Prevalence of Anemia and Renal Insufficiency in Non-Hospitalized Patients with Heart Failure

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Summary

Background: Heart Failure (HF) is a common disease with a high rate of mortality. Anemia and renal failure (RF) are often found in patients with HF associated with higher severity of the heart disease and a worse prognosis.

Objective: To evaluate the prevalence of anemia and RF, as well as the association between these two conditions, in non-hospitalized patients with HF.

Methods: Patients treated at the HF Outpatient Clinic of a university hospital were followed from July 2003 to November 2006. Anemia was defined as hemoglobin levels < 13 mg/dl for men and 12 mg/dl for women. Renal function was assessed by the glomerular filtration rate (GFR), calculated by the simplified formula of the MDRD (Modification of Diet in Renal Disease) study.

Results: Of the 345 patients included in this study, 26.4% (n = 91) had anemia and 29.6% had moderate to severe renal failure (GFR < 60 ml/min). The association between anemia and a higher prevalence of renal failure was statistically significant (41.8% *vs.* 25.2%; $p = 0.005$). The patients at functional class III and IV presented a higher incidence of anemia (39.0% *vs.* 19.4%; $p < 0.001$) and renal failure (38.2% *vs.* 24.8%; $p = 0.007$). No association was observed between anemia or renal failure and history of hypertension, diabetes, systolic function or etiology of HF.

Conclusion: The prevalence of anemia and renal failure was high in this population and was associated with the severity of the HF (functional classes III and IV). (Arq Bras Cardiol 2009; 93(3):249-254)

Key Words: Heart failure; anemia; renal insufficiency.

Introduction

Heart failure (HF) is a frequent clinical condition and is associated with high cost, disability and high mortality[1]. Anemia and renal insufficiency (RI) are frequent comorbidities found in patients with HF and are associated with higher severity of heart disease and worse prognoses[2,3]. About 40% of patients hospitalized with HF present anemia and up to 50% have moderate-to-severe RI[4]. These conditions are pathophysiologically interconnected, forming the Cardiorenal Syndrome (CRS), whereby each component (anemia, RI and HF) is capable of causing or overstimulating the other, resulting in a vicious cycle[4-6].

The aim of this study is to describe the prevalence and evaluate the association between anemia and RI in patients with HF, followed-up in a reference clinic in Salvador, Bahia, Brazil.

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Methodology

This was a cross-sectional study with patients followed-up at the heart failure clinic of the Professor Edgar Santos University Hospital (HUPES) - Federal University of Bahia (UFBA). This clinic provides reference service for HF patients in the State of Bahia, Brazil, an endemic zone for Chagas disease (CD). Patients admitted at the clinic between July 2003 and November 2006 were included in this study. Inclusion criteria were clinical and echocardiographic diagnosis of HF, with laboratory tests including serum creatinine and hemoglobin (Hb). Patients with kidney failure who had already undergone dialysis treatment at admission and those diagnosed with HF discharged in subsequent evaluations were excluded from the analysis. The investigation conforms to the principles outlined in the Declaration of Helsinki, and all subjects provided informed consent before participation. There are no conflicts of interest in this study, which was submitted to the HUPES Human Research Ethics Committee.

The following clinical and demographic characteristics were analyzed: gender, age, race, previous history of hypertension, diabetes mellitus (DM) and kidney failure, medications used, duration of illness in months, main etiology of the cardiomyopathy, and functional class (FC)

according to New York Heart Association (NYHA) criteria. HF was diagnosed by the attending physician, using clinical data and complementary exams brought in at the time of the initial visit. The main etiology of cardiomyopathy was attributed based on the patient's clinical history, physical and complementary examinations. At least two positive serological tests were necessary for the diagnosis of Chagas cardiomyopathy; history of angina; acute myocardial infarction, percutaneous transluminal coronary angioplasty, suggestive electrocardiographic abnormalities, obstructive lesion demonstrated on coronary angiography or ischemic changes on complementary examinations were needed for ischemic cardiomyopathy; previous history of uncontrolled hypertension, therapy with different antihypertensive drugs or presence of target-organ damage, such as left ventricular hypertrophy on electrocardiogram or echocardiogram, changed ophthalmoscopy or chronic kidney failure was necessary for hypertensive cardiomyopathy. When ischemic and hypertensive etiology were both present, the former was considered as the main one. Others etiologies (valvar, hypertrophic or restrictive cardiomyopathy, alcoholic, peripartum, viral, and endomyocardial fibrosis) were attributed according to individual patient data. Idiopathic cardiomyopathy was considered when all other etiologies were discarded.

Patients with HF symptoms and left ventricular ejection fraction (LVEF) equal to or greater than 45% on the echocardiogram (Teichholz method) were considered to have HF with normal systolic function (diastolic HF), in accordance with European Society of Cardiology criteria. The echocardiogram should be performed a maximum of 6 months from admission. Anemia was diagnosed when Hb serum level was lower than 13mg/dL for men and 12mg/dL for women on any patients' visits to the service. Blood analyses could be requested at any time from admission to the subsequent visits at the HF clinic. Renal function was evaluated through the estimated glomerular filtration rate (GRF) calculated by the Modification of Diet in Renal Disease (MDRD) simplified equation [GRF (ml/min/1.73m^2) = 186 x (Serum Creatinine)$^{-1,154}$ x year of age$^{-0,203}$ x (0,742 if woman) x (1.210 if Negro)], as suggested by the National Kidney Foundation. Kidney function was classified into five stages: normal kidney function (GRF ≥90ml/min); mild RI (GRF ≥60ml/min and <90ml/min); moderate RI (GRF ≥30ml/min to <60ml/min); severe RI (GRF ≥15ml/min to <30ml/min); and kidney failure (GRF <15ml/min)[7].

Statistical analyses were performed using SPSS for Windows, version 9.0 (SPSS Inc. Chicago, Illinois). Categorical data were presented as percentages. Continuous variables were expressed as mean and standard deviation when distribution was normal or median and 25-75 percentiles when distribution was abnormal. The following tests were used to compare variables: chi-square test when both variables were categorical, and Student's *t*-test and Mann-Whitney test when one of the variables was continuous with and without normal distribution, respectively. The P value used was 0.05.

Results

From 725 patients consecutively admitted in the clinic during the period, 345 were included in this study. Clinical and demographic characteristics of this population are summarized in Table 1.

Moderate-to-severe RI (GRF ≤ 60ml/min) was found in 29.6% (n=102) of all patients, while anemia was present in 26.4% (n=91). Chart 1 presents the stages of RI according to the GFR and Chart 2 shows the frequency of anemia in groups with different stages of RI.

Patients with anemia, in comparison to those without anemia, had higher prevalence of moderate-to-severe RI and

Table 1 - Clinical and demographical characteristics of patients included (n = 345).

Characteristics	Value
Male gender - % (N)	56.2 (194)
Negro race - % (N)	42.6 (147)
Age in years: Mean (Standard Deviation)	54.4 (13,3)
Duration of heart disease: Median (P25-P75)	41 (20-93)
Hypertension- % (N)	54.2 (156)
Diabetes Mellitus - % (N)	9.3 (32)
Medications used - % (N)	
Angiotensin-Converting Enzyme Inhibitors (ACEI)	74.3 (254)
Angiotensin II Receptor Blockers (ARB)	11.4 (39)
Spironolactone	46.4 (159)
Loop diuretics	66.7 (228)
Thiazide diuretics	24.6 (84)
Acetylsalicylic Acid	16.7 (57)
LVEF in %: Median (P25-P75)	36.0 (28.0-45.8)
Preserved Systolic Function (LVEF ≥ 45%) - %	28.7 (99)
NYHA Functional Class (FC) - % (N)	
FC I	21.2 (73)
FC II	43,2 (149)
FC III	27,0 (93)
FC IV	8,7 (30)
Heart Failure Etiology - % (N)	
Chagasic	43,9 (151)
Hypertensive	21,2 (73)
Idiopathic	11,6 (40)
Ischemic	9,9 (34)
Others	13,4 (46)

LVEF - Left Ventricular Ejection Fraction / NYHA - New York Heart Association

more frequently fell into the FC III or IV categories (Table 2). Comparing the patients with moderate-to-severe RI to those with GRF ≥ 60mg/dL, the former were older, tended to be female, had anemia, functional class III and IV and hypertensive etiology (Table 3). There was a lower prevalence of Negroes and idiopathic etiology in the first group (Table 3). Charts 3 and 4 show, respectively, prevalence of anemia and moderate-to-severe RI in patients with different functional classes (NYHA).

Discussion

The prevalence of anemia in this study was similar to that found in literature among non-hospitalized patients (26.4%) and was higher in patients with more severe disease (NYHA FC III or IV) and in those with moderate-to-severe RI. In previous studies, prevalence of anemia varied from 4% to 69.7%, depending on diagnostic criteria and population studied[8,9]. Characteristics of the studied population are important factors as many studies reveal, for example, a higher prevalence in older patients and in those with decompensated heart disease[2,8]. For Silverberg *et al*[10], patients in functional class IV (NYHA) were more affected by anemia, 79.1% *versus* 9.1% in patients with FC I. In non-hospitalized patients this prevalence varies from 4% to 23% and is usually associated with chronic renal disease, advanced age and more severe symptoms[9,11].

Many studies have associated anemia to adverse clinical events in patients with HF[2,8,12,13]. Sales *et al*[2] observed 16.8% mortality in patients with anemia *versus* 8% in patients without anemia. Anand *et al*[12] found 28% and 16% mortality in anemic and non-anemic patients, respectively, with hospitalization rates of 56% and 33%, during a mean follow-up period of 12 months. The authors observed that each 01g/dL of higher serum hemoglobin is associated with a reduction of 15.8% and 14.2% in risk of death and hospitalization, respectively. This influence does not depend on the type of HF according to the systolic function (preserved *vs.* deteriorated)[13,14]. However, the link between anemia, HF and events is not clear, because anemia may only be a marker of increasing severity of HF or merely yet another comorbidity, giving patients a poor prognosis[15].

Only 26% of patients evaluated had normal renal function, the majority (44%) presented mild RI with GFR between 60 and 90 ml/min and nearly 30% had moderate-to-severe RI. Chronic RI is a common comorbidity in HF patients,

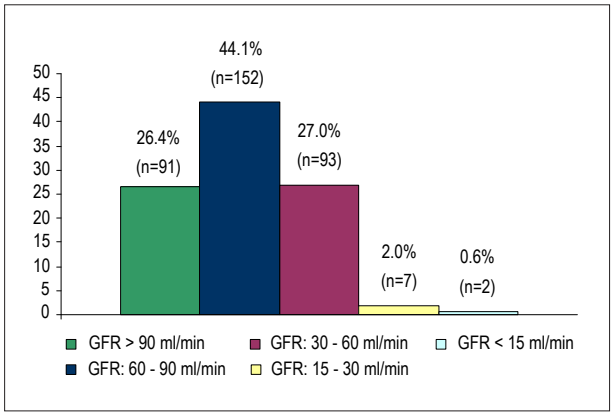

Chart 1 - *Classification of renal function according to estimated glomerular filtration rate (GRF) calculated by the simplified Modification of Diet in Renal Disease (MDRD) equation (n=345).*

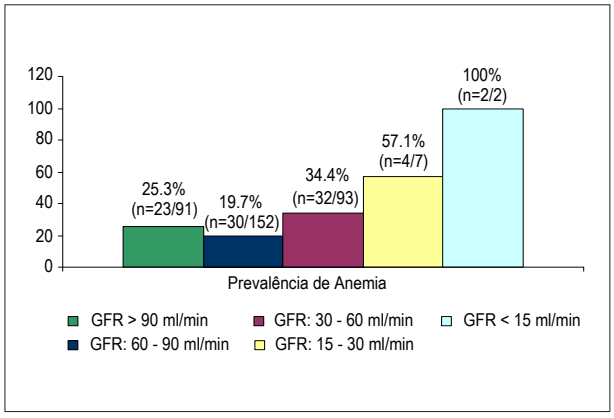

Chart 2 - *Prevalence of anemia in patients grouped according to estimated glomerular filtration rate (GRF) calculated by the simplified Modification of Diet in Renal Disease (MDRD) equation (n=345).*

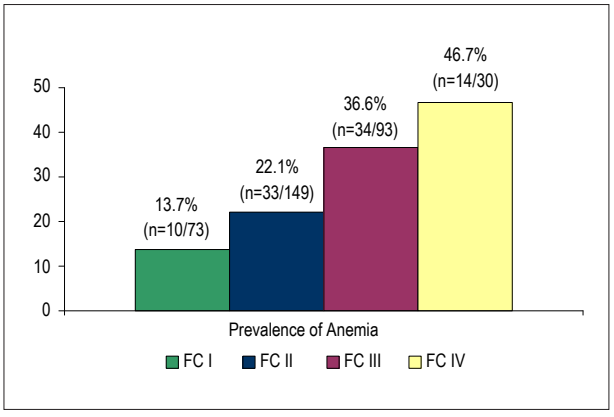

Chart 3 - *Prevalence of anemia in different groups of patients grouped according to New York Heart Association (NYHA) functional class (FC).*

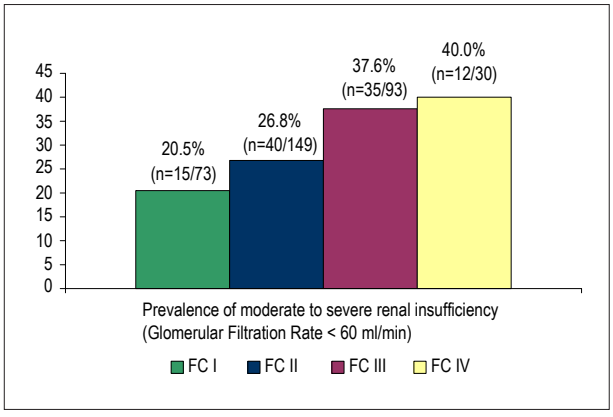

Chart 4 - *Prevalence of moderate-to-severe renal insufficiency (Glomerular Filtration Rate < 60 ml/min) in patients grouped according to New York Heart Association (NYHA) functional class (FC).*

Table 2 - Clinical characteristics of patients with and without anemia.

Characteristics	Without anemia N=254	With anemia N=91	P
Female gender - %	41.3	50.5	0.140
Age in years: Mean (Standard Deviation)	56.7 (13.5)	53.6 (13.1)	0.060
Negro race - %	41.7	45.1	0.622
Duration of heart disease: Median (P25-P75)	36 (21-84)	48 (15-96)	0.980
Hypertension- % (N)	54.8	52.7	0.243
Diabetes Mellitus - % (N)	9.4	8.8	0.853
LVEF in %: Median (P25-P75)	36.2 (27.5-45.0)	36.0 (28.5-47.0)	0.841
Preserved Systolic Function (LVEF ≥ 45%) - %	28.3	29.7	0.893
NYHA Functional Class (FC) III or IV - %	29.5	52.7	0.000
Moderate-to-severe renal insufficiency (Glomerular Filtration Rate < 60 ml/min) - %	25.2	41.8	0.005
Heart Failure Etiology - % (N)			
Chagasic	44.1	42.9	0.902
Hypertensive	22.0	18.7	0.552
Idiopathic	12.2	9.9	0.703
Ischemic	9.8	9.9	1.000

LVEF - Left Ventricular Ejection Fraction / NYHA - New York Heart Association

Table 3 - Clinical characteristics of patients with and without moderate-to-severe renal insufficiency (Glomerular Filtration Rate – GFR < 60 ml/min)

Characteristics	GFR ≥ 60 ml/min N=243	GFR < 60 ml/min N=102	P
Female gender - %	37.4	58.8	0.000
Age in years: Mean (Standard Deviation)	51.3 (12.5)	62.0 (12.1)	0.000
Negro race - %	49.8	25.5	0.000
Duration of heart disease: Median (P25-P75)	36 (18-84)	48 (24-96)	0.190
Hypertension- % (N)	53.3	56.4	0.248
Diabetes Mellitus - % (N)	9.1	9.8	0.840
LVEF in %: Median (P25-P75)	36.0 (28.0-45.0)	36.1 (27.5-45.9)	0.944
Preserved Systolic Function (LVEF ≥ 45%) - %	28.0	30.4	0.696
NYHA Functional Class (FC) III or IV - %	31.3	46.1	0.010
Anemia - %	21.8	37.3	0.005
Heart Failure Etiology - % (N)			
Chagasic	42.0	48.0	0.342
Hypertensive	18.1	28.4	0.043
Idiopathic	14.0	5.9	0.041
Ischemic	10.7	7.8	0.553

LVEF - Left Ventricular Ejection Fraction / NYHA - New York Heart Association

it is associated with the disease severity, poorer prognosis and higher prevalence of anemia. Almost 40% of patients with HF have RI and more than 64% of those who go to nephrologists with kidney failure have HF, most of them with anemia[10,16]. Heart disease is a major problem in chronic kidney failure patients, being the cause of death in 43.6% of cases[17]. For O'Meara *et al*[13], more than 50% of patients with HF and anemia have GFR below 60ml/min compared to only 30% of those without anemia. Research shows that RI is an independent risk factor of mortality and hospitalization in patients with HF[3].

Renal function must be accurately assessed using equations that estimate GFR from serum creatinine. International guidelines suggest the use of two formulas: Cockcroft-Gault or the simplified MDRD equation[7]. The use of serum creatinine as an isolated parameter to evaluate renal function is not recommended due to its low sensitivity in the early stages of RI. In this study, whenever serum creatinine values were considered alone, using the cut-off point of 1.3 mg/dL, only 18.3% of this population presented RI. Direct measurement of GFR through creatinine clearance would be the ideal method, although it is not superior to estimated GFR due to frequent errors in the 24-hour urine collection and daily variations in creatinine secretion, which is why this method is not routinely used.

The association of HF, anemia and CRS is responsible for faster progression of cardiac and renal diseases. Currently, mechanisms that lead to anemia in patients with HF are being studied to find treatments that can correct this complication and improve prognosis of these patients. Malnutrition, malabsorption and chronic gastrointestinal bleeding are common causes of anemia in HF patients, accounting for about 1/3 of the cases[18]. Excluding these situations, the mechanism involved in the development of anemia is generally related to deficient erythropoietin production[19]. Reduced hemoglobin concentration, in these cases, can also be caused by hemodilution resulting from the activation of the renin-angiotensin-aldosterone system (RAAS), which worsens prognosis[20,21].

Erythropoietin produced by renal cells is the main regulator of red blood cells formation and deficient production is the main cause of anemia associated with isolated RI or in patients with concomitant HF and RI[18]. Causes of this disturbance include inflammatory cytokines, which can alter expression of the erythropoietin gene. In addition to interfering in erythropoietin production, cytokines have an important impact on iron metabolism, reducing its availability for erythropoiesis. Therefore, anemia in patients with CRS can be explained mainly by hypervolemia and hemodilution and by changes in the pathways of erythropoiesis, either in production or effect of erythropoietin or changes in iron metabolism, both caused by the presence of pro-inflammatory cytokines.

Studies in literature have evaluated the impact of anemia correction on the prognosis of patients with HF. Some authors have suggested that treatment with erythropoietin analogues and intravenous iron can improve LVEF, FC and RI in patients with HF and anemia, as well as decrease hospitalization rates and improve quality of life[10,22-25]. Published studies, however, are limited by sample size, and there is no consensus regarding the need for aggressive treatment of anemia in HF patients, especially in those with mild anemia and without RI[15]. In patients with moderate-to-severe anemia and concomitant RI, treatment with erythropoietin and iron supplements is recommended to keep Hb greater than 12.0g/dL[9]. It is important that all patients be evaluated for potentially reversible causes of anemia, such as iron deficiency and occult blood loss, and receive adequate treatment. Silverberg *et al*. showed that anemia is still poorly investigated, recognized, and treated by cardiologists in the follow-up of non-hospitalized HF patients. These authors advocate cooperation between cardiologists and nephrologists to improve this data[26].

The results of the present study must be considered within the context of certain limitations. At the time of data collection during visits of patients, other associated conditions that could possibly alter the levels of Hb and creatinine, such as sickle cell anemia, malnutrition, intestinal parasitic infections or obstructive uropathy, were not considered. We did find, however, a frequency of anemia and RI similar to previous data found in other populations. Our population is different from that of previous studies due to the high prevalence of Chagas disease as the main etiology of HF. Hypertension and ischemic disease, which are generally reported in literature as major etiologies of HF in other populations, are associated to higher risk of developing RI regardless of the presence of HF, which is not observed in Chagas Disease. Therefore, although we might expect a lower frequency of this complication in Chagas patients, this was not observed. We did not find a different prevalence of anemia or RI in patients with HF caused by Chagas Disease compared to other etiologies. Nevertheless, this study is of vital importance as it highlights the relevance of investigating the presence of these conditions in non-hospitalized HF patients, since the majority of published studies were carried out with hospitalized patients.

Conclusion

The results of this study demonstrated the high prevalence of anemia and RI in our population, similar to those found in international literature. Patients with these conditions were more decompensated (NYHA FC III and IV). Further prospective studies specifically evaluating anemia and renal function in patients with HF are needed to provide greater knowledge on these factors and their importance in HF severity and prognosis.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any graduation program.

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