Risk Factors For Worsening Renal Function In Chronic Stable Heart Failure Patients

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Citation

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Abstract

Background: Renal dysfunction is a common problem in the heart failure (HF) population; however there are not well established risk factors that participate in this situation which complicates the HF evolution and prognosis. The objective of the present study was to determine the frequency and risk factors for worsening renal function (WRF) in stable heart failure outpatients. Methods: In a prospective study we examined 75 chronic and stable HF outpatients with not chronic renal failure diagnostic parameters. Clinical characteristics including age, gender, co-morbidities, New York Heart Association (NYHA) functional class, HF medication, as well as biochemical and echocardiographic characteristics (ECHO) were assessed at baseline and 6-month later. The MDRD formula was use to determine which patients fulfilled renal function impairment parameters, defined as impairment of the patient's KDOQI classification after follow-up. Results: Eighteen (21.4%) patients developed WRF, they were significantly older, had more fatigue, worse NYHA functional class, more frequency of left ventricular hypertrophy, higher loop diuretic dose and diastolic blood pressure, lower baseline estimated glomerular filtration rate; Daily loop diuretic dose (OR 1.048, 95% CI 1.01-1.09, p=0.02) and serum glucose (OR 1.02, 95% CI 1.01-1.03, p=0.01) were found as independent significant risk factors for WRF. Conclusions: Occurrence of WRF is frequent in HF outpatients and daily loop diuretic dose as well as higher glucose serum levels were the most important risk factors.

INTRODUCTION

Renal dysfunction is a common and progressive complication of chronic heart failure. Despite growing recognition of the frequent presentation of combined cardiac and renal dysfunction, or cardiorenal syndrome, most of the times can be under-diagnosed, its underlying pathophysiology is not well understood, and no consensus over its definition and appropriate management has been achieved. (1) The coexistence of heart failure and renal failure result in an increased mortality and healthcare-related costs compared to any of these organ failures alone (1-6).

It is estimated that around 20-30% of heart failure (HF) patients develop renal failure as well during a lifetime period, and because of the increasing prevalence of heart failure due to greater longevity and less myocardial infarction-associated deaths, this association is becoming more common (2, 7-9). Several studies have shown that around 30% of the heart failure patients had a rise in serum creatinine of ≥0.3 mg/dL. Other studies showed prevalence of glomerular filtration rates lesser than 60 mL/min in 56% of patients with chronic heart failure diagnosed (2, 10-13). Deterioration of renal function in heart failure patients can be present without any clinical evidence and is associated with poor outcome (3, 11, 13).

In addition, several studies have shown significant decreases in disease progression, as well as less renal impairment, with chronic angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) treatments (1,11,14-15). Loop diuretics, which have an important a role in the management of heart failure, can worsen renal insufficiency and the use of high doses has been associated with adverse outcome in stable chronic HF patients at long term (16-19).

Worsening renal function (WRF) among heart failure patients has predominantly been described in randomized clinical trials, hospitalized subjects or decompensate and their results cannot be accurately extrapolated to the stable

ambulatory patients. Moreover, very few studies have shown the evolution of the renal function on longstanding follow-up or in HF with preserved systolic function (13).

The aim of the present study was to determine the incidence and risk factors of WRF in stable heart failure outpatients due to left ventricular systolic or diastolic dysfunction.

METHODS

This observational, comparative and prospective study recruited stable chronic heart failure patients who were admitted as an outpatient in the Heart Failure Clinic of the "Instituto Nacional de Ciencias Medicas y Nutricion SZ".

Subjects were consecutively included if they were older than 18 years, with confirmed systolic or diastolic heart failure diagnosis as was defined by ESC, AHA/ACC guidelines (20-21), in any NYHA class, with no chronic renal failure diagnosis, defined by National Kidney Foundation Kidney Kidney Disease Outcome Quality Initiative (KDOQI) guidelines (22). Subjects were excluded if they had end-stage renal disease, those undergoing chronic renal replacement therapy, were renal transplant receptors, had hepatic failure, valve stenosis, restrictive miocardiopathies, recent acute coronary syndromes (unstable angina or acute myocardial infarct), and also, those who underwent myocardial revascularization procedures or invasive procedures requiring contrast administration within 3 month prior to study or were receiving cancer chemotherapy.

Patients were on standard HF therapy (diuretics, ACE inhibitors, Angiotensin II antagonists, aldosterone antagonist's receptors, digitalis and beta-blockers). There were no changes made on medical therapy during this 6-month period in all patients.

All subjects underwent to complete clinical and laboratory examination at baseline and 6-month later. Also a transthoracic Doppler-echocardiogram was performed in all of them

Estimated glomerular filtration rate (eGFR) was calculated by the simplified Modification of Diet in Renal Disease (MDRD) equation (23). The MDRD formula for estimating the glomerular filtration rate has been proved as the most precise and used formula in patients with cardiovascular disease, compared to serum creatinine and the Cockcroft-Gault formula (24), and is the preferred one for monitoring the renal function in this group of patients (3, 25-26).

Worsening renal function were defined using two methods. The primary method used was a deterioration in the eGFR category between (normal ≥90 mL/min, mild impairment 89–60 mL/min, moderate impairment 59-30 mL/min, and severe renal impairment ≤29 mL/min) values defined by K/DOQI guidelines (22). In addition, we also used an increase of ≥ 0.3 mg/dL in serum creatinine to assess changes in renal function over a period of 6-mo. Criteria previously used by other investigators (2, 3).

The protocol was approved by the Committee of Biomedical Investigation in Humans at the INCMNSZ. Written informed consent was obtained from each patient before inclusion in the study.

STATISTICAL ANALYSIS

Continuous variables are given as mean ± standard deviation (SD), and categorical variables are presented as absolute and relative frequency. Comparisons between laboratory variables at baseline and 6-month later were performed with paired t-test. Also patients were divided in two groups: the ones that presented renal function impairment, and those who did not change the eGFR. Comparisons of baseline variables between groups were made with Pearson's chi-square for categorical variables and unpaired t-test for continuous variables. A p value <0.05 was considered statistically significant.

Independent risk factors of WRF were identified by multivariable logistic regression. Variables were entered at an entry level of significance of $p<0.1$ in the bivariate analysis using the enter method to establish the independent contribution of each covariable (adjusted odds ratio) on WRF. Also 95% confidence intervals (95% CI) were calculated for adjusted OR. Analyses were performed using a commercially available package (SPSS for Windows, version 10.0 1999 Chicago SPSS Inc.).

RESULTS

A total of 83 consecutive patients were included. The baseline characteristics are shown in Table 1. At baseline, more than half of patients included had diabetes mellitus and/or arterial hypertension and most of them were in NYHA class II. In the echocardiogram variables, we observed diastolic ventricular dysfunction (38.6%) predominance and an elevated pulmonary artery systolic pressure. In laboratory parameters, elevated glucose levels, with normal creatinine, ureic blood nitrogen, serum electrolytes, and hemoglobin mean values were found.

Of this baseline group, 8 patients were lost to follow-up.

None of the patients died or was hospitalized during the study. Table 2 shows the baseline and 6-mo change in laboratory variables of the whole study population. The mean values of serum creatinine and ureic blood nitrogen increased significantly after follow-up; as well as the mean value of estimated glomerular filtration rate, was found to be significantly lower after follow-up. We also found a significant decrease of serum sodium mean values after 6 months.

Worsening renal failure defined as a rise in creatinine ≥ 0.3 mg/dL occurred in 9 (10.7%) patients and 18 (21.4%) patients when the criteria of deterioration in the eGFR category were considered. Figure 1 shows the percentage of patients in each category of eGFR (K/DOQI stages) at baseline and at follow-up. There was a significant impairment ($p<0.001$) of baseline eGFR. This was normal in 57.8% at the beginning and after 6-month only in 44%.

Characteristics of the patients with and without WRF according to deterioration in the eGFR category are compared in Table 3. The patients who developed WRF were significantly older, had worse NYHA functional class, and more fatigue. They also had more frequency of left ventricular hypertrophy and had lower eGFR at baseline. It is also important to notice that the group of patients that developed renal function impairment had higher glucose levels, higher diastolic blood pressure, and were more likely to have left ventricular diastolic dysfunction than those who did not worsen renal function and were receiving higher doses of furosemide. There were no differences between patients on ACE-Inhibitors and ARBs based-treatment groups.

Using a multivariable model, including baseline clinical characteristics, co-morbidities, laboratory test, and concomitant treatment, the only independent risk factors of developing WRF were blood glucose and furosemide daily doses entered as continuous variables after adjustment for other found risk factors as age, symptoms, left ventricular hypertrophy and diastolic arterial pressure. (Table 4)

The multivariable analysis was repeated entered as categorical variable the daily dose of furosemide (≥35 mg/day vs. <35 mg/day) and was found to have an OR=11.9 (95% CI 2.2-65.7, p=0.02) for WRF, after adjustment with the same variables previously mentioned.

Figure 1

Table 1. Clinical baseline characteristics

Variables	n = 83
Men/Women, n (%)	40 (48.2)/43 (51.8)
Age, years	62.7 (14.8)
Body Mass Index, kg/m2	31.2 (7.5)
Diabetes mellitus, n (%)	47 (56.6)
Arterial hypertension, n (%)	57 (68.7)
Myocardial infarction, n (%)	29 (34.9)
NYHA class, n (%)	
II	78 (93.9)
III	2 (2.4)
IV	3 (3.6)
Dyspnea, n (%)	44 (53)
Fatigue, n (%)	39 (47)
Peripheral edema, n (%)	32 (38.6)
Heart rate, bpm	74.1 (10.0)
Systolic blood pressure, mmHg	126 (19.9)
Diastolic blood pressure, mmHg	76.5 (12.2)
Left systolic ventricular dysfunction	28 (33.7)
Left diastolic ventricular dysfunction	32 (38.6)
Right ventricular dysfunction	23 (27.7)
Ejection fraction, (%)	50.9 (16.3)
LVEDd, mm	49.3 (8.3)
LVESd, mm	35.0 (10.5)
LAD, mm	44.1 (6.9)
RAD, mm	43.7 (8.8)
RVDd, mm	39.67 (8.6)
IVS, mm	10.9 (2.4)
PW, mm	10.1 (2.2)
PASP, mmHg	55.8 (15.7)
ACE-inhibitor, n (%)	26 (31.3)
ARBs, n (%)	57 (68.7)
Beta-blocker, n (%)	68 (81.9)
Furosemide, n (%)	36 (43.4)
Thiazides, n (%)	25 (30.1)
Aldosterone antagonist's receptors, n (%)	68 (81.9)
Digoxin, n (%)	31 (37.3)

LVEDd=left ventricular end diastolic diameter, LVESd=left ventricular end systolic diameter, LAD= left atrium diameter, RAD= right atrium diameter, RVDd=right ventricular diastolic diameter, IVS=interventricular septum, PW=posterior wall, PASP=Pulmonary arterial systolic pressure; Data is presented in mean (SD) or n (%).

Figure 2

Table 2. Comparison between biochemical variables at baseline and after 6 months.

Variables	Baseline n=75	6 months n=75	p
Glucose, mg/dL	133 (59.1)	126.7 (71.2)	0.45
Creatinine, mg/dL	0.81 (0.2)	1.01 (0.76)	0.02
BUN, mg/dL	15.7 (5.1)	18.9 (10.9)	0.01
Hemoglobin, g/dL	14.3 (2.3)	14.05 (2.2)	0.30
Hematocrit, %	42.2 (7.0)	41.5 (6.5)	0.33
Total cholesterol, mg/dL	180.1 (48.2)	180.0 (47.2)	0.45
LDL cholesterol, mg/dL	104.9 (40.4)	105.6 (44.0)	0.80
Triglycerides, mg/dL	199.3 (111.9)	206.6 (115.6)	0.58
Sodium, mg/dL	138.5 (3.0)	136.5 (3.0)	0.001
Potassium, mg/dL	4.5 (0.5)	4.6 (0.5)	0.26
Chloride, mg/dL	104.1 (3.9)	103.1(4)	0.06
Phosphorous, mg/dL	3.4 (0.6)	3.8 (0.6)	0.38
Magnesium, mg/dL	2.0 (0.1)	2.1 (0.2)	0.29
Calcium, mg/dL	8.9 (0.6)	9.2 (1.3)	0.25
CO2, mg/dL	25.5 (2.9)	24.9 (2.9)	0.10
eGFR, mL/min	98.9 (30.1)	87.56 (34.9)	<0.001

BUN= Blood urea nitrogen; Data is presented in mean (SD).

Figure 3

Table 3. Comparison between patients with renal function impairment and patients without renal function impairment.

Variables	With WRF n=18	Without WRF n= 57	p
Age, years	67.33 (8.9)	60.37 (16.2)	0.02
Men, n (%)	7 (38.9)	27 (47.4)	0.53
Diabetes Mellitus, n (%)	8 (44.4)	33 (57.9)	0.32
Arterial Hypertension, n (%)	13 (72.2)	38 (66.7)	0.66
Myocardial Infarction, n (%)	6 (33.6)	21 (36.8)	0.79
NYHA, n (%)			
II	17 (94.4)	55 (96.5)	0.02
III	0 (0)	2 (3.5)	
IV	1 (5.6)	0 (0)	
Dyspnea, n (%)	12 (66.7)	24 (47.4)	0.1
Fatigue, n (%)	13 (72.2)	21 (36.8)	0.01
Peripheral edema, n (%)	8 (44.4)	20 (35.1)	0.5
Glucose, mg/dL	155.3 (90.6)	124.5 (42.8)	0.05
Creatinine, mg/dL	0.83 (0.2)	0.80 (0.2)	0.6
BUN, mg/dL	15.4 (3.7)	15.74 (5.4)	0.8
Hemoglobin, g/dL	14.23 (2.7)	14.54 (2.1)	0.7
Sodium, mg/dL	137.7 (2.9)	138.8 (2.9)	0.2
Systolic blood pressure, mmHg	131.1 (18.1)	124.5 (20.5)	0.2
Diastolic blood pressure, mmHg	80.9 (8.8)	75.7 (12.8)	0.06
ACE-Inhibitors, n (%)	7 (38.9)	17 (29.8)	0.5
ARBs, n (%)	11 (51.1)	40 (72.2)	0.5
Thiazides, n (%)	5 (27.8)	19 (33.3)	0.7
Furosemide, n (%)	9 (50)	21 (36.8)	0.3
Furosemide, mg/day	62.2 (41.7)	27.6 (12.6)	0.04
Ejection fraction, mm	55.2 (10.3)	51.2 (17.0)	0.2
LVEDd, mm	46.7 (6.3)	49.6 (8.7)	0.2
RAD, mm	44.6 (10.4)	43.6 (8.3)	0.7
RVDd, mm	39.5 (7.6)	40.6 (8.9)	0.7
IVS, mm	12.5 (2.4)	10.5 (2.3)	0.002
PW, mm	11.1 (2.7)	9.9 (1.9)	0.05
PASP, mmHg	58.7 (18.0)	55.4 (15.2)	0.5
LVH, n (%)	7 (38.9)	4 (7.0)	0.003
Left diastolic ventricular dysfunction, n (%)	10 (55.6)	19 (33.3)	0.09
eGFR, ml/min	89.5 (16.1)	101.9 (32.9)	0.03

Data is presented in mean (SD) or n (%).LVEDd=left ventricular end diastolic diameter, RAD= right atrium diameter, RVDd=right ventricular diastolic diameter, IVS=interventricular septum, PW=posterior wall, PASP=Pulmonary arterial systolic pressure; LVH= left ventricular hypertrophy

Figure 4

Table 4. Baseline determinants of worsening renal function in chronic heart failure patients at multivariable analysis

Variable	Odds ratio	95% CI	p value
Age (years)	1.04	0.98 - 1.11	0.19
Fatigue (yes/no)	2.25	0.34 - 14.97	0.40
NYHA class (I-IV)	1.32	0.29 - 5.98	0.72
Glucose (mg/dL)	1.02	1.01 – 1.03	0.01
LVH (yes/no)	1.83	0.36 – 9.15	0.46
Diastolic blood pressure (mmHg)	1.02	0.96 – 1.08	0.55
Furosemide doses (mg/day)	1.05	1.01 – 1.09	0.02

LVH= left ventricular hypertrophy

DISCUSSION

The present prospective study is one of the few that reports the incidence of WRF in stable chronic heart failure patients with systolic or diastolic dysfunction. The incidence of WRF was 10.7 and 21.4% depending on the criteria used for defining it. This incidence is similar than those reported in patients with HF due to left ventricular systolic dysfunction (3) and lower compared with the obtained in patients hospitalized for decompensated or acute HF (10, 18).

We observed significant differences between the groups of patients with worsening renal function and the group without it, like age, arterial pressure and worse NYHA functional class that have been previously described as outcome-related factors for renal function impairment (2-3, 10,12,13). Also blood glucose level was and independent predictor of WRF. The relationship between hyperglycemia and renal complications has been previously described. Fasting plasma glucose levels are associated with the progression of renal damage (27).

The present study found that doses of furosemide ≥35 mg/day were associated with more frequent WRF. Especially, high doses have been related with a worse prognosis (2, 18-19). Diuretics are effective at producing short term symptomatic relief and facilitate a return to the euvolaemic state, but may be to expense of long-term deleterious cardiovascular effects and of increasing neurohormonal activation by plasma renin–angiotensin–aldosterone, norepinephrine, and the sympathetic nervous system, which in turn may decrease renal glomerular function. While poorer the renal glomerular function, the higher dose of diuretic required to relieve congestion, and this may lead to a vicious cycle, decreasing renal function and higher doses of diuretics needed (10).These deleterious effects can be explained because data are very limited concerning the duration, proper dose, and method of administration for diuretic therapy. Recently Lourenco et al (29) described that in outpatients with HF classified according to high (>80 mg/day) or low loop diuretic dose and, as hypervolemic (sodium retention score ≥3) or euvolaemic among euvolaemic patients, those on >80 mg/day furosemide performed worse outcomes than those on lower dose. Among hypervolemic patients, the diuretics dose had no prognostic implications. So examination of patients with HF with risk of renal dysfunction should begin with an evaluation of the patient's fluid status. Whether higher diuretic doses are responsible for WRF in HF stable patients or are a marker of higher risk requires further investigation.

In addition, we found a significant association between WRF and left ventricular hypertrophy, and a non-significant but strong association with diastolic heart failure. This can be explained on the basis that most of the patients with left ventricular hypertrophy probably have diastolic dysfunction.

Diastolic dysfunction, hard to define, and even harder to be

characterized, implies, in principle, a lower ventricular filling capacity and higher end-diastolic pressures. This phenomenon is also associated, even with normal circulatory volumes, with pulmonary congestion, clinically translated in dyspnea, fatigue, poor exercise tolerance and worse functional class, as was corroborated in this study. These clinical conditions usually are medically treated with high diuretics dose, especially with furosemide, considering that the described symptoms are always associated with volume overload in heart failure patients.

Based on the findings of the present study can be suggest that patients with left ventricular hypertrophy and diastolic dysfunction, that have normal circulatory volumes, the chronic high doses diuretic use could reduce the intravascular volumes and renal blood flow, with the consequent fall of the renal filtration rate. According to this hypothesis, the use of vasodilators in this group of patients can have beneficial reducing renal impairment; these drugs could decrease the symptoms lowering the end diastolic pressure and after load and as consequence the pulmonary congestion this kind of patients with no utilization or higher diuretics dose. (28).

LIMITATIONS OF THE STUDY

The number of patients was small; however, it is noteworthy that in spite of the small sample the results were statistically significant. Also, it is important to note that this was a nonrandom and nonrepresentative sample. Thus, these results may not be applicable to other populations. All these factors must be considered in future studies.

CONCLUSIONS

Renal function impairment in chronic heart failure patients is a common problem associated with factors as greater age, worse NYHA functional class, fatigue, higher glucose levels, left ventricular hypertrophy and left ventricular diastolic dysfunction. Chronic loop diuretic use, (≥ 35 mg/day), represents an independent risk factor for renal function impairment. There were no significant differences between ACEI and ARB-based treatments. More studies are needed to determine the long-term impact of this described risk factors, as well as the therapeutic options for the modification of this negative outcome.

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