Anemia in Patients with Advanced Heart Failure

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Abstract

Background: Anemia is linked with worsening of progress in patients with heart failure (HF). However, there are few studies of anemia in patients with advanced HF.

Objective: To evaluate the characteristics of anemia in HF at an advanced stage.

Methods: The study included 99 patients, aged ≥ 18 and LVEF ≤ 45%, who were hospitalized for HF compensation (FC IV/NYHA). Patients with hemoglobin (Hb) levels < 12 g/dl were considered anemic. Data on anemic and nonanemic patients were compared. The Student's t-test, Chi-square test and Fisher test were used. The relative risk (HF 95%) was calculated by the Cox regression.

Results: On average, the patients were monitored for 10.8 months (8.9), and 34.3% of patients with HF had anemia. On average, in comparison with nonanemic patients, anemic patients were older (64.1 ± 15.6 *versus* 54.8 ± 12.9 years old, p = 0.004), their creatinine level was higher (1.9 ± 1 *versus* 1.5 + 0.5 mg/dl, p = 0.018) and their BNP level was also higher (2,077.4 ± 1,979.4 *versus* 1,212.56 ± 1,080.6 pg/ml, p = 0.026). 38.24% of the anemic patients had iron deficiency anemia. After there was an improvement in the congestion, only 25% of patients with anemia were discharged with Hb ≥ 12 g/dl. Anemia was an independent marker of poor prognosis in the multivariate analysis (mortality of 47% *vs* 24.6%, p = 0.016, relative risk of 2.54).

Conclusion: Anemia affects approximately one third of patients with advanced HF, and iron deficiency is an important etiology. Anemic patients are older their renal function was more deteriorated. The improvement in the congestion was not enough to improve the anemia in most cases. In patients with advanced HF, anemia is an independent marker of poor prognosis. (Arq Bras Cardiol 2010; 95(4): 524-529)

Key words: Anemia/complications; heart failure/etiology; comorbidity; anemia, iron-deficiency.

Introduction

Heart failure (HF) is a frequent cause of hospitalization and, even though there are new therapies, the mortality rate of HF patients is still high, especially among the ones that have advanced HF. Studies show that anemia is a prevalent morbidity among patients with heart failure. The presence of anemia worsens progress and increases mortality[1-3]. It has been known for some time that anemia worsens HF, but in the past years, the magnitude of anemia linked with the worsening of HF has been more evident.

In the past, only hemoglobin levels below 9.0 mg/dl were taken into account, but today we know that any degree of anemia can worsen the progress of patients suffering from heart failure. The combined analysis of several studies reveals that a decrease of 1g/dl in the level of hemoglobin (Hb) increases mortality by 15.8%. Identifying patients with anemia among HF patients, as well as finding the etiology of the anemic process and adopting the appropriate specific therapy, may alter the progress of patients with HF. However, in a meta-analysis, Hessel et al[4] did not identify the actual effect of anemia correction on the reduction of mortality and suggested that further studies are needed[4-6].

Anemia may be the cause of HF, but it often occurs as a consequence. The pathophysiology of anemia in patients with HF is complex and it has been the subject of several studies. Among the mechanisms involved in its genesis, the following can be mentioned: deficiencies in the production of erythropoietin or erythropoietin resistance, hemodilution, neurohumoral activation, proinflammatory state (production of cytokines - IL 1.6 and 18) and iron deficiency. Some drugs used to treat HF can also cause anemia, such as the inhibitors of angiotensin-converting enzyme, carvedilol and angiotensin-I receptor blocker, because they cause the inhibition of the erythropoietin production[6-7]. Studies have shown that renal dysfunction, decrease in body mass index, old age, female sex and left ventricular dysfunction are factors that are linked with higher incidence of anemia[7].

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The prevalence of anemia depends on the population studied and the HF stage, according to studies that show the incidence between 9.0 % and 79.1%[6-13], and it is most frequent among the subgroups of black and elderly patients. The World Health Organization defines anemia in men for hemoglobin levels < 13.0 g/dl and in women for hemoglobin values < 12 g/dl. However, until now, there are no data that allow indicating the hemoglobin value for patients with HF. In a study involving 1,061 patients, Horowich et al[11] stated that the lower the Hb level, the higher the mortality. In such study, it was said that, for hemoglobin ranges < 12.5 g/dl, between 12.3 and 13.6 g/dl, between 13.7 and 14.8 g/dl and > 14.8 g/dl, the mortality rate is, respectively, 44.4%, 36.1% 28.6% and 25.6%[11].

The anemia in HF has been studied by several researchers who have assessed the prevalence and impact on prognosis. However, few studies have evaluated the etiology. The iron deficiency anemia occurs when there is a decrease in hemoglobin synthesis as a result of iron deficiency. This type of anemia affects two thirds of world population and it is the main cause of anemia in Brazil[14,15]. Therefore, either due to insufficient availability of iron, or little use of one's own reserves or insufficient intake of iron, iron deficiency anemia is a medical condition that arouses interest in this type of patient. The diagnosis of iron deficiency is made when the serum concentration is lower than 100 ng/ml and the transferrin saturation is less than 20%[15].

In this study, we tried to evaluate the presence of anemia in patients with advanced HF that were hospitalized for compensation. We compared the clinical characteristics of patients with anemia and patients without anemia, and we tried to determine the incidence of iron deficiency anemia among anemic patients.

Material and methods

We selected, in a prospective and consecutive way, patients with advanced HF, functional class IV and who had been hospitalized for compensation of heart failure.

HF patients whose heart failure was not compensated or whose condition did not improve after being treated at the Emergency Room of *Instituto do Coração* (Heart Institute) were hospitalized. Thus, the patients selected were those with the most serious symptoms. All patients were clinically evaluated and underwent laboratory tests that included blood count, hematocrit, levels of urea, creatinine, sodium, potassium and BNP. To characterize the presence of congestion, at least two of the following characteristics had to be present: jugular stasis, pulmonary rales, edema in the sacral region, lower limb edema or hepatomegaly.

The study included patients over 18 years of age and with left ventricular ejection fraction (LVEF) ≤ 45%. Patients were considered anemic when their hemoglobin level was < 12 g/dl, for both sexes. For patients that had anemia, laboratory tests were requested to evaluate the etiology of the anemia (levels of serum iron, ferritin, iron saturation, and iron binding capacity). Patients with the following characteristics were considered to have iron deficiency anemia: when the serum ferritin concentration was lower than 100 ng/ml and the transferrin saturation was below 20%

We excluded patients with evident cause of bleeding, patients with other neoplastic diseases, chronic infectious and inflammatory diseases, patients that had undergone surgery and had used iron or had received blood transfusion in the past three months.

A comparison was made between clinical and laboratory data and data on the progress of patients with and without anemia.

To identify the etiology of the heart failure, we used the following criteria:

1. *Ischemia* - inactive area on electrocardiogram, history of coronary artery bypass grafting or coronary obstruction demonstrated by cineangiography.
2. *Chagas disease* - seropositive by the ELISA method or indirect immunofluorescence method.
3. *High blood pressure* - history of systemic hypertension that rules out other causes of cardiomyopathy.
4. *Valvular heart disease* - primary valve alteration before cardiomyopathy, which rules out other causes.
5. *Alcohol ingestion* - patients who said that they had drunk large quantities of alcohol for more than ten years and who ruled out other causes.

For the statistical analysis, the Student's t-test, Fisher's exact test, chi-square test and the SPSS program were used. $P < 0.05$ was considered significant. The Kaplan-Meier model was used to make the survival curves, which were compared by the Log-Rank method. The relative risk (HF 95%) was calculated by the Cox regression.

Results

The study included 99 patients with advanced HF in the period from June to October 2007. The mean age (SD) of the population studied was 58 years-old (14.5), 61 patients (61.6%) were male, and the mean LVEF was 25.6% (8.8). Patients who were discharged were monitored for 10.8 months, on average[8,9]. Table 1 shows the main clinical and laboratory characteristics of the population studied.

Thirty-four (34) patients (34.3%) had anemia. The anemic patients, compared to non-anemic patients, were older (64.1 ± 15.6 years of age *versus* 54.8 ± 12.9 years of age, p = 0.004), their renal function was more compromised (serum creatinine 1.9 ± 1mg/dl *versus* 1.5 + 0.5 mg/dl p = 0.018), and their BNP levels were higher (2,077.4 ± 1,979.4 pg/ml *versus* 1,212.56 ± 1,080.6 pg/ml p = 0.026). In Table 2, we show the clinical and laboratory characteristics of patients, depending on the presence or absence of anemia.

When the etiology of anemia was studied, 38.24% of patients had iron deficiency and were diagnosed as having anemia. Congestion was found to be present in 88% of all hospitalized patients, but 97% of anemic patients had fluid overload (Table 2). Among the anemic patients with fluid overload at the beginning of hospitalization and who were discharged after there was an improvement in the congestion condition, there was an improvement in the anemia in only 25% of them (hemoglobin level[3] 12 g/dl). For such patients,

Table 1 - Main characteristics of patients with advanced HF

Variable	Percentage and mean (standard deviation)
n	99
Age (years)	58 (14.5)
Males	61 (61.6%)
Etiology:	
Chagas disease	33%
Ischemia	29%
High blood pressure	17%
Valvular heart disease	8%
Alcohol consumption	7%
Idiopathic	13%
Signs of congestion	87 (90%)
Inotropic support	73 (73.7%)
LVEF	0.25 ± 0.9
Hb at admission (g/dl)	13 (2.1)
Anemia (Hb < 12g/dl)	34 (34.3%)
HB at discharge (g/dl)	12.2 (3.6)
Creatinine (mg/dl)	1.6 (0.7)
Sodium (mEq/l)	137.7 (4)
BNP (pg/ml)	1,537 (1,531)
Days in hospital	36.6 (28.8)
Deaths during hospitalization	13%
Deaths during monitoring	32%

Table 2 - Characteristics of patients with and without anemia

Variable	With anemia	Without anemia	p
n	34 (34.3%)	65 (65.7%)	
Age	65 ±15.6	56 ± 12.9	0.004
Males	18 (53%)	43 (66%)	0.28
Signs of congestion	33 (97%)	55 (83.3%)	0.08
Inotropic support	25 (73.53%)	48 (73.85%)	0.83
Ejection fraction	0.26 ± 0.08	0.24 ± 0.09	0.19
Initial Hb	10.8 + 1	14.2 ± 1.5	<0.001
Final Hb	10.5 + 1.4	13.1 ± 4.1	<0.001
Initial hematocrit	34.2 + 3.1	42.9 ± 4.4	<0.001
High HT (%)	33.4 + 4.7	42.9 ± 4.4	<0.001
Creatinine (mg/dl)	1.9 ± 1	1.5 ± 0,5	0.018
Sodium (Meq/l)	137.6 ± 3.8	137.8 ± 4.2	0.78
BNP (pg/ml)	2,077 ± 1,979	1,213 ± 1,081	0.02
Days in hospital	36.4 ± 22.8	36.7 ± 31.6	0.96
Deaths in hospital	17.6%	10.8%	0.51
Total of deaths	47%	24,6%	0,016

there was no significant difference between the level of hemoglobin (initial Hb = 10.9 g/dl ± 1 *versus* final Hb = 10.8 g/dl ± 1.2 p = 0.82) and initial and final hematocrit levels (34.6 g/dl ± 3 *versus* 34.5 g/dl ± 4, respectively, p = 0.91)

A multivariate analysis was carried out with the following variables: BNP, age, etiology, renal function, LVEF and presence or absence of anemia. This analysis revealed that anemia was the only independent marker of poor prognosis in the group studied. The mortality rate (Chart 1), throughout the entire monitoring of anemic patients, was of 47% *versus* 24.6% of non-anemic patients, relative risk of 2.54, p = 0.016 and HF of 95% (1.19 - 5.44).

Discussion

Our findings show that the prevalence of anemia among patients with advanced HF is high. The characteristics of the group studied were compatible with those of patients with advanced HF. All of them were functional class IV, their LVEF was too low and most of them needed vasoactive drugs for compensation purposes. In addition, their average BNP level was very high. The comparison between the clinical characteristics of anemic patients and the characteristics of nonanemic patients revealed that anemic patients were older, their renal function was more deteriorated and their plasma BNP levels were higher.

With respect to the incidence, we found anemia in 34.3% of patients whose condition was serious and who had been hospitalized for HF compensation. This number is larger than those described in studies evaluating outpatient populations or in large clinical trials that show an average incidence of around 15%[4,7]. However, the incidence is similar to the one found in the records and cohorts of hospitalized patients. Silva et al[16] reported anemia in 32% of patients hospitalized for compensation. In the OPTIMIZE-HF study, Young et al[17] studied 49,612 patients and found anemia in 50% of the cases.[17] In the STAMINA-HF study, which included 1,076 patients, there was prevalence of anemia in 34% of cases[18]. A meta-analysis of 153,180 patients hospitalized for compensation revealed that 37.2% of the patients were anemic[4]. Sales et al[10], in Rio de Janeiro, in the EPICA study, found anemia in 62.6% of hospitalized patients. The higher incidence of anemia among hospitalized patients, that is, those whose medical condition was more critical than the condition of patients evaluated in the clinic, is consistent with the view that anemia is a marker of a more severe disease.

With respect to the clinical characteristics of patients with anemia, our data do not differ much from those described in the literature. The relationship between renal dysfunction and anemia is found in almost all studies, as well as the fact that age is a risk factor for the onset of anemia. The most pronounced clinical manifestation is also a common finding in studies. Our data are also consistent with published data showing that the progress of anemic patients is worse than in non-anemic patients.

The etiopathogenesis of anemia is complex, with multiple factors involved. In this study, we observed that iron deficiency was a common factor and that there was some type of change

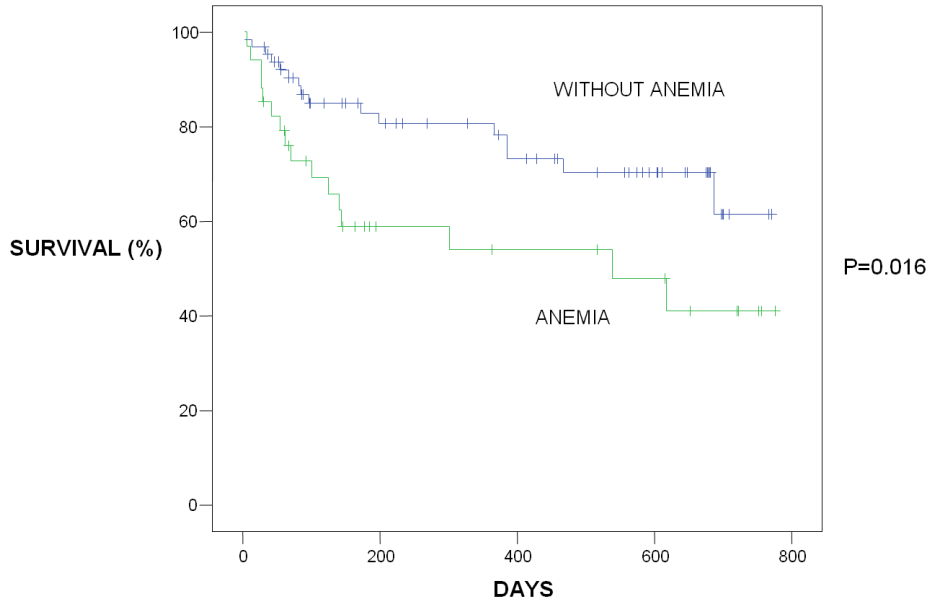

Chart 1 - Survival curve during monitoring of patients with and without anemia.

in the iron deposits of 38.24% of patients with anemia. It is important to emphasize that, even though most patients had fluid overload, there was no increase in hemoglobin levels and hematocrit levels after compensation, suggesting that hemodilution was not a major factor in the etiology of anemia in this patient group. Therefore, the role of hemodilution needs be better evaluated for such patients.

The cause of anemia is complex, as there is the combined participation of multiple pathogenic factors[1-5,9,17,19-22]. Iron deficiency, the systemic inflammatory process of HF and renal dysfunction stand out as important elements. Their participation varies according to the characteristics of the population studied. In the study conducted by Nanas et al[23], which excluded patients with creatinine levels above 3.0 mg/dl, the leading cause of anemia was iron deficiency[24]. When patients with renal failure were excluded, iron depletion and deficiency of other factors related to the production of hemoglobin, such as vitamin B12 and folic acid, appeared as the most frequent causal factors. In the study conducted by Silva et al[16], 1/3 of patients with anemia had a deficiency of hematinic factors (iron, vitamin B12 and folic acid)[16].

Other authors have not found the same frequency of hematinic changes. Opasich et al[24], in a review of anemia in HF, calls attention to the blocking of erythropoietin, the main element of which is the systemic inflammatory process. Ezekowitz et al[19] showed that, in 58% of anemia cases, anemia had the characteristics of a chronic disease. As one may see, the cause of anemia varies a lot and it depends on the characteristics of the population that is analyzed.

The etiopathogenesis of anemia becomes important when we discuss the treatment options. We do not know if anemia is only a marker of more severe HF, or if it is responsible for the worsening of the progress, or both. The iron depletion found in our patients results most likely from several factors found in patients with HF: inappetence that reduces iron intake; inflammation with increase in TNF-alpha that inhibits the absorption of iron; losses due to the frequent use of aspirin, in the case of ischemic cardiomyopathy. Iron replacement could probably change these symptoms. In the work of Okonko et al[25] with isolated replacement of iron, there was an average increase of 0.5 g/dl in the hemoglobin level. In the work of Bolger et al[26], the increase in the hemoglobin level was of 1.2 g/dl. In both studies, there was evidence of an improvement in anemia, with improvement in symptoms and physical capacity, but without significant impact on mortality. It is important to highlight the both had a small sample of cases.

In general, at the moment of the therapy, we must consider that the renal failure is prevalent among patients with HF and that, in many cases, the replacement of iron alone may not be very effective. According to the literature, the best treatment results have been achieved by the use of erythropoietin and with iron replacement, with records of reduction in symptoms in hospital readmissions and in mortality rate[16,20,21,24]. It is important to highlight that the studies were made up of a small number of cases and that a large study is needed to confirm these findings. With respect to the role of iron replacement, the Brazilian study called IRON-HF is currently being carried out. This study may answer some questions about the effectiveness of iron replacement.

We must consider that, in patients with HF, anemia is a frequent finding that heightens the clinical manifestations of HF and which is related to the worsening of the prognosis. There is not a consensus on the treatment of anemia yet, but the progress of patients without anemia is better than

the progress of anemic patients. There has been growing evidence that it is possible to change the progress by making the correction, but more consistent evidence is still needed.

Potential Conflict of Interest

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

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Study Association

This study is not associated with any post-graduation program.

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