Clinical and Functional Profile of Patients with Systolic Heart Failure and Renal Dysfunction

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SUMMARY

Background
Renal dysfunction is strongly associated with chronic heart failure, and is a frequent and progressive complication of this condition, with clinical outcomes which depend on the functional class and pharmacological treatment.

Objectives
To define the prevalence and the clinical and functional profile of patients with renal dysfunction in the setting of heart failure with depressed ejection fraction.

Material and Methods
Creatinine clearance was measured in 132 patients with heart failure and an ejection fraction <40%. Renal dysfunction was defined as a creatinine clearance <60 ml/min. Patients underwent routine lab tests, echocardiogram, bioelectrical impedance analysis and 6-minute walk test.

Results
The prevalence of renal dysfunction was 43.2% (57 patients). Among these patients, there was a greater prevalence of women and elder subjects, yet the prevalence of coronary artery disease was low. Lab tests showed lower levels of hemoglobin, albumin, ferritin and triiodothyronine, and greater prevalence of measurable levels of troponin T. Body mass index (BMI), basal metabolic rate, muscle mass and phase angle were lower, while the ratio of extracellular water to total body water was greater in patients with renal dysfunction. The distance walked in the 6-minute test was lower. The use of beta blockers and amiodarone was the only difference in therapy. At multivariate analysis, age, NT-proBNP level, the presence of positive troponin T and muscle mass as a continuous variable were independent predictors of renal dysfunction in patients with systolic heart failure.

Conclusions
Renal dysfunction is frequent in patients with heart failure with depressed ejection fraction and is associated with distinctive features that may contribute to explain the clinical picture.

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Key words > Heart Failure - Renal Failure - Electrical Impedance - Body Composition

Abbreviations >

ARB II	Angiotensin II receptor blocker	**NT-proBNP**	N-terminal pro B-type natriuretic peptide
RD	Renal dysfunction	**T_3**	Triiodothyronine
EF	Ejection fraction	**T_4**	Thyroxine
CHF	Congestive heart failure	**TSH**	Thyroid-stimulating hormone
ACEI	Angiotensin-converting enzyme inhibitor	**ESR**	Erythrocyte sedimentation rate

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BACKGROUND

Congestive heart failure (CHF) is the fastest-growing cardiovascular disease in the last years. [(1-3) Renal dysfunction (RD) is a frequent and progressive complication of this condition, with clinical outcomes which depend on the functional class and the pharmacological treatment. (1-5)

The presence of RD has proved to be an independent predictor of worse outcomes in CHF. (5-7) The mechanisms probably involved include the presence of comorbidities, increased toxicity related to diagnostic and therapeutic procedures, accelerated atherosclerosis and the fact that patients with both conditions are less likely to receive proven efficacious therapies. (3-7)

Multicenter studies do not represent the total population of patients with CHF. These studies generally include male patients, younger, with systolic dysfunction and less number of comorbidities. (8) Thus, patients with RD are almost completely excluded from the trials, limiting the clinical evidence.

The aim of this study was to define the prevalence and the clinical and functional profile of patients with RD in the setting of CHF with systolic dysfunction.

MATERIAL AND METHODS

From August 2006 to April 2008 we included 132 consecutive outpatients > 18 years with a diagnosis of chronic CHF of any etiology, with an ejection fraction (EF) ≤ 40%. All patients were receiving full medication for CHF and were clinically stable within 90 days previous to enrollment.

Renal dysfunction was defined as a creatinine clearance < 60 ml/min/m^2, according to the National Kidney Foundation guidelines. (9, 10) Creatinine clearance was calculated using a 24-hour urine sample and creatinine blood levels.

The history of diabetes mellitus, hypertension, dyslipemia and comorbidities (chronic obstructive pulmonary disease, neoplasms, blood diseases, asthma, hypothyroidism, hyperthyroidism and osteoporosis) was registered. The diagnosis and the etiology of CHF were based on the criterion of the attending physician and on data from the clinical record.

The following blood tests were performed: complete blood count, biochemical analysis, hormonal profile (T_3, T_4 and TSH) and biomarkers (troponin T and NT-proBNP).

Troponin T values > 0.01 ng/ml were considered positive.

Microalbuminuria was defined as levels of urine albumin between 30 and 300 mg in a 24-hour urine sample.

All patients underwent transthoracic color-Doppler ecochardiography (Philips IE33echo system) from the left parasternal window (long-axis and short-axis views) and left ventricular apex (4-chamber and 2-chamber views). Ejection fraction was determined using the formula of Simpson.

Human body composition was evaluated with a tetrapolar bio-electrical impedance analyzer (BioScan MSR-916, Maltron International Ltd.). This technique is based on the opposition to the flow of a low-level electric current through water and body tissues. Four electrodes are applied to the right hand, wrist, foot and ankle. The study was performed in the outpatient clinic, with the patient in the supine position. The patient was asked to fast for 6 hours, not to exercise within 12 hours of testing, to void the bladder and not to carry metal objects on the body.

Functional capacity was evaluated with the 6-minute walk test.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range (25-75%) for normal and abnormal distributions, respectively. Student's *t* test was used to compare continuous variables with a normal distribution and Wilcoxon test was used in cases of abnormal distribution.

Categorical variables were expressed as percentages and chi square test was used to compare differences between groups.

The different variables in patients with RD and without RD with a p value < 0.10 were recorded in a multivariate model to define those variables that were independently associated with RD.

RESULTS

Mean age was 63.4 ± 11.5 and most patients were men. The most frequent etiology of CHF was coronary artery disease; mean EF was 27.5% ± 7.6% and most patients were in functional class I-II (Table 1).

Mean creatinine clearance was 70.6 ± 35.5 ml/min. The prevalence or RD was 43.2% (57 patients). The population was divided into two groups according to the creatinine clearance in order to determine the characteristics of patients with RD: with RD (57 patients, 43.2%) and without RD (75 patients, 56.8%).

The prevalence of female gender was higher in the group with RD. Patients with RD were older, with greater prevalence of non-coronary etiology and had a trend towards more comorbidities (Table 1).

Blood levels of hemoglobin, ferritin and T_3 were lower, but potassium, troponin T, erythrocyte sedimentation rate (ESR) and NT-proBNP levels were higher (Table 2). The use of beta blockers and amiodarone was significantly different (Table 3).

There were no significant differences in the values obtained by color-Doppler echocardiography. Patients with RD showed a trend towards higher ventricular mass (Table 4).

The analysis of bio-electrical impedance showed that body mass index, muscle mass, protein mass, phase angle and rest metabolic rate were lower in the group with RD, while extracellular/ total body water volume ratio was greater.

The distance walked in the 6-minute walk test was lower in patients with RD (Table 5).

At multivariate analysis, age, plasma logarithm of NT-proBNP levels , the presence of positive troponin T and muscle mass as a continuous variable were independent predictors of RD in outpatients with systolic dysfunction (area under the ROC curve 0.87) (Table 6 and Figure 1).

Variable	Total n =132	RD n = 57 (43.2%)	Without RD n = 75 (56.8%)	p (RD versus without RD)
Age, years	63.4 ± 11.5	70 ± 7.8	58 ± 11.3	< 0.001
Female gender (%)	22 (16.73)	14 (24.5)	8 (10.6)	0.034
Hypertension (%)	71 (53.8)	29 (50.8)	42 (56)	ns
Diabetes (%)	33 (25)	14 (24.6)	19 (25.3)	ns
Dyslipemia (%)	72 (54.5)	27 (47.3)	45 (60)	ns
Functional class III-IV (%)	40 (30.3)	20 (35.1)	20 (26.7)	ns
Coronary etiology (%)	70 (53)	24 (42.1)	46 (61.3)	0.02
Comorbidities (%)	46 (34.8)	24 (42.1)	22 (29.3)	0.01

Table 1. General characteristics of the population and of patients with RD and without RD

Variable	Total n =132	RD n = 57 (43.2%)	Without RD n = 75 (56.8%)	p (RD versus without RD)
Hemoglobin, g/dl	13.9 ± 1.6	13.4 ± 1.7	14.3 ± 1.4	< 0.001
Potassium, mEq/L	4.7 ± 0.5	4.9 ± 0.5	4.6 ± 0.4	< 0.001
Sodium, mEq/L	140.7 ± 3.8	141.1 ± 4.6	140.4 ± 3.1	ns
Albumin, g/dl	3.96 ± 0.3	3.8 ± 0.3	4 ± 0.3	0.002
Ferritin, ng/ml*	241 (140-434)	199 (108-369)	280 (145-281)	0.01
T_3. ng/ml	1.02 ± 0.2	0.9 ± 0.2	1 ± 0.2	0.009
Serum cretinine, mg/dl	1.4 ± 0.5	1.6 ± 0.6	1.1 ± 0.2	< 0.001
BUN, mg/dl	56.8 ± 22.6	66.9 ± 27.4	49.1 ± 14.2	< 0.001
ERS, mm*	15 (5-20)	15 (5-30)	6 (3-15)	0.001
NT-proBNP (pg/ml)*	1.113 (468-2.432)	3.851 (2.554-5.147)	1.006 (765-1.246)	< 0.001
Troponin T > 0.01 (%)	64 (48.4)	38 (66)	26 (34.6)	< 0.001

* Los valores se expresan en mediana y rango intercuartil 25-75.

Table 2. Laboratory data in the population and in patients with RD and without RD

Variable	Total n =132	RD n = 57 (43.2%)	Without RD n = 75 (56.8%)	p (RD versus without RD)
Acetyl salicylic acid (%)	70 (53)	31 (54.3)	39 (52)	ns
Furosemide (%)	104 (78.8)	46 (80.1)	58 (77.3)	ns
Beta blockers (%)	119 (90.15)	46 (80.7)	73 (97.3)	0.001
Spironolactone (%)	82 (62.12)	33 (57.9)	49 (65.3)	ns
ACEI/ARB ii (%)	100 (75.8)	42 (73.7)	58 (77.3)	ns
Digital (%)	30 (22.7)	13 (22.8)	17 (22.6)	ns
Calcium channel blockers (%)	4 (3.03)	2 (3.5)	2 (2.7)	ns
Nitrates (%)	7 (5.3)	4 (7)	3 (4)	ns
Amiodarone (%)	53 (40.1)	29 (50.8)	24 (32)	0.02
Statins (%)	52 (39.4)	19 (33.3)	33 (44)	ns
Anticoagulant agents (%)	44 (33.3)	20 (35)	24 (32)	ns

IECA/ARA: Inhibidores de la enzima convertidora de la angiotensina/Bloqueantes de los receptores de angiotensina.

Table 3. Pharmacologic treatment of the popultion and of patients with RD and without RD

DISCUSSION

The relation of causality in patients with RD and chronic CHF may be difficult to delimit due to the co-dependence between the kidneys and the heart. (1-3, 6, 7) Renal dysfunction is an underappreciated prognostic factor in CHF and is associated with changes in vascular and intravascular physiology: disorders of coagulation and hemostasis, abnormal vascular calci-

Tabla 4. Resultados del ecocardiograma de la población y de pacientes con DR y sin DR

Variable	Total n =132	RD n = 57 (43.2%)	Without RD n = 75 (56.8%)	p (RD versus without RD)
LVEDD, mm	64.3 ± 8	64.3 ± 9	64.3 ± 7	ns
LVESD, mm	53.2 ± 10	53.8 ± 12	52.8 ± 10	ns
EF (%)	27.5 ± 7.6	26.9 ± 8	28 ± 7.3	ns
Left atrial area, cm^2	26 ± 6.8	26.7 ± 7	25.4 ± 6.7	ns
Left ventricular mass, g/m^2	171.8 ± 52	181.5 ± 57.6	164 ± 46.8	0.06

LVEDD/LVESD: Left ventricular end-diastolic diameter/Left ventricular end-systolic diameter.

Table 5. Bio-electrical impedance and 6-minute walk results in the population and in patients with RD and without RD

Variable	Total n =132	RD n = 57 (43.2%)	Without RD n = 75 (56.8%)	p (RD versus without RD)
Rest matabolic rate	1.451.6 ± 234	1.324 ± 205	1.550 ± 208	< 0.001
BMI. kg/m^2	28.8 ± 5.7	27.4 ± 4.1	29.9 ± 6.5	0.01
Protein mass. kg	8.69 ± 2	7.8 ± 2.2	9.3 ± 1.6	< 0.001
Muscle mass. kg	27.8 ± 6.3	24.9 ± 5.3	29.9 ± 5.8	< 0.001
Total body water (%)	54.8 ± 4.8	55.9 ± 5.3	54.2 ± 4.2	0.1
Extracell./total body water (%)	42.2 ± 5.5	44.5 ± 6	40.5 ± 4	< 0.001
Ángulo de fase* (°)	6.52 (5.45-7.92)	5.97 (4.88-7.49)	7 (6.2-8.1)	0.004
6-minute walk test. m*	280 (190-380)	230 (120-340)	310 (230-420)	< 0.001

* Values are expressed as median and interquartile range (25-75%).

Table 6. Predictors of RD in patients with CHF

Variable	Odds ratio	p	95% CI
Age (years)	1.1	0.001	1.04-1.17
Log NT-proBNP	4,4	0.008	1.46-13.34
Troponin T (>0.01ng/dl)	3	0.034	1.08-8.47
Mucscle mass (kg)	0.9	0.006	0.81-0.96

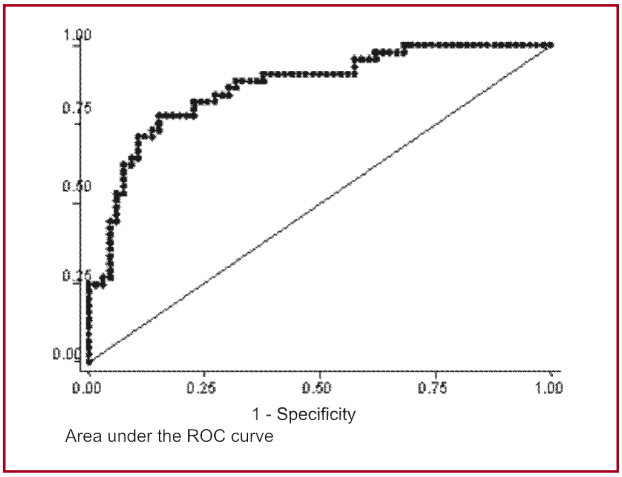

Fig. 1. ROC curves analysis for the predictors of renal dysfunction in congestive heart failure.

fication, endothelial dysfunction, hyperhomocysteinemia, insulin resistance, elevated C-reactive protein levels and ESR, endothelin/nitric oxide imbalance, electrolyte disturbances (hyperkalemia and hypermagnesemia), and hyperactivity of the sympathetic nervous system and of the renin-angiotensin-aldosterone system. (4, 5, 7, 11, 12) These abnormalities, together with impaired ventricular function, might determine worst outcomes with increased rate of cardiovascular events. (4, 7, 11)

In our series, the prevalence of RD in patients with chronic CHF was similar to the one reported by international publications (approximately 30-50%). (1-3, 12, 13)

In the group with RD, mean age was higher than in patients with preserved renal function; this might be due to a physiologic age-related decrease in the glomerular filtration rate (0.8 ml/min/1.73 m^2 per year after the age of 30). (9, 10)

The percentage of women was greater in this group; however male gender was more prevalent in both groups. Previous studies have reported gender-related differences in the pharmacokinetics of loop diuretics. Women need higher doses than men to achieve the same natriuretic response. This situation might produce a greater depletion of the plasmatic volume which, in turn, would activate the neurohormonal system, contributing to a progressive impairment of renal and cardiac functions. (14, 15) In our

series, the percentage of total body water in women was lower.

Coronary artery disease and renal disease have many factors in common and, for this reason, systolic dysfunction due to coronary artery disease is more frequent in patients with RD. (1-3) Yet, we did not find this association in our series.

Hemoglobin and ferritin levels were lower in patients with RD, expressing a greater trend towards iron deficiency anemia, anemia of inflammatory disease and/or dilution anemia. Previous studies have demonstrated that anemia is associated with both CHF and RD. (12, 16, 17) In our series, the prevalence of anemia was 17.4% (21% in patients with RD and 15% in patients without RD; this difference was not significant). The interrelation between anemia, RD and CHF has not been completely elucidated yet. Several hypotheses have been suggested: renal interstitial chronic ischemia and fibrosis, increased circulating cytokines (as tumor necrosis factor-alpha), hemodilution due to plasma volume expansion in patients with RD, and side effects following the use of certain drugs (enalapril, diuretics, beta blockers, antiarrhythmic agents and digoxin). (18, 19) Yet, Bansal et al. suggest that anemia might reflect advanced CHF; in this way, patients with advanced-stage CHF would be more prone to RD progression and anemia. (16)

Microalbuminuria, a marker of endothelial dysfunction, constitutes a risk factor for the development and progression of RD. Paradoxically, we did not find differences in the presence of albuminuria in both groups. This might be attributed to the fact that a similar percentage of subjects in both groups were receiving ACEI/ARB II and were clinically stable.

Potassium levels were similar in both groups, yet it was slightly higher in patients with RD. Renal insufficiency predisposes to hyperkalemia and might limitate the use of certain drugs as spironolactone and ARB II; however, this did not occur in our series.

Elevations of troponin T and BNP from normal, detected at any time during clinical follow-up in patients with CHF, are highly associated with increased risk of events, (20-22) therefore monitoring these biomarkers is useful for a better risk assessment. The levels of troponin T and BNP were higher in our patients with RD, indicating a more severe myocardial damage and worse outcomes. A Spanish study reported that the levels of BNP in patients with RD were higher compared to the general population; BNP was considered a marker of cardiovascular disease and left ventricular hypertrophy. An inverse correlation was found between the levels of BNP and creatinine clearance in patients with CHF. This finding is due to the fact that BNP in influenced by the glomerular filtration rate, parenchymatous mass and tubular function.

The clinical significance of ESR in CHF is controversial and has not been established yet in RD. (23, 24) In our study, ESR was greater in the group of patients with RD; however, its value was lower than the one reported in previous studies. Elevated ERS might be related to age, greater prevalence of anemia and to abnormalities in the morphology of red blood cells in chronic diseases.

Patients with severe chronic conditions receiving multiple drugs may show changes in the metabolism and peripheral concentrations of thyroid hormones. (25-27) Plasma levels of T_3 were lower in patients with RD, probably due to reduced peripheral conversion of T_4 to T_3, abnormalities in the thyroid hormone transport proteins and side effects secondary to the use of amiodarone. Thyroid dysfunction might aggravate the progression of CHF and RD.

Left ventricular mass determined by echocardiography was greater in patients with RD ($p = 0.06$). This finding may be related to hemodynamic adaptations compensating for anemia, myocardial ischemia-fibrosis-remodeling or ventricular dilation due to volume overload; all these situations are more frequent in patients with RD. (16, 19)

During the last years, progress in the pharmacologic treatment of CHF has improved the survival of patients. Some of these drugs have beneficial effects in patients with RD despite producing certain degree of increase in serum creatinine levels. Thus, RD is considered a relative contraindication for certain therapies. Treatment of CHF is different in patients with RD. McAlister et al. observed that patients with decreased creatinine clearance were less likely to receive prescription of beta blockers, ACEI and spironolactone. (2) In our group with RD, amiodarone was the drug more frequently prescribed, as opposed to beta blockers. This situation might probably be due to advanced CHF, greater incidence of ventricular arrhythmias secondary to electrolyte imbalance, intolerance to beta blockers related to hypotension and less frequency of non-coronary etiology in the groups with RD.

There is strong evidence suggesting that body composition is a systemic maker of disease severity in chronic conditions such as CHF and renal insufficiency. (28-30) Involuntary weight loss (cachexia) is related with increased morbidity and mortality that does depend on the severity of the disease. According to the results of bio-electrical impedance, patients with RD had a lower body mass index due to a reduction in protein mass and, therefore, lower muscle mass. This situation, together with low serum albumin levels, suggests an unfavorable nutritional status, a condition that is sometimes underestimated in these patients. Total body water was similar in both groups, yet the percentage of extracellular water was significantly higher in the group with RD, reflecting the difficulty these patients have in the management of fluid and electrolyte balance.

One third of our population was in FC III-IV on an equal proportion in the two groups. Despite this finding, the distance walked in the 6-minute walk test

was lower in patients with RD, probably due to the fact that these patients were older, with more severe anemia, worse nutritional status, lower muscle mass and worse physical fitness. A substudy of the DIG (31) trial that employed the 6-minute walk test reported that patients in the lower two quartiles of creatinine clearance were significantly older, had a higher proportion of female patients, more hospitalizations for CHF, were in functional class III-IV, required regular diuretic therapy and had shorter 6-minute walk distances.

Study Limitations

Our study has few limitations. Firstly, creatinine clearance was obtained from a 24-hour urine sample. This method has inconveniencies: incomplete urine collections would tend to underestimate the true creatinine clearance; on the other hand, when the glomerular filtration rate decreases, secretion of creatinine increases as a compensatory mechanism, overestimating creatinine clearance. Secondly, this series of patients belong to a group of cardiologists specialized in CHF. Thirdly, we did not perform screening for renal disease: urinary sediment, evaluation of the renal structure, funduscopy and study of the renal artery. Finally, our data were obtained from patients with systolic dysfunction and should not be extrapolated to patients with heart failure and preserved systolic function.

CONCLUSIONS

Renal dysfunction is frequent in patients with CHF with depressed EF and is associated with distinctive features that may contribute to explain the adverse outcomes: age, elevated troponin T and BNP, and lower muscle mass.

RESUMEN

Introducción

La disfunción renal está fuertemente asociada con la insuficiencia cardíaca crónica. Es una complicación habitual y progresiva de esta condición, con una evolución clínica que fluctúa con la clase funcional y el tratamiento farmacológico.

Objetivos

Definir la prevalencia y el perfil clínico y funcional de pacientes con disfunción renal en el contexto de insuficiencia cardíaca con baja fracción de eyección.

Material y métodos

En 132 pacientes con insuficiencia cardíaca y fracción de eyección < 40% se midió la depuración de creatinina. Se definió disfunción renal a una depuración de creatinina < 60 ml/min. Se realizaron analítica sanguínea, ecocardiograma, bioimpedanciometría y caminata de 6 minutos.

Resultados

La prevalencia de disfunción renal fue del 43,2% (57 pacientes). Comparados con el resto, en estos pacientes hubo mayor prevalencia de sexo femenino, mayor edad y menos frecuentemente etiología coronaria. En el laboratorio tuvieron valores menores de hemoglobina, albúmina, ferritina y triyodotironina y mayor prevalencia de troponina T dosable. Fueron menores el índice de masa corporal (IMC), la tasa metabólica basal, la masa muscular y el ángulo de fase, mientras que la relación agua extracelular/agua corporal total fue mayor. La distancia recorrida en la prueba de 6 minutos fue menor. Respecto del tratamiento, sólo difirió el uso de betabloqueantes y amiodarona. En el análisis multivariado, la edad, el nivel de NT-proBNP, la presencia de troponina T positiva y la masa muscular como variable continua fueron predictores independientes de disfunción renal en pacientes con insuficiencia cardíaca sistólica.

Conclusiones

La disfunción renal es frecuente en pacientes con insuficiencia cardíaca con baja fracción de eyección y se vincula con características distintivas que pueden contribuir a explicar el cuadro clínico.

Palabras clave > Insuficiencia cardíaca - Insuficiencia renal - Impedancia eléctrica - Composición corporal

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