Anemia and Heart Failure in a Community-based Cohort: Comparison with a Specialized Outpatient Clinic

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Abstract

Background: Anemia is common in patients with heart failure (HF). Its prevalence in patients with HF from a community-based cohort is unknown in our country.

Objectives: To evaluate the prevalence and characteristics of patients with anemia in a non-selected population with HF from a community-based cohort, comparing it with that of a HF population treated at a specialized outpatient clinic.

Methods: This was a transversal, prospective, observational study, carried out from January 2006 to March 2007. The patients with HF met the Boston criteria, with a score ≥ 8. Anemia was defined through the criteria of the World Health Organization as hemoglobin levels < 13 g/dL for men and <12 g/dL for women. Patients treated at a primary care program in the community were randomly selected, as well as patients treated at a Heart Failure Outpatient Clinic in a university hospital.

Results: A total of 206 patients were assessed, with a mean age of 61.3±13.1 years, of which 53.4% were females. The prevalence of anemia in the community-based cohort (n=114) was 21% and at the outpatient clinic (n=92), of 25% (p=0.50). The patients from the community-based cohort presented a lower rate of kidney dysfunction (GFR<60 mL/min/1,73^{-5}), predominance of HF with normal ejection fraction and female sex. Kidney function parameters (urea or creatinine) independently correlated with anemia in both populations.

Conclusion: The prevalence of anemia was similar in the studied populations. Kidney function was the only factor that independently correlated with anemia in both populations. (Arq Bras Cardiol 2010; 94(1) : 95-101)

Key Words: Anemia; prevalence; heart failure; comparative study; outpatient clinics, hospital.

Introduction

Herat failure (HF) is considered a public health problem in the United States[1] The disease is the main reason for seeking medical help and there is a growing number of hospital admissions due to it[2,3].

In Brazil, HF is the third major reason for hospital admissions among all causes and the first among cardiovascular diseases (CVD) at the Brazilian Public Health System (SUS) in patients older than 65 years, which increases the costs of the disease[4,5]. The impact on the Brazilian public health system can also evaluated through a study which assessed hospital admissions due to HF in public and private hospitals of a Brazilian city in 2001, showing that the patients treated in public hospitals are, on average, 10 years younger and present longer hospital stays than those from private hospitals[6].

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Population studies show that the HF has a high prevalence in the community, with a predominance of HF with normal ejection fraction (HFNEF)[7,8]. Although HFNEF used to be seen as a minor disease in the past, current data show its clinical importance due to the increase in the annual mortality from 5% to 8% (compared to 10% to 15% of HF with decreased ejection fraction – HFDEF)[9].

Anemia is a common finding in patients with HF and it has been proposed as a new therapeutic target in this population. Silverberg et al[10-12] were the first to detail the role of anemia in HF and introduced the concept that the correction of anemia can contribute to a clinical improvement of patients with HF[10-12].

A common condition in patients with HF, particularly among the elderly, anemia has a higher prevalence when the disease is more severe[10-12]. The prevalence of anemia in patients with HF varies from 4% to 62% in literature[13-20]. Such varied results are due to the different criteria used to diagnose anemia and the different populations studied.

Several studies have established that the presence of anemia in patients with HF is associated to a worse prognosis and a higher cardiovascular morbidity and mortality[13-27].

There have been few studies in our country on the prevalence of anemia in communities. The advantage of these studies is to obtain data from non-selected populations, differently from studies carried out in tertiary environments, where more severe patients are treated. A recent national study confirmed that, in the studied community, there was a predominance of HFNEF in relation to HFDEF[28], which differs from what has been observed in Reference Services for HF.

The objective of this study was to determine the prevalence and the clinical characteristics of patients with anemia in a population with chronic HF from a community-based cohort, comparing these data with those obtained from patients treated at an outpatient clinical specialized in HF.

Methods

This was an observational, transversal, prospective study, which included patients with a diagnosis of HF that were treated at a Family Medicine Program (FMP) and patients from an outpatient clinic specialized in HF from a university hospital (UH). The Basic Health Units (BHU) of the FMP from different districts were visited in order to catalogue the cases suspected of having HF, among individuals aged 18 and older, identified by family physicians. The information was collected through questionnaires that contained clinical history data, life style habits, physical examination, anthropometric data, functional class (FC) assessment according to the New York Heart Association (NYHA) and analysis of complementary examinations (electrocardiogram, chest x-ray and Doppler echocardiogram) and current medications. The patients were referred to the HF outpatient clinic of UH for data completion of the questionnaire, when they could not be obtained during the visit to the BHU.

The Doppler echocardiogram was carried out in all patients. Those that had not undergone the test were submitted to it at the Echocardiography Service of the UH. The left ventricular ejection fraction (LVEF) was measured by the Simpson method and patients were classified as having HFDEF when LVEF was < 50% and HFNEF when it was ≥50%.

The patients from the UH had received a prior diagnosis of HF and used adequate medication. They were submitted to new laboratory and imaging assessment when they agreed to participate in the study. All patients with a diagnosis of HF met the Boston criteria for HF with a score ≥8. The study inclusion period was January 2006 to March 2007. Patients with advanced-stage kidney disease (undergoing dialytic therapy) were excluded.

Anemia was defined according to the criteria defined by the World Health Organization (WHO), which characterize as anemic male individuals with serum hemoglobin <13 g/dL and female individuals with values <12 g/dL. Kidney function was evaluated through serum urea and creatinine levels and the estimated glomerular filtration rate (GFR), calculated through the sMDRD (Simplified Modification of Diet in Renal Disease) formula.

This formula has been validated in many studies, in different populations and it has been used to estimate GFR in patients with HF. Obesity was defined as the presence of body mass index (BMI) > 30 and malnutrition as BMI < 17.

Statistical analysis

The continuous variables were expressed as means and their respective standard deviations and compared using Student's *t* test. The categorical variables were expressed as absolute values and percentages and were compared by Chi-square test or Fisher's Exact Test for samples with expected values < 5. The variables with p value < 0.10 at the univariate analysis were included in the multivariate analysis (logistic regression), with the objective of verifying which ones presented an independent association with the presence of anemia. The analysis was carried out with the statistical programs EPIINFO 3.4 and SPSS, version 11.0. P values <0.05 were considered statistically significant. The criterion for significance determination was established at 5%.

Bioethics

The study was approved by the Ethics Committee in Research of our hospital and it is in accordance with the Declaration of Helsinki; all participants gave their free and informed consent.

Results

The study included 206 patients with a diagnosis of HF, from 2 distinct populations (specialized outpatient clinic and a community-based cohort). Mean age was 61.3±13 years and 53.4% (110) of the studied individuals were females. The presence of anemia was observed in 47 (22.8%) of the 206 patients. When comparing the prevalence of anemia in the two populations, we observed that, although the prevalence was slightly higher in the UH group (23 [25%] *vs.* 24 [21%]), there was no statistically significant difference between them (Figure 1).

Table 1 shows the clinical and demographic characteristics of the two populations. In the UH, there was a predominance of the male sex, a higher prevalence of coronary artery disease (CAD), worse kidney function, worse ejection fraction (EF) and lower values of heart rate (HR), systolic arterial pressure (SAP) and diastolic arterial pressure (DAP). In the FMP group, there was a predominance of the female sex, higher prevalence of systemic arterial hypertension (SAH), dyslipidemia and cerebrovascular accident (CVA). In the UH group, there was a

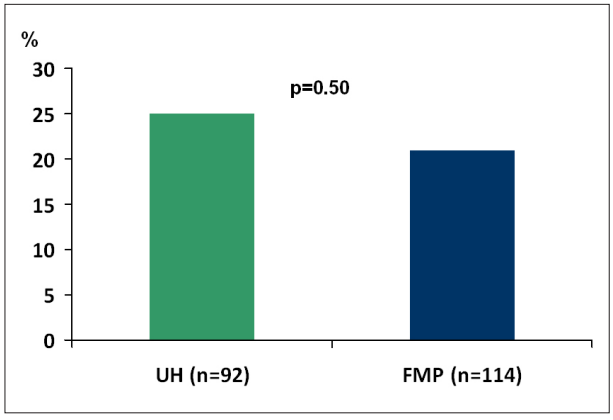

Figure 1 - Prevalence of anemia in the two populations; UH - University Hospital; FMP - Family Medicine Program.

predominance of LV systolic dysfunction (54.3%), whereas the opposite was observed in the FMP group, with a prevalence of 82.4% of HFNEF. The UH group presented a higher incidence of use of beta-blockers, digoxin and loop diuretics.

Tables 2 and 3 show the basal characteristics of anemic and non-anemic patients in the two populations, respectively. It can be observed that in the FMP group, anemia was associated with a lower SAP, presence of peripheral edema, lower levels of total cholesterol, lower EF, higher levels of plasma urea and higher incidence of use of digoxin and loop diuretics. In the UH group, there was an association with levels of serum creatinine and glomerular filtration rate.

At the logistic regression analysis, used to establish the variables independently associated with the occurrence of anemia, urea was the only significant variable when the population was analyzed as a whole and when the analysis included only the FMP group. In the UH population, creatinine was the only variable independently associated with anemia (Table 4).

There was a large number of patients with preserved systolic function, with a predominance of the FMP group (Table 1). In the population as a whole, 90 patients had HFDEF and 119 had HFNEF. GFR was lower in the group with HFDEF (57.6±66.2 *vs.* 94.8±36.6 ml/min/1.73m^2; p=0.01). There was no difference regarding the prevalence of anemia in the two groups (23.3% *vs.* 18.5%; p=0.34). The prevalence of moderate to severe kidney dysfunction was higher in the group with HFDEF (32.2% vs. 16.8% p=0.01).

Discussion

In the present analysis, anemia was present in 22.8%

Table 1 – Basal characteristics of the patients from the University Hospital and the Family Medicine Program (community)

Variable	University Hospital (n= 92)	Family Medicine (n= 114)	P value
Male sex	51 (55.4%)	45 (39.5%)	0.022
Age (yrs)	59±13.2	62.5±12.9	0.14
Body Mass Index (Kg/m^2)	27.1±5.7	28.7±5.9	0.072
Previous myocardial infarction	19 (21.1%)	15 (13.2%)	0.13
Coronary artery disease	37 (41.6%)	16 (14.0%)	< 0.0001
Systemic arterial hypertension	69 (77.5%)	103 (90.4%)	0.012
Diabetes mellitus	26 (29.2%)	29 (25.4%)	0.54
Dyslipidemia	21 (23.6%)	46 (40.4%)	0.012
Cerebral Vascular Accident	1 (1.1%)	15 (13.2%)	0.002
Anemia	23 (25.0%)	24(21.1%)	0.5
Heart rate (bpm)	74±13.1	81.9±17.8	0.0006
Systolic arterial pressure (mmHg)	133.3±26.3	151.9±28.7	< 0.0001
Diastolic arterial pressure (mmHg)	79.8±13.1	89.8±14.3	< 0.0001
Edema	23 (25.0%)	47 (41.2%)	0.014
Total cholesterol (mmol/L)	194.7±54.7	206.2±44.2	0.11
HDL cholesterol (mmol/L)	40.3±11.3	45.9±14.5	0.003
Creatinine (mg/dL)	1.2±0.62	0.99±0.35	0.011
GFR (mL/min/1,73m^2)	65.6±66.1	94.1±35.8	0.006
Hemoglobin (mg/dL)	13.6±2.6	13.5±1.4	0.96
Serum sodium (mEq/L)	139.0±3.7	140.5±3.3	0.004
Ureia (mg/dL)	45.3±25.1	36.2±13.1	0.005
LVEF (%)	46.4±17.6	60.8±15.0	<0.0001
ACEI	69 (78.4%)	82 (71.9%)	0.29
Beta-blockers	59 (67.1%)	31 (27.2%)	< 0.0001
Digoxin	44 (50.0%)	23 (20.2%)	< 0.0001
Acetylsalicylic acid	34 (38.6%)	43 (37.7%)	0.89
Thiazide diuretics	27 (30.7%)	43 (37.7%)	0.29
Loop diuretics	52 (59.1%)	40 (35.1%)	0.001
ARB	7 (8.1%)	13 (11.4%)	0.43

ARB - angiotensin receptor blockers; ACEI - angiotensin-converting enzyme inhibitors; GFR - glomerular filtration rate; LVEF - Left ventricular ejection fraction.

Table 2 – Correlation between basal characteristics and the presence of anemia in the family doctor (community) group. P values in bold refer to the variables with p<0.10, which were included later at the multivariate analysis

Variable	Anemia present n=24	Anemia absent n=90	P value
Male sex	12 (50.0%)	33 (36.7%)	0.23
Age (years)	64.5 ± 14.3	61.9 ± 12.6	0.38
Body Mass Index (Kg/m^2)	27.3 ± 6.8	29.0 ± 5.6	0.2
Systolic arterial pressure (mmHg)	141.6 ± 26.9	154.7 ± 28.6	0.047
Edema	16 (66.7%)	31 (34.4%)	0.004
Total cholesterol (mmol/L)	191.3 ± 45.9	210.2 ± 43.1	0.062
Creatinina (mg/dL)	1.10 ± 0.41	0.97 ± 0.33	0.15
GFR (mL/min/1,73m^2)	85.2 ± 28.9	96.4 ± 37.1	0.21
Urea (mg/dL)	42.9 ± 19.1	34.6 ± 10.9	0.097
LVEF (%)	55.9 ± 15.4	62.1 ± 14.7	0.072
ACEI	19 (79.2%)	63 (70.0%)	0.37
Beta-blockers	9 (37.5%)	22 (24.4%)	0.2
Digoxin	8 (33.3%)	15 (16.7%)	0.068
Acetylsalicylic acid	9 (37.5%)	15 (16.7%)	0.98
Loop diuretics	13 (54.2%)	27 (30.0%)	0.028

ACEI - angiotensin-converting enzyme inhibitors; GFR - glomerular filtration rate; LVEF - Left ventricular ejection fraction.

Table 3 – Correlation between basal characteristics and the presence of anemia in the university hospital group. P values in bold refer to the variables with p<0.10, which were included later at the multivariate analysis

Variable	Anemia present n=23	Anemia absent	Valor de p P value
Male sex	14 (60.9%)	37 (53.6%)	0.54
Age (years)	62.0 ± 13.9	59.0 ± 13.0	0.34
Body Mass Index (Kg/m^2)	25.9 ± 5.6	27.7 ± 5.7	0.2
Systolic arterial pressure (mmHg)	135.1 ± 26.9	132.7 ± 26.2	0.7
Edema	7 (30.4%)	16 (23.2%)	0.48
Total cholesterol (mmol/L)	189.4 ± 49.0	196.3 ± 56.5	0.62
Creatinine (mg/dL)	1.39 ± 0.62	1.12 ± 0.61	**0.02**
GFR (mL/min/1,73m^2)	60 ± 26.2	95.1 ± 73.7	**0.0006**
Uréia (mg/dL)	52.1 ± 36.9	42.9 ± 19.0	0.3
LVEF (%)	50.3 ± 18.2	45.1 ± 17.3	0.22
ACEI	19 (86.4%)	50 (75.8%)	0.23
Beta-blockers	13 (59.1%)	46 (69.7%)	0.35
Digoxin	10 (45.5%)	34 (51.5%)	0.62
Acetyl salicylic acid	6 (27.3%)	28 (42.4%)	0.2
Loop diuretics	15 (68.2%)	37(56.1%)	0.31

ACEI - angiotensin-converting enzyme inhibitors; GFR - glomerular filtration rate; LVEF - Left ventricular ejection fraction.

of the patients of the population as a whole, in 25% of the UH group and 21.1% of the FMP group, with no statistically significant difference between the two groups. Prevalence data vary greatly according to the definition used for anemia and according to the studied population. In studies that analyze patients with mild to moderate systolic dysfunction and in asymptomatic patients, the prevalence values are similar to the ones found in the present study[13,20].

To understand the problem of anemia in HF, it is important to know the factors that influence the prevalence of anemia and know the consistency of the association between anemia and mortality in several populations of patients with HF. A recently published systematic review aimed at evaluating the

Table 4 – Variables independently associated with anemia in the two groups and in the population as a whole, obtained through the logistic regression analysis

Population	Significant variable	Coefficient	Standard error	P value	RR	95% CI	
Total sample	Urea	0.023	0.009	0.014	1.023	1.005	1.041
Family doctor	Urea	0.038	0.018	0.037	1.038	1.002	1.076
UH	Creatinine	0.65	0.392	0.048	1.915	1.082	4.134

UH - university hospital; CI - confidence interval; RR - relative risk for the increase of one unit.

prevalence of anemia, separating the publications according to the definition of anemia used in the study, the clinical characteristics of the patients involved, the prevalence of anemia in the studied sample and the association between anemia and mortality. When the prevalence of anemia was analyzed in outpatient clinic patients, 10 studies were selected and the prevalence rates varied between 15% and 61%[29].

Such distinct prevalence rates were analyzed and based on the comparison of the clinical characteristics of these outpatient clinic patients (from different centers), it was observed that the prevalence of anemia was higher in populations with higher mean age, more severe HF (estimated by the NYHA classification) and a higher prevalence of comorbidities such as diabetes mellitus (DM) and chronic kidney disease (CKD)[29]. Studies that evaluated the prevalence of anemia in outpatient clinic centers for the treatment of HF found prevalence rates that were similar to those found in the present study, varying between 15% and 30%[29].

Anemia seems to be an important comorbidity, not only in patients with HFDEF, but also in those with HFNEF. In a study that assessed the prevalence and the importance of anemia in 137 patients with HFNEF, a high prevalence (40%) was observed, as well as its association with a worse prognosis[30]. Similarly to the present study, that study did not show a statistically significant difference regarding the prevalence of anemia in patients with or without decreased EF, demonstrating that anemia in HF can be quite prevalent, regardless of the ejection fraction.

Our study confirms that kidney dysfunction is a factor that is independently associated with anemia. The presence of moderate to severe kidney dysfunction (GFR<60 mL/min) is associated with a decrease in the production of erythropoietin (EPO) and a progressive decrease in hemoglobin values[10,13].

The decreased kidney function can be associated with adverse events in HF and it can be a marker of severity or a reflex of the coexisting kidney disease[31]. A study that evaluated kidney function in symptomatic and asymptomatic patients with LV systolic dysfunction showed that moderate degrees of kidney dysfunction confer a poor prognosis[31].

A recent study analyzed the impact of anemia on the decline of kidney function in patients with HF. A rapid decrease in kidney function was defined as the decrease in GFR≥6 ml/min/1.73m^2/year. A total of 6.360 patients were assessed, with a mean age of 59 years and 31% presented chronic kidney failure and 6% presented anemia. The time of follow-up was 2 years and anemia was associated with a rapid decrease in kidney function in patients with HF, particularly patients that already presented kidney function alteration[32].

Anemia is often associated with decreased BMI values, a finding that suggests that patients with cachexia present a higher risk of anemia[16]. Serum levels of cytokines and inflammatory markers are elevated in patients with cachexia and can contribute to the development of anemia through a series of mechanisms[16].

In the present study, although we found BMI values that were slightly lower in patients with anemia, there was no statistically significant association between this variable and anemia. It is worth mentioning that none of the patients in the present study met the criteria for cachexia or malnutrition.

Anemia can also be related to the use of some medications such as ACEI and acetylsalicylic acid[22]. In the present study, we did not find an association between anemia and these medications. In the FMP group, however, the use of loop diuretics was more frequent in the anemic than in the non-anemic individuals. This finding probably does not mean a causal association, but a reflex of the worsening in kidney function, when thiazide diuretics are substituted by loop diuretics. Nevertheless, a possible role of diuretics in the worsening of kidney function in patients with HF has been suggested[33]. It is not clear, therefore, whether the diuretics are the cause of the worsening in kidney function or if they work as risk markers, as their use is associated with more severe cases[33].

The limitations of the present study include the fact that we did not study all possible mechanisms of anemia. Although the kidney dysfunction showed to be associated with the presence of anemia, we cannot establish a cause-and-effect relation and we cannot state whether or not additional mechanisms contributed to the occurrence of anemia.

Conclusions

The prevalence of anemia in patients with HF treated by family doctors in the community was similar to that found in a specialized outpatient clinic of a university hospital, showing that it is prevalent even in non-selected populations. Kidney function, assessed through urea or creatinine levels, was the only factor that was independently associated with the presence of anemia in the two populations.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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