated with NGAL levels in three subgroups (p>0.05). GFR estimated by Cockroft-Gault and MDRD formulas showed no correlations with serum and urinary NGAL levels in overall study population (p>0.05).

PAPs were not correlated with serum NGAL (r=0.14 and r=-0.04) and urine NGAL (r=-0.22 and r=-0.08) in PAH and NICMP subgroups.

Moreover, neither CI measured by echocardiography (r= -0.22, 0.06 and 0.27), nor CI assessed by ICG (r=-0.05, 0.10 and 0.35) showed a correlation with serum NGAL in PAH, NICMP and control subgroups. Similarly, either CI measured by echocardiography (r=-0.15, r=0.24 and r=0.34), or CI assessed by ICG (r=-0.16, r=0.23 and r=0.18) was not found to be related to urine NGAL in three subgroups, respectively.

Discussion

In the present study, for the first time, we investigated both serum and urine NGAL levels in two types of HF; right-sided HF due to severe PAH, and left-sided HF due to NICMP. Despite the mild impaired eGFR, neither serum NGAL, nor urinary NGAL levels were found to be elevated in PAH and NICMP subgroups as compared to those in controls. Two subgroups of HF had comparable serum and urinary NGAL levels. Moreover, the close correlation between serum and urine NGAL levels noted in controls seems to be attenuated in HF, irrespective of the right or left-sided pathology. Serum or urinary NGAL levels were not associated with flow status as assessed by echocardiography and transthoracic ICG, echocardiographic measures of LV and RV functions, PAPs and finally BNP.

From the perspective of cardiorenal interaction, NGAL has mainly been studied in acute renal failure secondary to cardiopulmonary bypass operation (16, 17), acute myocardial infarction and contrast-induced nephropathy (14, 18, 19), and in chronic HF (10, 11). In these settings, NGAL has been proposed as a non-invasive marker for worsening renotubular function due to acute or chronic HF.

A greater than ten-fold increase in plasma NGAL and a greater than 100-fold increase in urine NGAL have been reported in patients with acute renal failure secondary to sepsis, ischemia, or nephrotoxins as compared to those in normal controls. Furthermore, an intense accumulation of immunoreactive NGAL in 50% of the cortical tubules was found in these patients (6). Both serum and urine NGAL have been found to be correlated highly with serum creatinine levels (20-23). In a prospective study children undergoing cardiopulmonary bypass, a ten-fold or greater increase of NGAL in the urine and plasma within 2-6 hours of surgery predicted subsequent acute renal failure (16).

Chronic renal hypoxia due to decreased cardiac output resulting in insufficient arterial blood supply and/or venous congestion might be one of most important mechanisms in genesis of renotubular injury. This may play a pivotal role in genesis of renal failure secondary to hypertension and chronic HF, and an increased NGAL levels have been reported in these situations (11, 20-22). In chronic setting, urinary NGAL was documented to be associated with severity of left-sided HF, indices of renal function including eGFR and urinary albumin excretion, and plasma N-terminal-pro-brain-natriuretic peptide (NT-proBNP) level (11). In addition, several studies showed that urinary concentration of NGAL increased in patients with chronic HF and mildly reduced GFR (11, 24).

Despite the limited data concerning the NGAL as a marker for worsening renotubular function in chronic HF, significance of NGAL in right-sided HF with high venous pressures remains to be determined. Venous congestion is also an important determinant of GFR in CHF, with lower GFR in subjects with the highest venous pressure. This might be due to chronically increased renal interstitial pressure and consequent renal damage. In present study, we assessed in serum and urinary NGAL levels in two settings of HF which may be associated with low renal arteriovenous perfusion gradients, in left-sided HF due to NICMP and in right-sided HF secondary to severe PAH. Both groups of HF were characterized by a decreased CI as compared to healthy controls. However, patients with NICMP had an impaired LV function with relatively normal PAPs in contrast to patients with severe PAH having high pulmonary arterial systolic pressures and preserved LV systolic function. We hypothesized that comparison of two types of HF predominantly affecting the arterial and venous sides of the cardiovascular system might reveal the impact of the RV hemodynamics on renal function and serum and urinary NGAL production. Despite the mildly impaired eGFR, neither serum NGAL, nor urinary NGAL levels were elevated in PAH and NICMP subsets in comparison to those in controls. Furthermore, the correlation between serum and urine NGAL levels seems to be attenuated in HF as compared to controls, irrespective of the right or left-sided pathology. Serum and urinary NGAL were not associated with systemic arterial flow status as assessed by echocardiography and transthoracic impedance cardiography, pulmonary arterial systolic pressure, echocardiographic measures of LV and RV functions, and BNP.

This study highlights that NGAL cannot simply replace serum creatinine as a clinical tool, since they measure different circumstances. In our study, serum NGAL was found much higher than urinary NGAL. These results may be explained that serum NGAL is not only derived from the kidneys but also derived from other tissues.

Study limitations

Our results on relationship between cardiorenal impairment and serum and/or urinary NGAL levels addressed to a population with a mildly depressed CI and eGFR, and may not be extrapolated to more severe settings of left or right-sided HF. Therefore, from a theoretical standpoint, a probable association between elevation of NGAL levels and impairment in cardiorenal axis may not be excluded. In addition, this study is hampered by its small size, and a limited number of events. Therefore observed associations may

not represent the general CHF population. However, despite the mild impairment in CI and eGFR, increased BNP levels in both subsets of HF, a severe PAH and preserved LV EF % in right-sided HF, and moderate to severe LV dysfunction concomitant with nearly normal PAPs in NICMP might provide an opportunity to investigate the NGAL production in these subsets of HF. Furthermore, absence of the direct pressure data derived from the level of renal veins may be considered a limitation for our hypothesis concerning the interactions among venous congestion, renotubular dysfunction and NGAL production.

Conclusion

Despite the impaired eGFR in left-sided HF due to NICMP and right-sided HF due to PAH, neither serum NGAL, nor urinary NGAL levels are elevated in these patients. In the absence of severe renotubular dysfunction, serum or urinary NGAL may not be associated with flow status and indices of LV and RV functions as assessed by BNP, echocardiography and ICG.

Conflict of interest: None declared.

References

1. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006; 113: 671-8. [CrossRef]
2. Ruilope LM, van Veldhuisen DJ, Ritz E, Luscher TF. Renal function: the Cinderella of cardiovascular risk profile. J Am Coll Cardiol 2001; 38: 1782-7. [CrossRef]
3. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. Circulation 2006; 114: 1572-80. [CrossRef]
4. National Kidney Foundation. k/DOQI: Clinical Practice Guidelines for chronic kidney disease: Evaluation, clasification, and stratification. Am J Kidney Dis 2002; 39: S1-S266. [CrossRef]
5. Nguyen MT, Deverajan P. Biomarkers for the early detection of acute kidney injury. Pediatr Nephrol 2008; 23: 2151-7. [CrossRef]
6. Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, et al. Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Invest 2005; 115: 610-21. [CrossRef]
7. Cai L, Rubin J, Han W, Venge P, Xu S. The origin of multiple molecular forms in urine of HNL/NGAL. Clin J Am Soc Nephrol 2010; 5: 2229-35. [CrossRef]
8. Mori K, Nakao K. Neutrophil gelatinase- associated lipocalin as the real-time indicator of active kidney damage. Kidney Int 2007; 71: 967-70. [CrossRef]
9. Aghel A, Shrestha K, Mullens W, Borowski A, Tang WH. Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. J Card Fail 2010; 16: 49-54. [CrossRef]
10. Bolignano D, Basile G, Parisi P, Coppolino G, Nicocia G, Buemi M. Increased plasma neutrophil gelatinase-associated lipocalin levels predict mortality in elderly patients with chronic heart failure. Rejuvenation Res 2009; 12: 7-14. [CrossRef]
11. Damman K, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure. Eur J Heart Fail 2008; 10: 997-1000. [CrossRef]
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41. [CrossRef]
13. Levey AS, Berg RL, Gassman JJ, Hall PM, Walker WG. Creatinine filtration, secretion and excretion during progressive renal disease. Modification of diet in Renal Disease Study Group. Kidney Int Suppl 1989; 27: 73-80.
14. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Poniatowski B, Pawlak K, et al. NGAL (neutrophil gelatinase-associated lipocalin) and cystatin C: are they good predictors of contrast nephropathy after percutaneous coronary interventions in patients with stable angina and normal serum creatinine? Int J Cardiol 2008; 127: 290-1. [CrossRef]
15. Otto CM. Textbook of Clinical Echocardiography. 3rd ed. Philadelphia, PA, Elsevier Saunders, 2004.
16. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury following cardiac surgery. Lancet 2005; 365: 1231-8. [CrossRef]
17. Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, et al. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology 2006; 105: 485-91. [CrossRef]
18. Hemdahl AL, Gabrielsen A, Zhu C, Eriksson P, Hedin U, Kastrup J, et al. Expression of neutrophil gelatinase-associated lipocalin in atherosclerosis and myocardial infarction. Arterioscler Thromb Vasc Biol 2006; 26: 136-42. [CrossRef]
19. Marenzi G, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 2004; 44: 1780-5. [CrossRef]
20. Ljungman S, Laragh JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. Drugs 1990; 39: 10-21. [CrossRef]
21. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol 2006; 17: 17-25.
22. Malyszko J, Bachorzewska-Gajewska H, Malyszko JS, Pawlak K, Dobrzycki S. Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in hypertensive and normontensive patients with coronary artey disease. Nephrology 2008; 13: 153-6. [CrossRef]
23. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Dobrzycki S. Neutrophil gelatinase-associated lipocalin (NGAL) correlations with cystatin C, serum creatinine and eGFR in patients with normal serum creatinine undergoing coronary angiography. Nephrol Dial Transplant 2007; 22: 295-6. [CrossRef]
24. Damman K, Van Veldhuisen DJ, Navis G, Vaidya VS, Smilde TD, Westenbrink BD, et al. Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. Heart 2010; 96: 1297-302. [CrossRef]