CARDIOPULMONARY EXERCISE TESTING IN CARDIORENAL SYNDROME

MINODORA TEODORU[1], IOAN MANIŢIU[2], LIANA BERA[3], ADRIAN TEODORU[4]

[1,2,3,4] *"Lucian Blaga" University of Sibiu*

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Abstract: *Introduction: The cardiorenal syndrome (CRS) is a heterogeneous pathology with important prognostic significance when present. Aim of the study: In this study, we aimed at identifying some of the risk factors influencing the prognosis of CRS patients. Materials and Methods: We analyzed 85 patients with heart failure hospitalized in Monzino Cardiology Centre in Milan during a 3-month period. The glomerular filtration rate (GFR) was calculated using the MDRD equation (Modification of Diet in Renal Disease) and maximal oxygen consumption (VO$_2$max) was measured during cardiopulmonary exercise testing. Results: VO$_2$ max was significantly decreased correspondingly to the decrease of the GFR. Patients with a GFR <30ml/min/1, 73m^2 had more major risk factors (advanced age, NYHA class 4, anemia, diabetes, BNP> 600pg/ml, VO$_2$max <14ml/kg/min) than the patients with higher GFR. Conclusions: The presence of cardiorenal syndrome is associated with an increased incidence of major cardiovascular risk factors and a poor performance during exercise.*

Cuvinte cheie: *test de efort cardiopulmonar, insuficienţa cardiacă, insuficienţă renală*

Rezumat: *Introducere: Sindromul cardiorenal este o patologie heterogenă cu importante semnificaţii prognostice atunci când este prezent. Scopul lucrării: Prin acest studiu ne propunem identificarea unora dintre factorii de risc ce influenţează prognosticul acestor pacienţi. Materiale şi metode: S-a analizat un lot de 85 de pacienţi cu insuficienţă cardiacă internaţi în Centrul Cardiologic Monzino din Milano într-o perioadă de 3 luni. S-a calculat rata filtrării glomerulare (RFG) utilizând ecuaţia MDRD (Modification of Diet in Renal Disease) şi s-a măsurat consumul maxim de oxigen (VO$_2$max) în timpul testului de efort cardiopulmonar. Rezultate: VO$_2$ max a fost semnificativ scăzut în funcţie de valoarea RFG. Pacienţii cu RFG <30ml/min/1,73m2 au avut mai mulţi factori de risc majori (vârsta avansată, clasa NYHA 4, anemie, diabet zaharat, BNP> 600pg/dl, VO$_2$max<14ml/kg/min) faţă de cei cu RFG mai mare. Concluzii: Prezenţa sindromului cardiorenal se asociază cu o incidenţă crescută a factorilor de risc majori cardiovasculari şi cu o performanţă scăzută la efort.*

INTRODUCTION

Heart failure has a growing prevalence due to the more efficient treatment of cardiac disease resulting in prolonged survival of patients and due to the higher presence of associated diseases.(1,2) Heart failure often coexists with chronic kidney disease (CKD), renal failure and so, a new syndrome was described, the cardiorenal syndrome (CRS), heterogeneous in definition and regarding the pathophysiological mechanisms involved.

PURPOSE

The link between decreased glomerular filtration rate and increased mortality in heart failure is well known.(3) This paper aims at identifying some of the risk factors that determine the prognosis in CRS by studying a group of patients with heart failure and various degrees of renal impairment in terms of biological parameters and the cardiopulmonary exercise test.

METHODS

Study population

The current study is conducted prospectively on a group of 85 patients diagnosed with heart failure admitted at the Monzino Cardiologic Centre in Milan during July to September 2011.

The inclusion criteria selected clinically stable patients with NYHA class 2-4 heart failure, under standard heart failure treatment according to the institutional guidelines.(4) Exclusion criteria included comorbidity that did not allow the performance of the exercise test and major cardiovascular events during the last 6 months.

The demographics and personal pathological history of patients was noted. Patients were investigated in this clinic following the existing protocols and the laboratory tests and cardiopulmonary exercise testing were registered.

Biological data

The biological parameters were determined: creatinine, urea (normal values < 50mg/dl), uric acid (normal < 7mg/dl), BNP (normal < 100 pg/ml), hemoglobin (normal > 13.5 g / dl), all determined in the laboratory of the clinic.

We aimed at evaluating the degree of impairment of renal function by estimating the glomerular filtration rate (GFR) calculated by the MDRD formula (Modification of Diet in Renal Disease).(5)

$$]GFR = 186\times[\text{Plasma creatinine}]^{-1.154}\times[\text{age}]^{-0.203}\times[0.742 \text{ if the patient is female}]$$

According to the National Kidney Foundation Kidney Disease classification Outcomes Quality Initiative (5), the values thus calculated are used to define the stages of renal impairment: GFR $\geq$ 90 ml/min/1, 73 m² (stage I renal

dysfunction), 60-89 ml/min/1, 73 m² (stage II), 30-59 ml/min/1, 73 m² (stage III), 30-15 (stage IV), <15 ml/min/1, 73 m² (stage V). Patients with GFR ≤ 60 ml/min/1, 73 m² were considered as having a significant impairment of renal function and have been diagnosed as having CRS.

Cardiopulmonary exercise testing

Patients performed maximal or symptom limited cardiopulmonary exercise test on cicloergometre with incremental load.(6) The patients were monitored for 12-lead ECG during exercise and blood pressure was measured before, during and after exercise. Heart rate was measured before starting the test and at maximum effort. The oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE) were measured breath by breath. The device was calibrated daily for gas analysis prior to effort testing. The anaerobic threshold derived from respiratory measurements was determined using the V slope method (6), estimating the appearance of the metabolic acidosis.

The O_2 pulse was calculated as the ratio of VO_2 and heart rate, reflecting stroke volume and oxygen consumption at each contraction. The respiratory quotient (RQ) was calculated as the ratio VCO_2/VO_2, a value > 1.1 signifying a maximal exercise test. The respiratory reserve was measured as the ratio of VE/VO_2. The VE/VCO_2 ratio was calculated as an expression of pulmonary vascular damage.

All these parameters were studied and the exercise capacity limitation causes were defined as cardiac, respiratory or deconditioning.

Statistical analysis

The studied characteristics were expressed numerically, the arithmetic averages were calculated and the qualitative characteristics were expressed as percentage. A Pearson correlation coefficient was used and its sign indicates the direction of the relations between variables. The positive t value indicates a direct link and a negative sign shows a reverse link. Linear model was used to study the variables comparing them to the GFR as dependent variable. P value < 0.05 was considered statistically significant.

RESULTS

Demographic characteristics of the study population

From the 85 patients included in the study, there was a significantly greater number of men included. The average age of patients was 68 years old, approximately 30% of patients were aged > 75 years, thus marking a population of patients at high risk for cardiovascular events. There was a statistically significant relation between increasing age and decreasing GFR (table no. 1).

All features were expressed in terms of the GFR. The study population was delineated into four categories according to the National Kidney Foundation GFR classification Kidney Disease Outcomes Quality Initiative (5) and there were not observed patients with GFR <15ml/min/1, 73m².

Table no. 1. Clinical characteristics of the study batch

Clinical characteristics	GFR stage					P value
	Total	I	II	III	IV	
Age, years	68.30	57.00	64.54	71.45	72.00	0.023
Age >75 years	29.40	0	16.12	42.85	25.00	0.031
Feminine, %	27.06	100	3.22	35.72	37.5	0.001
Masculine, %	72.94	0	96.78	64.28	62.5	0.001
Systolic BP, mmHg	122.25	112	121	133	123	0.121
Diastolic BP, mmHg	72.5	71	73	71	75	0.213
BMI, kg/m²	32.25	34.00	33.00	33.00	29.00	0.091

NYHA Class (2/3/4),%	62/31/7	61/32/7	65/30/5	60/34/6	63/29/8	0.08/0.12/0.32
HR rest, bpm	61.00	62.00	64.00	60.00	59.00	0.381
Associated disease,%		0	9.67	19.04	37.50	0.182
HT	16.47	0	22.58	33.33	25.00	0.299
Valvulopathies	27.05	90.00	74.19	69.04	50.00	0.211
DCM	70.58	0	25.81	28.57	12.5	0.340
IC	24.71	0	12.9	4.76	25.00	0.249
DM	9.41	0	0	4.76	12.5	0.278
CVA	3.53	0	25.81	26.19	12.5	0.389
COPD	23.53					

HT- Hypertension, BP- blood pressure, DCM - Dilated cardiomiopathy, IC - Ischemic cardiopathy, DM - diabetus mellitus, CVA - Cerebrovascular accident, COPD - Chronic obstructive pulmonary disease, BMI - body mass index, NYHA - New York Heart Association, HR - heart rate, bpm - beats per minute

Clinical Features

The mean systolic and diastolic pressure had no statistically significant variations according to GFR. The NYHA functional class designated by the treating physician was predominantly class 2 at all stages of CKD. Table no. 1 presents the risk factors for heart failure and renal failure and the associated diseases with a similar distribution of the four stages of GFR, so that the risk profile and associated pathology were similar.

Table no. 2. Laboratory characteristics of the study batch

Laboratory characteristics	GFR stage					P value
	Total	I	II	III	IV	
Creatinine, mg/dl	1.43	0.90	1.12	1.49	2.64	0.009
GFR, ml/min/1,73m2	52.20	92.00	66.90	43.26	22.25	0.001
Urea, mg/dl	68.22	49.00	50.52	68.07	147.25	0.005
Uric acid, mg/dl	7.33	4.70	7.71	8.34	9.11	0.027
BNP, pg/ml	499.60	191.00	294.44	617.74	809.00	0.049
Hb, g/dl	12.74	13.00	13.09	12.38	12.49	0.342

GFR - glomerular filtration rate, BNP - brain natriuretic peptid, Hb - hemoglobine

Laboratory Features

The biological parameters studied are presented in table no. 2, with mean creatinine of 1.43 mg/dl and mean GFR of 52.2 is ml/min/1, 73m². Significantly elevated levels of urea and uric acid were observed corresponding to GFR stages. BNP values were proportionally increased with decreasing GFR, so stage IV presents significantly higher values compared to the other stages. Mean hemoglobin is 12.74 g/dL corresponding to anemia presence, with lower but not statistically significant values in stages three and four of renal failure.

Table no. 3. Cardiopulmonary exercise test characteristics

CPET variables	GFR stage					P value
	Total	I	II	III	IV	
VO_2max, % VO_2 predicted	63.26	98.00	65.23	55.93	45.60	0.033
VO_2 max<14ml/kg/min, %	8.70	0	3.22	7.14	37.50	0.001
VO_2 la AT, % VO_2 predicted	37.11	45.00	40.60	33.00	32.66	0.021
PO, ml/b	86.61	95.00	91.26	82.31	74.4	0.004

HRmax, % HR predected	73.27	70.00	70.94	72.28	79.00	0.001
BRC, %	43.80	50.00	43.48	45.76	31.83	0.001
VE/VCO^2, panta	28.76	25.00	26.74	31.52	28.33	0.001
RQ	1.11	1.10	1.13	1.10	1.07	0.122
Cardiac limitation, %	38.00	0	25.00	33.33	25.00	0.063
Pulmonary limitation, %	4.00	0	3.22	2.40	25.00	0.036
Deconditioning,%	42.00	0	37.80	62.90	47.50	0.034
Periodical breathing, %	12.00	0	13.40	12.00	12.50	0.213

VO^{2}max – maximal oxygen consumption, AT – anaerobic threshold, HR - heart rate, BRC – breathing reserve capacity, VE - minute ventilation, VCO2 – carbon dioxid volume, RQ – respiratory quotient

Cardiopulmonary exercise testing (CPET) characteristics

The patients performed a symptom limited TECP whose parameters are expressed in table no. 3. The mean values of VO$_2$ max decreased progressively with impaired GFR, the lowest values registered for patients in stage IV. Oxygen pulse was significantly lower in advanced stages of GFR decline. Respiratory reserve was lower in stage IV of impaired GFR, along with the existence of an effect on pulmonary vascular resistance expressed by the ratio VE/VCO$_2$, but both parameters are within normal limits. RQ values were comparable in all groups, indicating a similar effort and the achievement of the anaerobic threshold equivalent in all groups.

The mechanism of the functional capacity limitation and the reason for ceasing the exercise test was in most patients that of the de-conditioning and cardiac limitation, with maximum incidence in stage III of GFR. In stage IV of renal impairment, there is a statistically significant pulmonary limitation mechanism.

An interesting aspect was that of the periodic breathing as a negative prognostic marker. There was a significant correlation between the presence of periodic breathing and cardiac effort limitation, without being able to see a correlation with other causes (pulmonary, vascular or deconditioning).

We also studied the relation between BNP and exercise capacity defined by VO$_2$max and cardiac performance defined by O$_2$ pulse. The Pearson coefficient is negative and there is a statistically significant relation for both variables for any value of GFR (table no. 4). This reflects the importance of BNP values in determining prognosis in patients with heart failure. It was observed that the values over 600 pg/ml are associated with the presence of the cardiorenal syndrome.

Table no. 4. BNP value stratification

BNP, pg/ml	GFR stage					Likelihood ratio p
	Total, %	I, %	II, %	III, %	IV, %	
<100	14.11	25.0	25.8	7.10	0	
100-300	14.11	75.0	10.2	11.9	12.50	
300-600	28.23	0	54.8	14.3	12.50	0.000
600-900	24.70	0	9.20	38.1	25.00	
>900	18.80	0	0	28.6	50.00	

BNP - Brain natriuretic peptide, GFR - glomerular filtration rate

The analysis of all clinical, laboratory and CPET data according to GFR reveals that the most risk factors incidence was in patients with impaired GFR. Indeed, the major risk factor analysis showed a high proportion of advanced age and anemia in stage III of GFR and a high proportion of low VO$_2$max, anemia, elevated BNP and diabetes in stage IV (figure no. 1). In stage I, there was at most one major risk factor and the proportion increased to stage IV, when all six risk factors were present simultaneously in 25% of patients.

Figure no. 1. Density of major cardiovascular risk factors according to GFR
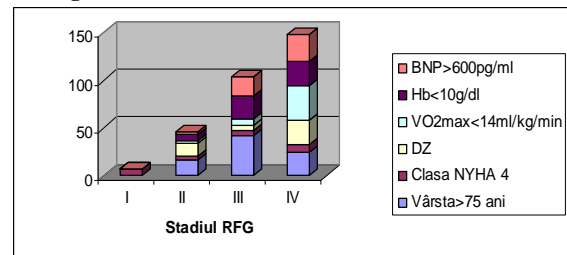
DM - diabetus mellitus, VO$_2$max - maximal oxygen consumption, Hb - hemoglobine, BNP - brain natriuretic peptide

DISCUSSIONS

This study aims at highlighting the risk profile of the patient with cardiorenal syndrome.

We wished to integrate the information derived from the clinical observations, biological investigations and cardiopulmonary performance during exercise. The groups of patients had the same clinical characteristics without statistically significant differences for the GFR, except for age and gender. The influence of age on renal function consists in about 10% decline of GFR in each decade of age.(7) In our study, the age difference was 38 years between the extremes of age, with the most advanced age in class III GFR.

A significant increase in BNP values corresponded to the demage of the renal function, thus emphasizing the relation between increased heart failure with increasing renal impairment. The BNP increase occurs beyond the NYHA functional class, which did not vary significantly between groups, in the context of lung pathology present in a significant number of patients. The prognostic value of elevated BNP in heart failure are known (8,9), but a threshold with prognostic value for the cardiorenal syndrome has not yet been studied. In this study, we have identified elevated BNP over 600pg/ml that correlate with the presence of CRS and values over 900pg/ml correlated with the degree of impairment of GFR in stage IV.

Studies have shown that the parameter of the CPET with the greatest prognostic importance is VO$_2$ max.(10) In our study, its values were significantly correlated with increased risk profile of patients respectively with decreasing GFR. The O$_2$ pulse had the same distribution, indicating an impairment of cardiac performance in the patients with progressive alteration of GFR. Effort limitation was mainly due to cardiac causes and de-conditioning, confirming the heart failure patient profile. These patients have a lower exercise capacity due to the impairment of cardiac pump function and cardiac output decrease, and due to the inactivity that appears in a chronic disease. The impaired renal function leads to increased blood urea, fluid retention and metabolic acidosis with increased symptoms of heart failure and decreased left ventricular systolic function.(11) The hormonal disorders and low levels of erythropoietin lead to anemia and low exercise capacity with ventricular remodelling and impaired peripheral oxygenation.(12,13) Cardiac limitation was predominant in stage III GFR, probably because at this stage, there were more patients over 75 years of age.

By studying the risk factors and the most important prognostic factors, we looked for their share in the four stages of GFR: advanced age, diabetes, NYHA class, low VO$_2$max, moderate anemia and elevated BNP. The load of these major risk factors is much higher in stage IV, when it was observed a significantly higher proportion of patients with all these six factors present at the same time, providing further evidence that advanced renal failure is an increased cardiovascular risk status in heart failure patients.

All these observations suggest the need to develop a score including clinical and paraclinical parameters easily available to further stratify the risk of cardiovascular events in patients with heart failure.

This study involved patients with chronic cardiorenal syndrome without seeking either the causes of renal function deterioration or the renal pathology context in which it occurred.

The GFR stages I and II were not investigated for kidney damage, such as proteinuria. The patients were not inquired for the treatment received, without knowing the importance of the medication used in determining prognosis.

CONCLUSIONS

The presence of cardiorenal syndrome and reduced glomerular filtration rate is associated with an increased incidence of major cardiovascular risk factors and a poor performance during exercise.

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