International Heart and Vascular Disease Journal • Volume 9, № 29, March 2021

Journal of the Cardioprogress Foundation

Predicting renal dysfunction in patients with chronic heart failure

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Abstract

Objective. *To determine informative methods for the identification of renal dysfunction (RD) in patients with chronic heart failure (CHF).*

Materials and methods. *The study included 325 patients with coronary heart disease (CHD) with I (n= 92), II (n= 140) and III (n= 93) functional class (FC) of CHF. All patients underwent clinical examination, 6-minute walk test (6MWT), echocardiography (EchoCG), doppler ultrasound of renal blood flow of the right and left renal artery (RA); serum creatinine assessment (Cr), glomerular filtration rate (GFR) was estimated by the CKD-EPI formula (eGFR). All the patients were divided into 3 groups according to eGFR: group 1 with eGFR⩽ 60 (eGFR= 30–60) ml / min / 1.73 m² (n= 92), group 2 with eGFR= 60–90 ml / min / 1.73 m² (n= 158), group 3 with eGFR⩾90 ml / min / 1.73 m² (n= 69).*

Results. *Patients with CHF had subclinical impairment of renal function: 30.1 % of examined patients with I–III FC of CHF had eGFR below 60 ml / min / 1.73 m², 44.6 % had microalbuminuria (n= 145). The level of microalbuminuria and albumine / creatinione ratio were significantly higher in patients with CHF compared with the control group. Patients with I–III FC of CHF showed significant increase in resistant and pulsative indicators of the right and left RA, and decreased linear blood flow.*

Conclusion. *All the studied methods, including eGFR identification as the gold standard, as well as the assessment of the pulsative and resistant indices of RA, albumine / creatinine ratio, and microalbuminuria can be considered informative for the assessment of renal functional state in patients with CHF.*

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Key words: *chronic heart failure, renal dysfunction, glomerular filtration rate, microalbuminuria, renal blood flow.*

Conflict of interest: none declared.

Received: 08.07.2020 **Accepted:** 14.07.2020

Introduction

Chronic heart failure (CHF) is one of the most urgent medical and social issues of increased concern worldwide. The prevalence and unfavorable prognosis of CHF is constantly increasing [1]. The development of renal dysfunction (RD) in patients with CHF can be explained by neurohumoral imbalance that leads to excessive sodium and water retention, as well as the progression of CHF [2]. It has been found that impaired renal function is an independent risk factor for heart failure that progressively aggravates the course of CHF and complicates the treatment of such patients [3]. According to some reports, impaired renal function have more pronounced effect on clinical course and mortality of patients with CHF compared with functional class (FC) of heart failure and left ventricular ejection fraction [4]. The CHARM study found that the presence of microalbuminuria (MAU) in patients with CHF increases the risk of adverse clinical events [5]. Currently, MAU is considered as one of the most significant predictors for the development of cardiovascular complications and can be used for the diagnosis of RD in patients with CHF [6]. Data of most clinical trials, large retrospective analyzes from the PRIME II and SOLVD Prevention and Treatment studies, and the meta-analysis of publications for over 60 years indicates that RD negatively affects outcomes, length of stay in a hospital and overall mortality in patients with CHF [3,7]. However, the results of these studies are based on the evaluation of blood creatinine, MAU and glomerular filtration rate (GFR), when the state of renal hemodynamics and its association with GFR in patients with CHF remains unknown. In connection with the above, it is essential to optimize the early diagnosis of kidney damage in patients with CHF with the identification of RD predictors [8, 9, 10]. Therefore, we decided to assess renal function in patients with CHF and without primary renal and / or endocrine pathology and to determine the most significant methods for early diagnosis of RD in patients with CHF.

Objective

To identify the most informative methods for the diagnosis of RD in patients with CHF.

Materials and methods

The study included 325 patients with coronary heart disease (CHD) and with I (n=92), II (n=140) and III (n=93) FC of CHF. Average age of study participants was 62,5±8,14 years. The control group included 20 healthy participants. Clinical characteristics of included patients is presented in table 1.

All the patients underwent general clinical examination including: 6-minute walk test (6MWT), echocardiography (EchoCG), doppler ultrasound of renal blood flow with color doppler mapping with the assessment of peak systolic velocity (PSV), end-diastolic velocity (EDV), time-averaged velocity (TAV), resistance index (RI), pulsatile index (PI) of the right and left renal artery (RA) [7].

The state of renal filtration function was estimated by serum creatinine assessment (Cr), glomerular filtration rate (GFR) was estimated by the CKD-EPI formula (eGFR) [10], albumin/ creatinine ratio (Al/Cr) (mg/mmol) in morning urine. Albumin excretion in urine was determined by enzyme-linked immunosorbent assay (ELISA) by Al /Cr ratio (mg/g), MAU was determined if this ratio was over 20 mg/g, high normal level of albuminuria — over 10 mg/g [4]. All the patients were divided into 3 groups according to eGFR: group 1 with eGFR⩽ 60 (eGFR= 30–60) ml/min/1.73 m^2 (n=92), group 2 with eGFR= 60–90 ml/min/1.73 m^2 (n=158), group 3 with eGFR⩾90 ml/min/1.73 m^2 (n=69).

The study was performed in accordance with the standards of Good Clinical Practice and the principles

Table 1. **Clinical characteristics of included patients**

Parameter	Total	Men	Women	I FC of CHF	II FC of CHF	III FC of CHF	Arterial hypertension (AH)	Postinfarction cardiosclerosis (PICS)
n (number of patients)	325	205	120	92	140	93	298	166

of Helsinki Declaration. The study protocol was approved by Ethical Committees of all clinical centers. Written informed consent was received from all the participants prior to the study.

Statistical analysis was performed using Microsoft Office Excel-2013 and STATISTICA-6,0 software. Methods of parametric and non-parametric statistics were used with the estimation of means (M), standard deviation (SD), standard error of the mean (m) and relative values (frequency, %). Differences between groups were compared with Student t-test (t) with the calculation of error probability (p). Kurtosis value was used to determine whether the data set was modeled for normal distribution. p<0,05 was set as the level of significance.

Results and discussion

The analysis of Cr level and eGFR showed that 98 patients (30.1%) with I–III FC of CHF had eGFR<60 ml/min/1.73 m^2, 227 patients (69.9%) — over 60 ml/min/1.73 m^2, of which 158 patients had eGFR over 60 ml/min/1.73 m^2, but under 90 ml/min/1.73 m^2 that corresponds to stage II CKD and 69 patients had eGFR≥90 ml/mi/1.73 m^2. Patients with I FC of CHF had Cr and eGFR of 86.5±15.35 mcmol/L and 74.5±15.1 ml/in/1.73 m^2, respectively, patients with FC II — 93.1±20, 4 mcmol/L and 72.7±16.1 ml/min/1.73 m^2, respectively; and with III FC of CHF –103.6±22.2 mcmol/L and 60.4±16.2 ml/min/1.73 m^2, respectively. Patients with III FC of CHF had significantly higher Cr level and lower eGFR — 16.5% (p<0.05) and 18.9% (p<0.05), respectively, compared with I FC of CHF. 38 (40.1%) patients with significant GFR decrease (<60 ml/min/1.73 m^2) had III FC of CHF.

Albumin excretion (AE) in morning urine was determined by Al /Cr ratio. MAU was determined in 44,6% (n=145) patients. High normal level of albuminuria (HNLA) was determined in 11,4% (n=37) patients. AE was associated with GFR level (r= –0,32, p= 0,01). As it can be seen from table 2, MAU level was significantly higher in I–III FC of CHF compared with the control group.

The state of renal hemodynamics and its relationship with the severity of clinical symptoms and prognosis is worth further investigation. Therefore, the parameters of renal blood flow of the right and left RA were investigated. Patients with I FC of CHF at the level of the right and left RA had increased PI — by 29.1% (p<0.001) and 23.8% (p<0.001), RI — by 6.8% (p<0.001) and 1% (p>0.05), decreased TAV — by 40.9% (p<0.001) and 35.5% (p<0.001), decreased EDV — by 21.4% (p<0.005) and 3% (p>0.05) cm/s, respectively, compared with the control group (Table 3). Patients with II FC of CHF had increased PI — by 30.2% (p<0.001) and 24.6% (p<0.001) and RI — by 7.6% (p<0.001) and 1% (p>0.05), decreased TAV — by 56.9% (p<0.001) and 56.2% (p<0.001), EDV — by 35.2% (p<0.001) and 19,7% (p<0.001), PSV — by 15.8% (p<0.001) and 15.6% (p<0.001), re-

Table 3. **Renal blood flow parameters of the left and right RA in patients with I–III FC of CHF (M±SD)**

Parameter	Right renal artery				Left renal artery			
	Control group	I FC	II FC	III FC	Control group	I FC	II FC	III FC
PSV, sm/sec	59.57± 1.95	57.52±14.77	51.42±13.11^	49.42±14.51^	59.64±3.34	57.33±13.08	51.58±12.93^	50.1±13.27^
RI	0.669± 0.016	0.718±0.030^	0.724±0.046^	0.718±0.036^	0.710±0.01	0.716±0.052	0.716±0.092	0.712±0.054
EDV sm/sec	19.72± 0.52	16.25±4.27****	14.59±4.9^	14.38±4.76^	17.24±0.866	16.78±3.6	14.4±4.69^	14.49±4.21^
TAV sm/sec	39.64±0.924	28.14±4.85^	25.27±4.75^	24.53±5.52^	38.44±2.032	28.36±4.09^	24, 6±4.93^	24.77±4.58^
PI	1.00± 0.036	1.42±0.222^	1.44±0.255^	1.43±0.262^	1.1±0.024	1.45±0.277^	1.46±0.291^	1.41±0.282^

Footnote. * — the result is significant with p<0,05; ** — the result is significant with p<0,02; *** — the result is significant with p<0,01; **** — the result is significant with p<0,005; ^ — the result is significant with p<0,001 compared with the control group.

Table 2. **Renal function parameters in patients with I–III FC of CHF (M±SD)**

№ п/п	Parameter	Control group (n=20)	I FC of CHF (n=92)	II FC of CHF (n=140)	III FC of CHF (n=93)
1	Cr, mcmol/l	53.8±12.4	86.5±15.4	93.1±20.4	103.6±22.2
2	eGFR, ml/min/1.73 m^2	126.5±5.5	74.5±15.1	72.7±16.1	60.4±16.2
6	Al/Cr in the morning urine (mg/mmol)	-	10.1±3.2	10.3±8.7	12.8±4.4

Table 4. **RD criteria in patients with CHF (M±SD)**

Parameter	Patients with I–III FC of CHF					
	group 1 (eGFR≤60 ml/min/1.73 m²)	p (group 1 vs. group 2)	group2 (eGFR=60–90 ml/min/1.73 m²)	p (group 1 vs. group 3)	group3 (eGFR>90 ml/min/1.73 m²)	p (group 2 vs. group 3)
Cr, mcmol/l	120.7±27.0	p<0.001	88.2±11.5	p<0.001	63.4±11.9	p<0.05
eGFR, ml/min/1.73 m²	50.7±8.5	p<0.01	75.0±8.6	p<0.005	96.7±6.2	p<0.05
Al/Cr in the morning urine (mg/mmol)	37.3±9.7	p<0.05	10.3±5.7	p<0.001	2.8±4.4	p>0.05
PSV, right RA/ left RA sm/sec	50.4±6.9/ 49.5±6.8	p>0.05	53.84±9.08/ 52.77±9.51	p>0.05	54.4±6.2/ 55.25±5.5	p>0.05
EDV, right RA/ left RA sm/sec	14.5±2.9/13.9±3.5	p>0.05	15.98±3.88/ 15.8±3.38	p>0.05	15.3±2.8/ 16.0±2.6	p>0.05
RI, right RA/ left RA sm/sec	0.86±0.055/ 0.81±0.066	p<0.05	0.751±0.042/ 0.752±0.056	p<0.05	0.688±0.047/ 0.677±0.066	p>0.05
PI, right RA/ left RA sm/sec	1.477±0.229/ 1.465±0.256	p<0.05	1.27±0.13/ 1.26±0.11	p<0.05	1.156±0.175/ 1.18±0.18	p>0.05

spectively, compared with the control group. Patients with III FC had increased PI — by 29.9 % (p<0.001) and 21.9 % (p<0.001), decreased TAV — by 61.6 % (p<0.001) and 55.2 % (p<0.001), EDV- by 37.1 % (p<0.001) and 19 % (p<0.001), PSV — by 20.5 % (p<0.001) and 19 % (p<0.001), respectively, compared with the control group. Renal blood flow parameters in patients with CHF are presented in Table 3.

Linear velocities of blood flow (EDV, PSV) were lower in most patients with CHF, and resistance and pulsatile indices were higher compared with healthy controls (p<0,05). Similar blood flow parameters (linear and volumetric) correlated between right and left RA that indicates the absence of renal stenosis of only one artery in included patients (r=0,85, p<0,001).

eGFR reduced to the level of stage 3 CKD in 30 % of patients with CHF and without renal pathology, 58 % of patients with CHF had eGFR over 60 ml/min/1.73 m², but under 90 ml/min/1.73 m² that corresponds to the 2nd stage of CKD. Table 4 presents renal function parameters in patients with eGFR<60 ml/min/1.73 m², eGFR=60–90 ml/min/1.73 m² and eGFR≥90 ml/min/1.73 m² including eGFR, renal blood flow parameters and albuminuria level (Al/Cr).

Patients with various stages of RD had significant differences in parameters: group with eGFR≤60 ml/min/1.73 m² compared with eGFR=60–90 ml/min/1.73 m² and eGFR>90 ml/min/1.73 m² had 3,6 and 13,3 higher level of Al/Cr in the morning urine (p<0,05), respectively, RI at the level of the RA increased by 12,7 % and 30,2 %, respectively, and PI — by 14 % and 21,7 %. At the same time linear parameters of renal blood flow (PSV and EDV) did not differ significantly between groups.

The search for new biological markers of RD in patients with cardiorenal syndrome is worth further investigation [4,11]. The importance of MAU as an isolated precursor of chronic kidney disease (CKD) and cardiovascular mortality has been noted in many prospective and epidemiological studies, especially in patients with diabetes mellitus and arterial hypertension [12,13]. It is known that MAU is associated with atherosclerosis and CKD. It also remarkable that MAU affects mortality in the entire population, and can be used as the indicator of generalized endothelial damage [1,5].

In our opinion even "isolated" CHF can lead to the functional impairment of kidneys [2]. We have assessed the parameters of kidneys functional state in patients with CHF with minimal number of additional factors that can lead to kidney damage. Even in such sample, 30.1 % of patients showed decreased eGFR below 60 ml/min/1.73 m², MAU was detected in 44.6 % (n=145) of patients with CHF. MAU that was established by Al/Cr ratio in patients with I–III FC of CHF was higher compared with the control group an increased with the degree of RD. Patients with I–III FC of CHF showed significant decrease in linear blood flow, an increase of RI and PI as indicators of vascular resistance compared with the control group; as well as significant increase of RI and PI with the degree of RD at the level of the right and left RA. Patients with CHF showed subclinical impairment of renal function, characterized by decreased GFR, MAU, decreased velocity parameters and increased pulsative and resistant indices in the study, which indicate RD and, therefore, can be considered as reliable tool for the identification of RD in these patients. The determination of eGFR, Al/Cr ratio and renal hemodynamics in patients with CHF can be used for the early diagnosis of RD.

Most patients with CHF showed subclinical renal dysfunction [3]. It is known that RD in patients with CHF is associated with decreased ejection fraction followed by renal hypoperfusion and increased renal vascular resistance [7]. The involvement of kidneys is one of the key points in the progression of CHF and, therefore, preservation of renal function is essential in secondary prevention of CHF [2]. Today it is well-known that many risk factors that are associated with the development of CHF are also considered general cardiovascular risk factors. The problem of the association between heart and kidneys is described from two points of view: for one hand, the primary myocardial damage causes the impairment of renal function and central hemodynamics, circulatory hypoxia and humoral changes, for the other hand, renal dysfunction leads to the development and progression of cardiovascular pathology and aggravates disease prognosis [4, 13].

Conclusion

Patients with CHF showed subclinical renal function impairment: 30,1 % of included patients with I–III FC of CHF had decreased eGFR below 60 ml/min/1.73 m^2, 44,6 % (n=145) had MAU.

Patients with I–III FC of CHF showed increased MAU and Al/Cr ratio, increased resistance and pulsative indices and decreased linear blood flow parameters compared with the control group. Increased pulsative and resistance indices of the RA, MAU were associated with GFR decrease, and these parameters can be considered as early predictors of renal function impairment in patients with CHF.

Conflict of interest: none declared.

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