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CLINICAL STUDY

Functional and circulatory renal changes in advanced heart failure

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Abstract: *Objectives:* The aim of the study was to describe the relations between heart and renal functions and to investigate whether reduced glomerular filtration rate is influenced more by reduced perfusion or venous congestion.
Methods: A prospective cohort study of 101 patients (69 men, 32 women) with chronic heart failure aged 52 (49–54) (median, 95 % confidence interval) years. We analyzed the blood samples, parameters of echocardiography and right heart catheterization.
Results: Left ventricular ejection fraction correlated with the estimated glomerular filtration rate eGFR (r = 0.214, p = 0.036) in the whole sample of patients.
We found a correlation between cardiac output and renal perfusion pressure in the whole sample (r = 0.232, p = 0.0225) and in patients with chronic heart failure (r = 0.254, p = 0.0278).
In the whole sample the mean pulmonary artery pressure (PAP) correlated with the variables determining renal function: PAP and renal perfusion pressure (r = –0.345, p = 0.002),PAP and eGFR (r = –0.299, p = 0.009) . In the other two studied groups these correlations were not significant.
Conclusion: In the group of heart failure patients left and right ventricular functions were the main determinants for renal function. Current cardiac output or right atrial pressure as markers of renal perfusion were not associated with renal functions in advanced but stable heart failure patients with low burden of extracardiac comorbidities *(Tab. 1, Fig. 4, Ref. 13)*. Text in PDF *www.elis.sk.*
Key words: renal venous congestion, cardiac output, renal perfusion, cardiorenal syndrome, advanced heart failure.

Introduction

Patients with advanced heart failure with signs of decreased renal function usually have a typical clinical picture including hypervolemia, oliguria and resistance to diuretic drugs. This condition is called the cardio-renal syndrome (1). Renal dysfunction in patients with heart failure is ascribed to low renal perfusion due to decreased cardiac output which causes decreased glomerular filtration. The theory is supported by the presence of neurohumoral activation in heart failure, which leads to renal hypoperfusion (2).

Changes in the renal morphology and function are a part of the spectrum of congestive heart failure syndrome. These are the results of complex disorders of renal perfusion and congestion (3). Prognosis of heart failure patients with renal dysfunction is significantly worse in comparison to patients with normal renal function. With the development in the epidemiology of chronic heart failure and advances in treatment, as well as advances in other radical treatment modalities (orthotopic heart transplantation, implantation of mechanical heart support) the question of reversibility of circulatory failure and lesions of vital organs is becoming crucial (4).

Materials and methods

In the prospective cohort study 101 patients (69 men, 32 women) aged 52 years (49–54) (median, 95 % confidence interval) were enrolled. The patients were hospitalized during 2010–2013 at the Department of Heart Failure and Transplantation at the National Institute of Cardiovascular Diseases in Bratislava, Slovak Republic. They were hospitalized due to acute decompensation of heart failure or repeated evaluation. We evaluated 78 patients with advanced chronic heart failure (CHF) as potential candidates for orthotopic heart transplantation or implantation of mechanical cardiac support and 23 patients with pulmonary arterial hypertension (PH). All enrolled patients, underwent right-sided catheterization procedures as part of the assessment of heart failure and clinical evaluation of PH. Comorbidity data were obtained from the medical records. Arterial hypertension was considered, if systemic arterial pressure was above 140/90 mmHg or even lower in patients treated with antihypertensives. Patients with body mass index (BMI) above 30 kg/m² were considered obese.

Biochemical analysis of blood samples was performed after an overnight fasting on the same day as the echocardiography and invasive examination. This was in average on the third hospitalization day. The laboratory parameters included: high-sensitive C-reactive protein, NT-proBNP, a highly specific troponin

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T (TnT), bilirubin, AST, ALT, sodium, potassium. We examined the hematology and coagulation parameters, namely hemoglobin, leukocytes, erythrocytes, platelets, APTT, fibrinogen. The level of NT-proBNP was determined by quantitative immunoenzymatic assay (Elecsys proBNP - Immuno Assay), TnT by GLORIA technology (Gold Labelled Optically Read Immuno Assay). Serum creatinine was analyzed using a kinetic Jaffé method and eGFR was calculated according to the formula CKD – EPI (GFR = 141 X $\min(Scr/\kappa,1)^{\alpha}$ X $\max(Scr/\kappa,1)^{-1.209}$ X 0.993^{vek} X 1.018 (if its woman) (5). Renal perfusion pressure was calculated by the formula: Mean arterial pressure minus central venous pressure (MAP – CVP) (6).

Echocardiographic examinations were carried out within 24 hours of laboratory tests on the device Phillips iE 33. Parameters to assess myocardial dysfunction were following: left ventricle (LV), left ventricular ejection fraction (LVEF), intraventricular septal thickness (IVS), left ventricular posterior wall (LVPW), left atrium (LA), right atrium (RA), right ventricle (RV), Tricuspid Annular Plane Systolic Excursion (TAPSE), tricuspid regurgitation (TR), mitral regurgitation (MR), mitral stenosis (MS), aortic stenosis (AS), aortic insufficiency (AI).

Right heart catheterization was performed with thermodilution catheter (Swan–Ganz catheter) using Seldinger technique through the internal jugular vein into the pulmonary artery. Systolic pulmonary arterial pressure (PAPs), diastolic pulmonary arterial pressure (PAPd), mean pulmonary arterial pressure (PAP), pulmonary wedge pressure (PWP), gases in mixed venous blood, central venous pressure (CVP), cardiac output (CO), cardiac index (CI), transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR) were measured.

Statistical analysis

Statistical analysis was done in Excel (+ macros in Excel) and StatsDirect 2.9.7 created by SAS. Difference in mean between two quantitative variables was evaluated using unpaired Student's t-test for normally distributed data and the non-parametric Mann–Whitney test for abnormally distributed data. Association between variables was analyzed by Pearson correlation coefficient r, the nonparametric Spearman correlation coefficient rho and using partial correlation coefficients. Graphically the relationship between two quantitative variables is presented using a scatter chart, along with the estimated regression line using the least squares method. In the presence of influential outlying observations we used Theil-Sen method. Non-parametric Kruskal–Wallis test was used to test for significance of differences between three independent groups. Relationship between two dichotomous variables was analyzed by Fisher's exact test. All hypotheses were tested at the significance level $\alpha = 0.05$.

Results

The clinical characteristics of all patients and two groups of patients with chronic heart failure and pulmonary hypertension are shown in Table 1. The etiology of chronic heart failure in the first group was in 57 % ischemic and in 43 % non-ischemic. In the whole cohort, 24 (23.7 %) patients had diabetes mellitus, 30 (30 %) patients were obese and 43 (42.6 %) patients had arterial hypertension.

The left heart and right heart hemodynamic parameters were evaluated separately. The former were represented by LVEF, CO and MAP, the latter by TAPSE, CVP and PAP.

The relationship between the left heart hemodynamic parameters and renal function

All three selected variables indicating renal function significantly correlated with left ventricular ejection fraction (Fig. 1). For complete set of patients, we found a significant negative correlation between LVEF and serum creatinine ($r = –0.26$, $p = 0.0098$) and a significant correlation between LVEF and eGFR ($r = 0.214$, $p = 0.036$). After we divided the complete set of the patients into groups with chronic systolic heart failure and pulmonary hypertension this relationship was no longer statistically significant. Cardiac output and serum creatinine, or eGFR did not correlate in either group.

In the complete set, we found a significant correlation between cardiac output and renal perfusion pressure ($r = 0.232$, $p = 0.0225$) (Fig. 2). In the group of patients with chronic heart failure, we

Tab. 1. The clinical characteristics of patients.

	All patients (n=101)	Chronic heart failure (n=78)	Pulmonary hypertension (n=23)
Age	53 (48–59)	53 (48–58)	59 (37–68)
Men; women	69; 32	63; 15***	6; 17
MAP (mmHg)	87 (85–90)	86 (83–87) **	92 (88–96)
NTpro BNP (ng/ml)	3296 (2400–4191)	3843 (2706–4979) ***	1656 (751–2560)
Serum creatinine (μmol/l)	102 (94–110)	110 (101–119) ***	77 (68–86)
eGFR CKD–EPI (ml/s/1.73 m²)	1.2 (1.1–1.3)	1.2 (1.1–1.3) ***	1.5 (1.2–1.8)
LV ejection fraction (%)	30 (20 – 60)	25 (20 – 35)***	60 (60 – 70)
TAPSE (mm)	16 (15–17)	15 (14–16)**	18 (16–20)
PAPs (mmHg)	50 (45–54)	46 (42–50) **	62 (50–74)
PAPd (mmHg)	23 (21–25)	22 (20–24)	27 (21–32)
PAP (mmHg)	34 (31–37)	31 (28–34) **	43 (34–52)
CO (l/min)	4.3 (4–4.5)	4.2 (3.9–4.4)	4.6 (3.9–5.1)
CI (l/min/m²)	2.2 (2.1–2.3)	2.1 (3.9–4.4) ***	2.7 (2.4–2.9)
CVP (mmHg)	7 (4–13)	8 (4–13)	6.5 (5–13)

MAP – mean arterial pressure, LVEF – left ventricular ejection fraction, TAPSE – Tricuspid Annular Plane Systolic Excursion, PAPs – Systolic pulmonary artery pressure, PAPd – diastolic pulmonary artery pressure, PAP – mean pulmonary artery pressure, CO – cardiac output, CI – cardiac index, CVP – central venous pressure, * $p < 0.01$ CHF vs PH, ** $p < 0.05$ CHF vs PH, *** $p < 0.001$ CHF vs PH. The differences were calculated for CHF and PH groups only. The values are given as medians (95 % CI).

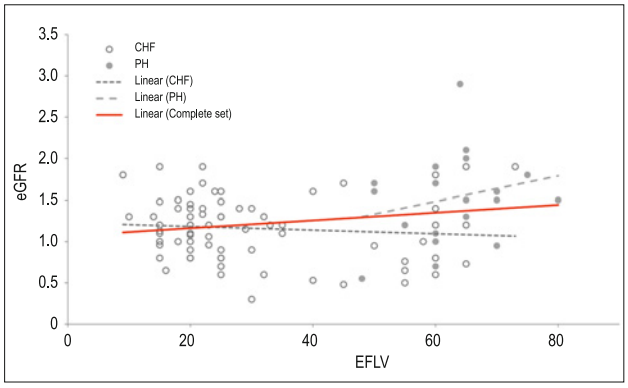

Fig. 1. The relationship between left ventricular ejection fraction and eGFR (r = 0.214, p = 0.036).

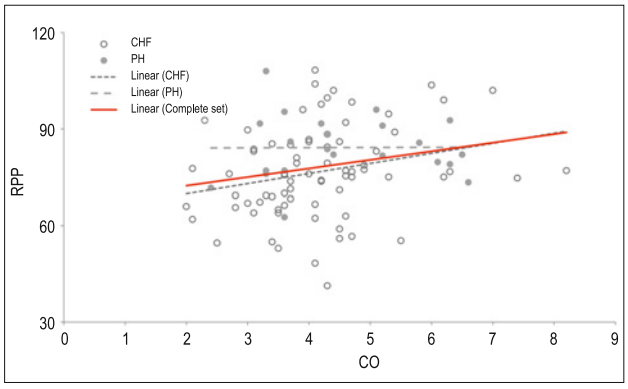

Fig. 2. The relationship between cardiac output and renal perfusion pressure. The complete group of patients (r = 0.232, p = 0.0225). Chronic heart failure group (r = 0.254, p = 0.0278).

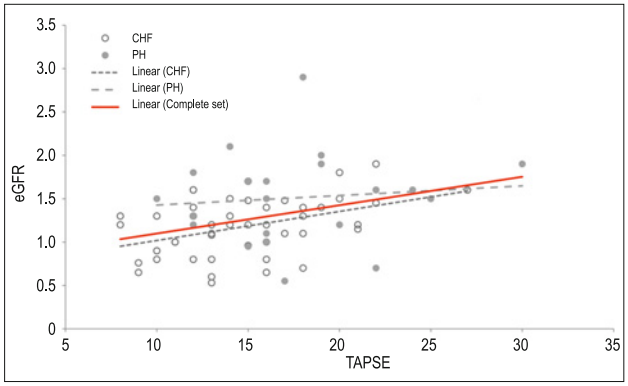

Fig. 3. The relationship between TAPSE and eGFR. The complete group of (r = 0.351, p = 0.0033) chronic heart failure group (r = 0.417, p = 0.0039).

found a significant correlation between cardiac output and renal perfusion pressure (r = 0.254, p = 0.0278), whereas no significant correlation was found in patients with pulmonary hypertension.

The relationship between the right heart hemodynamic parameters and renal function

There were no significant correlations between central venous pressure and serum creatinine or eGFR in any of the studied

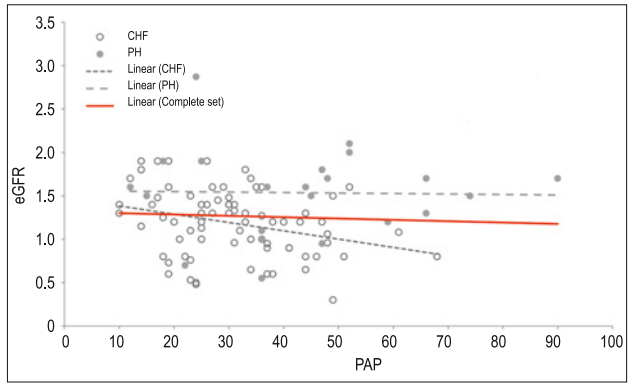

Fig. 4. The relationship between pulmonary artery pressure and eGFR (r = –0.299, p = 0.009).

groups. From echocardiographic monitoring of right heart sections, we found significant negative correlations between TAPSE and serum creatinine in the complete set of patients (r = –0.396, p = 0.0008) and in patients with chronic heart failure (r = –0.429, p = 0.0029), but not in the PH group. There were significant correlations between TAPSE and eGFR in the complete set (r = 0.351, p = 0.0033) and in chronic heart failure (r = 0.417, p = 0.0039), but not in the PH group (Fig. 3). We found no significant correlation between TAPSE and renal perfusion pressure in any of the studied groups.

As a final endpoint from the group characterizing the hemodynamics of right heart sections we monitored the pressure in pulmonary artery (PAP). In patients with chronic heart failure, PAP correlated with parameters determining renal hemodynamics and filtration – PAP and renal perfusion pressure (r = –0.345, P = 0.002), PAP and serum creatinine (r = 0.238, p = 0.041), PAP and eGFR (r = –0.299, p = 0.009) (Fig. 4). In the other two studied groups the correlations were not significant.

Discussion

The aim of our study was to assess the correlations between HF characteristics and renal function and to found which of quantitative HF characteristics influence the most renal function and renal hemodynamics. We also try to delineate that renal function is more impacted by venostasis or perfusion. We found a significant correlation between the values of left ventricular ejection fraction and renal function in the complete set of patients with advanced heart failure.

In the retrospective study from the results of the SOLVD Prevention and Treatment Trials, total of 4228 patients, which consisted mostly of asymptomatic, New York Heart Association (NYHA) class I patients, but approximately one-third of patients in the Prevention Trial were classified with NYHA class II symptoms. The Treatment Trial randomized a total of 2569 patients, all of whom had symptomatic heart failure. In both trials participants were required to have a recently documented ejection fraction ≤35%. The renal dysfunction was defined as GFR <90 ml/min/1.73m2, was present in 121 patients with heart failure (57.9%), while mod-

erate or severe renal dysfuncion (moderate renal insufficiency is defined as a baseline creatinine clearance <60 ml/min, as estimated from the Cockroft-Gault equation) was present in 23.3% of the total sample. Comparing the age of the set of patients, is the study by Dries very comparable to ours. The prevalence of moderate or severe RD was twice as high in patients with heart failure with reduced ejection fraction compared with heart failure with preserved ejection fraction (32.2 % vs 16.8 %, p = 0.01) (7).

In total 51 consecutive patients were included in the Ljungman study (8).The aim of this study was to investigate the relationship between venous congestion and glomerular filtration rate (GFR) in patients with cardiac dysfunction. Renal failure in heart failure is related to decreased cardiac output. However, little is known about its association with venous congestion. Twenty eight patients (55 %) had idiopathic pulmonary arterial hypertension. Secondary pulmonary hypertension was mostly due to pulmonary embolism. Mean MPAP (60 ± 16 mm Hg) and RAP (11 ± 6 mm Hg) were elevated and the cardiac index was decreased (2.1 ± 0.7 l/min/m^2, normal range 2.5–4.0 l/min/m^2). GFR was mildly impaired (73 ± 19 ml/min/1.73 m^2) in combination with an increased filtration fraction. No differences in baseline characteristics were found between patients with idiopathic and secondary pulmonary hypertension.

According to the Ljungman study, the major factor affecting renal function in patients with chronic heart failure is the kidney perfusion. In his work he mentioned that the reduction in cardiac output (CO) has resulted in a disproportionate reduction in renal perfusion, which leads to a reduction in glomerular filtration rate (8).

There were non significant correlations between renal functions and invasively measured cardiac output. One of the reasons for this observation cloud be the fact that patient in our cohort were in general young, with no or very little comorbidities, that is why we suppose intact renal microcirculation. We think that the intact intrarenal regulation of microcirculation helps the kidney to ensure appropriate filtration despite depressed macrocirculation.

In the cardiorenal syndrome the initiating event is the heart disease (9). On the other hand we are observing increase of cardiovascular death initiated by the kidney dysfunction, this clinical situation is called renocardiac syndrome (10). The aim of Mullens study was to determine whether venous congestion, rather than impairment of cardiac output, is primarily associated with the development of worsened renal function (WRF) in patients with advanced decompensated heart failure. In the study cohort (age 57 ± 14 years, cardiac index 1.9 ± 0.6 l/min/m^2, left ventricular ejection fraction 20 ± 8 %, serum creatinine 1.7 ± 0.9 mg/dl), 58 patients (40 %) developed WRF. Patients who developed WRF had a higher central venous pressure (CVP) on admission (18 ± 7 mm Hg vs 12 ± 6 mm Hg, p < 0.001) and after intensive medical therapy (11 ± 8 mm Hg vs 8 ± 5 mm Hg, p = 0.04). The development of WRF occurred less frequently in patients who achieved a CVP < 8 mm Hg (p = 0.01). Furthermore, the ability of CVP to stratify risk for development of WRF was apparent across the spectrum of systemic blood pressure, pulmonary capillary wedge pressure, cardiac index, and estimated glomerular filtration rates. Mullens et al demonstrated that venous congestion is the most important hemodynamic factor driving worsening renal functions in decompensated patients with advanced heart failure.

This is a comprehensive inter-organ „crosstalk“, which requires cooperation between cardiologist and nephrologist. Renal-cardiac syndrome requires an understanding of and intervention in these two different syndromes (11).

There are very few data about the relationship between renal venous congestion and its effect on renal function. Kos (12) in their study showed the relationship between venous congestion and renal flow in patients with heart failure. They examined the relationship between haemodynamic variables obtained during right heart catheterization and plasma levels of endothelin on renal function in 8 males aged 52 ± 3 years. They determined the values of renal plasma flow by using para-aminohippurate clearance and values of GFR by using iothalamate clearance. The authors have shown an inverse relationship between the rate of renal flow and central venous pressure. By monitoring the levels of serum creatinine and eGFR we did not find a correlation with central venous pressure in any of the studied groups. In our work we correlated the most commonly used renal parameters, serum creatinine and eGFR. These parameters are not as specific as those used in above mentioned study.

In current practice, the diagnosis of acute kidney injury is mostly based on serum creatinine concentration. In acute changes of renal function the serum creatinine levels are not a reliable indicator. These parameters are noticeable only after the clinical stabilization of the patient- precisely after the stabilization of renal function. It may take several days. Along with this, it is important to find some new renal biomarkers e.g. urinary neutrophil gelatinase-associated lipocalin (NGAL), intereleukin IL-18, cystatin C, Kidney Injury Molecule-1 (KIM-1), that would be detectable in the early diagnosis and help to to start a prompt and correct treatment (13).

Conclusions

The objective of our work was to verify the important measurable cardiac values, which can indicate a later formation of the renal dysfunction. We have tried to find answers to these questions by evaluating the level of influence of heart failure on changes in renal function. In this study, we confirmed the important influence of so called left heart hemodynamics on renal function. Although we did not find a correlation with the invasively measured cardiac output, we confirmed a significant relationship between left ventricular ejection fraction and glomerular filtration rate. The decreased renal perfusion pressure correlates with the worsening renal parameters. On the other hand, we found a significant correlation between the renal congestion due to heart failure and decreased glomerular filtration rate. There was a significant correlation between renal parameters and pulmonary artery pressure. From the echocardiography parameters the tricuspid annular plane systolic excursion correlated with renal parameters. We did not confirm the theory that a low cardiac output influences the changes in renal function. There were no significant correlations between renal function and invasively measured cardiac output. We suppose that

the cardiac output did not correlate with the renal function due the intact renal microcirculation in our patients. The studied patients were in general young, with no or very little comorbidities, that is why we suppose intact renal microcirculation. We think that the intact renal microcirculation helps the kidney to recover from the pathological hemodynamics.

In our work we have confirmed the existence of cardio-renal syndrome. We found out that in the population of patients with chronic heart failure the impairment of renal function is caused by low renal perfusion as well as by renal venostasis.

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