Markers of symptomatic heart failure in chronic kidney disease patients with normal left ventricular ejection fraction

[1]Diana Zilisteanu, [1]Elena Rusu, [1]Teodora Atasie, [2]Monica Rosca, [2]Andreea Calin, [3]Cristiana Tanase, [1]Mihai Voiculescu

[1]Carol Davila University of Medicine and Pharmacy, Nephrology Department, Fundeni Clinical Institute,
[2]Carol Davila University of Medicine and Pharmacy, Cardiology Department, "Prof. Dr. CC. Iliescu" Institute for Cardiovascular Diseases
[3]"Victor Babes" National Institute for Research and Development in Pathology and Biomedical Sciences

Background and aim of the study

- Heart failure (HF) is common among chronic kidney disease (CKD) and contributes to high mortality in this patients category. HF appears early in the evolution of CKD, and has a complex pathogenesis.
- The aim of our study is to identify markers associated with symptomatic HF in CKD patients with normal left ventricular ejection fraction.

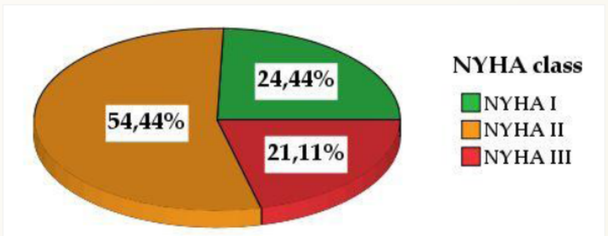
Methods

- We prospectively enrolled 90 CKD patients in pre-dialysis (eGFR > 15 ml/min/1.73m^2).
- Cardiac functional status was defined according to the New York Heart Association (NYHA) classification.
- xMAP technology (Luminex® 200™) was used to evaluate inflammatory and mineral metabolism markers: FGF-23, fetuin A, osteopontin, osteoprotegerin, osteocalcin, iPTH, IL-6, TNFalpha.
- Were evaluated echocardiographic parameters of cardiac structure and function: systolic and diastolic left ventricular (LV) volumes, LV mass index (LVMI), left atrial volume index (LAVI), LV ejection fraction (LVEF), ratio of mitral velocity to early diastolic velocity of the mitral annulus (E/E`), and ratio between the early maximal ventricular filling velocity and the late filling velocity (E/A).
- Peripheral pulse wave analysis was performed using SphygmoCor device; we recorded C(PWV), augmentation index (Aix), left ventricular ejection duration index (EjD%), subendocardial viability ratio (SEVR% = DTPI/STPI).
- Dipper pattern was estimated by 24 hour ambulatory blood pressure monitoring (ABPM).

RESULTS

- We enrolled 90 CKD patients in pre-dialysis
  - 10 patients CKD stage 2
  - 58 patients CKD stage 3
  - 22 patients CKD stage 4
- Gender: men = 64 (71.1%),
- Mean age=64.8 ± 11.4 years (range 35 – 86 years)
- All study patients had LVEF ≥ 50% (range: 50 – 69%)
- According to cardiac functional status, 22 patients (24.44%) were NYHA class I, while 49 patients (54.44%) were NYHA class II and 19 patients (21.11%) were NYHA class III.

- Thus, three quarters of our patients with normal LVEF (≥ 50%) had symptomatic heart failure (NYHA ≥ II).



- Patients with symptomatic HF were older, had higher systolic blood pressure, and more frequently associated coronary artery disease.

Clinical parameters	NYHA I	NYHA II-III	p
Age (years)	56 ± 161	68 ± 10	< 0.05
Gender (males, %)	68.2	72.1	NS
Etiology of kidney disease			
Diabetic nephropathy (%)	18.2	26.5	NS
Hypertensive nephropathy (%)	31.8	50	NS
Tubulointerstitial disease (%)	36.4	23.5	NS
Coronary artery disease (%)	27.3	58.8	< 0.05
Peripheral artery disease (%)	4.5	16.2	NS
Stroke (%)	9.1	22.1	NS
Systolic BP (mean, mmHg)	122 ± 19	133 ± 19	< 0.05
Diastolic BP (mean, mmHg)	72 ± 14	73 ± 12	NS
Dipper pattern (%)	63.2	49.2	NS

- Symptomatic HF patients had higher LVMI, lower E/A and higher E/E`, as well as higher LAV and LAVI

Echocardiographic parameters	NYHA I	NYHA II-III	p
LV systolic volume (ml)	29.1 ± 4.1	30.5 ± 5.9	NS
LV diastolic volume (ml)	47.8 ± 4.6	49.6 ± 6.2	NS
LVMI (g/m^2)	105.5 ± 23.6	120.7 ± 29.9	< 0.05
E/A	1.04 ± 0.37	0.84 ± 0.25	< 0.05
E/E`	9.82 ± 2.78	12.63 ± 3.52	< 0.05
LA volume (ml)	62 ± 23	80 ± 32	< 0.05
LAVI (g/m^2)	32.8 ± 10.7	42.5 ± 17.5	< 0.05

RESULTS

- In symptomatic HF patients, we found significantly more impaired renal function, higher level of inflammation expressed by fibrinogen and IL6, and higher levels of mineralization inhibitors osteopontin and osteoprotegerin.

Biological parameters	NYHA I	NYHA II-III	p
eGFR (ml/min/1.73m2)	55.1 ± 23.1	37.4 ± 12.8	< 0.05
Uric acid (mg/dl)	6 ± 1.6	7.3 ± 1.8	< 0.05
Hemoglobin (g/dl)	13.5 ± 1.4	12.9 ± 1.9	NS
Albumin (g/dl)	4.3 ± 0.6	4.1 ± 0.6	NS
Calcium (mg/dl)	9.6 ± 0.7	9.5 ± 0.7	NS
Phosphate (mg/dl)	3.7 ± 1.1	3.8 ± 8	NS
iPTH (pg/ml)	69.2 ± 75.7	84.5 ± 65.5	NS
Fibrinogen (mg/dl)	355.5 ± 93.2	412.6 ± 117	< 0.05
Interleukin 6 (pg/ml)	4.4 ± 2.7	7.6 ± 4.2	< 0.05
TNF alpha (pg/ml)	3.2 ± 1.8	4.2 ± 2.2	NS
FGF 23 (pg/ml)	57 ± 80.4	134.4 ± 211.5	NS
Fetuin A (µg/ml)	504.2 ± 97.4	441.3 ± 123	NS
Osteopontin (pg/ml)	7730 ± 7624	15458 ± 10495	< 0.05
Osteoprotegerin (pg/ml)	512 ± 153	777 ± 317	< 0.05
Proteinuria (g/d)	0.35 ± 0.46	0.86 ± 1.62	NS

- No pattern regarding peripheral pulse wave analysis was identified.

Pulse wave analysis parameters	NYHA I	NYHA II-III	p
Pulse wave velocity	9.2 ± 2.6	9.9 ± 2.8	NS
Augmentation index	47.8 ± 4.6	49.6 ± 6.2	NS
Ejection duration	105.5 ± 23.6	120.7 ± 29.9	NS
Subendocardial viability ratio	1.04 ± 0.37	0.84 ± 0.25	NS

- In **univariate analysis**, symptomatic HF was correlated with:
  - Systolic blood pressure (p=0.009),
  - Renal function: eGFR (p<0.0001),
  - Uric acid (p=0.003),
  - Inflammation markers: IL-6 (p=0.015), fibrinogen (p=0.041),
  - LA and LV structure and function: LAVI (p=0.02), LVMI (p=0.043), E/A (p=0.024), E/E` (p=0.001),
  - Mineralization inhibitors: OPG (p=0.003), OPN (p=0.02).
- No correlations with history of coronary/cerebrovascular/peripheral disease, dipper pattern, pulse wave velocity parameters were identified.
- **Binary logistic regression analysis** identified eGFR (p=0.029), OPG (p=0.003) and E/E` (p=0.035) as markers associated with symptomatic HF.

	Exp(B)	CI for Exp(B)	p
eGFR	0.936	0.890 – 0.983	0.029
OPG	1.006	1.003 – 1.011	0.003
E/E`	1.561	1.084 – 2.247	0.035

Conclusions

- In our study, 75.6% CKD patients with normal LV ejection fraction had symptomatic HF, diagnosed as NYHA ≥ II.
- Our results suggest that severity of renal failure, serum levels of mineralization inhibitor osteoprotegerin, and LV diastolic dysfunction assessed by echocardiographic parameter E/E' ratio correlate with presence of heart failure symptoms in CKD patients with normal LV ejection fraction.

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Corresponding author: Diana Zilisteanu, MD, PhD. Email: diana@nefrolog.ro