

Anemia as a Prognostic Factor in a Population Hospitalized due to Decompensated Heart Failure

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Objective

To study the prevalence and prognostic value of anemia in a population hospitalized due to decompensated heart failure.

Method

From July to September, 2001, 204 patients were included in a multicenter hospital registry of heart failure (EPICA Study - Niterói). This retrospective analysis comprised 142 patients with data about hematocrit and hemoglobin levels collected on hospital admission. The mean age was 69.5 ± 13.3 years, and 72 (50.7%) patients were men. Hemoglobin levels < 13.5 g/dL for men and < 12 g/dL for women were considered anemia. The relation between anemia and in-hospital mortality was assessed through univariate and multivariate analysis with logistic regression.

Results

Anemia was observed in 89 (62.6%) patients, 52 (58%) men and 37 (42%) women. Mortality in anemic patients was 16.8% and, in nonanemic, it was 8% ($P=0.11$). In both sexes, the mortality rates in anemic and nonanemic patients were, respectively, 19.2% vs 0% ($P=0.034$) and 13.5% vs 12.2% ($P=0.86$). Through multivariate analysis, the following variables were found to be independently related to in-hospital mortality: hyponatremia [RR=7.0; 95% confidence interval (95% CI)=6.1 to 8.7; $P=0.0001$], anemia (RR=3.1, 95% CI=2.4 to 4.3; $P=0.024$), and presence of NYHA functional class IV (RR=1.9; 95% CI=1.3 to 2.6; $P=0.04$).

Conclusion

In the population studied with decompensated heart failure, the presence of anemia was an independent marker of in-hospital mortality. Mortality in the group with anemia was significantly high among men.

Key words

heart failure, anemia, prognosis

Patients with heart failure, mainly after one hospital admission, have a poor prognosis¹⁻³. Several prognostic factors have been described in an attempt to identify the greatest risk and how to better allocate resources. Recently, patients with heart failure have been shown to frequently have anemia, and its prevalence increases with the severity of the disease^{4,5}. In addition, some authors have reported the existence of a relation between anemia and mortality in patients with heart failure⁴⁻⁷. Recognition of those patients is important, because, in addition to identifying individuals at risk, it provides an opportunity to influence disease evolution through correction of the anemia.

Our study aimed at determining the prevalence of anemia and at establishing the prognostic value of the presence of anemia in a population hospitalized due to heart failure decompensation.

Methods

From July to September, 2001, 204 patients were included in a multicenter registry of patients hospitalized due to heart failure (EPICA Study - Niterói). Ten hospitals took part in this study, 4 being public and 6 private. The diagnosis of heart failure was defined according to the Boston criteria. Because ejection fraction was not considered an inclusion criterion, patients with heart failure and preserved systolic function were also included in the study. Of all patients, 142 had data on hematocrit and hemoglobin levels collected on hospital admission and were included in this retrospective analysis. The mean age was 69.5 ± 13.3 years, and 72 (50.7%) patients were of the male sex. All patients were in New York Heart Association (NYHA) functional class III or IV. The protocol was approved by the committee on ethics of our hospital and the patients signed a written informed consent.

The diagnosis of anemia was established according to the criteria of the Center for Disease Control and Prevention (CDC), considering serum hemoglobin level < 13.5 g/dL for men and < 12 g/dL for women.

The data obtained were presented as mean and respective standard deviations. For comparison of proportions, the chi-square (χ^2) test was used or the Fisher exact test, when the chi-square test could not be used. Comparison of the quantitative variables between 2 groups was analyzed by using the Student *t* test for independent samples or the Mann-Whitney test (nonparametric test). Multivariate analysis was performed through logistic regression for assessing the simultaneous influence of the variables on in-hospital mortality; the variables with $P < 0.10$ were included in the univariate analysis. In this model, the factors analyzed as

independent variables were age, sex, functional class, presence of systolic dysfunction, serum creatinine, presence of hyponatremia, presence of anemia, previous use of acetylsalicylic acid, and use of angiotensin-converting enzyme inhibitors. The significance level adopted was 5%, and the analysis was performed by using the SPSS statistical package, version 6.0.

Results

The basal characteristics of the patients are shown in table I. Anemia was observed in 89 (62.6%) patients, 52 (58%) being of the male sex and 37 (42%) of the female sex. Mortality was 16.8% in the anemic patients and 8% in nonanemic patients ($P=0.11$). In the male sex, in-hospital mortality was significantly greater among anemic patients than among nonanemic patients (19.2% vs 0%, respectively, $P=0.034$). In the female sex, no significant difference in mortality was observed between anemic and nonanemic patients (13.5% vs 12.2%, $P=0.86$) (fig. 1). No significant difference in mortality was observed between the group analyzed and the 62 patients who were excluded from the analysis because they did not have data on hematocrit and hemoglobin (13% vs 11%, $P=0.38$). The characteristics of the patients who survived and those who did not survive are shown in table II.

No significant difference was observed between the anemic and nonanemic groups in regard to the use of acetylsalicylic acid, use of angiotensin-converting enzyme inhibitors, serum creatinine, and serum sodium.

The logistic regression analysis showed that the following variables were independently related to in-hospital mortality: hyponatremia [RR=7.0; 95% confidence interval (95%CI)=6.1 to 8.7; $P=0.0001$], anemia (RR=3.1; 95% CI=2.4 to 4.3; $P=0.024$), and the presence of NYHA functional class IV (RR=1.9; 95% CI=1.3 to 2.6; $P=0.04$) (tab. III).

Discussion

Anemia is a comorbidity whose prognostic importance has been well recognized in a series of cardiovascular diseases, acute myocardial infarction included. In heart failure, anemia has only recently received attention, and its prevalence has ranged from 16 to 48%, depending on the age of the patients studied, the severity of the disease, and the criteria used for the diagnosis of anemia. In our study, a high prevalence of anemia (63%) was found, which may be explained by the predominance of elderly patients with advanced heart failure, although that prevalence may have been overestimated by the limitations of a retrospective study.

Data in the literature have also suggested that, in addition to being frequent, anemia relates to prognosis. In a study with 1,061 patients⁵, mortality at different hemoglobin levels was as follows: hemoglobin < 12.3 g/dL, 44.4%; between 12.3 and 13.6 g/dL, 36.1%; between 13.7 and 14.8 g/dL, 28.6%; and hemoglobin > 14.8 g/dL, 25.6%. In our study, anemia was an independent predictor of mortality. In univariate analysis, greater mortality was observed in men with anemia than in those without anemia. Interestingly, among women, no difference in mortality was observed. This difference regarding sex requires further investigation. However, at least one other author⁸ has found that relation pre-

viously. In a Canadian population-based study, which assessed 791 patients recently hospitalized due to recent-onset heart failure, anemia was a predictor of events in the male sex, but not in the female⁸. Curiously, that author, who used, as we did, the CDC criteria for the diagnosis of anemia, found a higher prevalence of anemia among men, similar to that observed in our study (45% in the general population, 50% among men, and 40% among women). Therefore, as different criteria exist for the diagnosis of anemia according to sex, the effect of anemia on mortality may also be different according to sex.

Our case series included not only patients with systolic dysfunction, but also those with preserved systolic function (22.5%). The results of multivariate analysis in our study have suggested that anemia influences the prognosis independently of the type of ventricular dysfunction.

It is still unknown whether a cause and effect relation between the presence of anemia and poor prognosis exists or whether it is only an epiphenomenon due to the severity of heart failure and its complications. The latter, however, seems unlikely because anemia has been shown to be an independent predictor of events. In a study of patients with functional class III and IV heart failure, the hemoglobin rate was an important prognostic factor independently of pulmonary capillary pressure, body mass index, serum albumin, and serum creatinine⁵. In 2 other studies^{6,9}, anemia was a predictor of mortality independent of serum creatinine. In our study, anemia remained a predictor of events, independently of age, serum creatinine and sodium, presence of systolic dysfunction, and previous use of acetylsalicylic acid or angiotensin-

Variables	n (%)
Age (years)	69.5±13.3
Male sex	72 (50.7%)
NYHA functional class	3.7±0.8
Ischemic etiology	88 (62%)
Serum creatinine (mg/dL)	1.3±0.6
Serum sodium (mEq/L)	135.3±4.2
Hemoglobin (g/dL)	12.1±1.6
Systolic dysfunction	110 (77.5%)
Use of acetylsalicylic acid	66 (46.4%)
Use of ACEI	101 (71%)

ACEI - angiotensin-converting enzyme inhibitor.

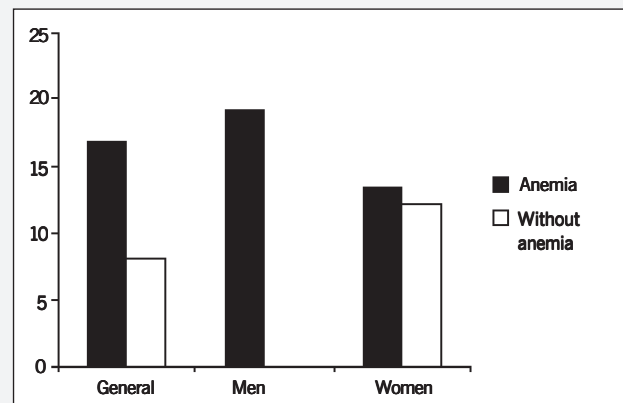


Fig. 1 - In-hospital mortality in anemic and nonanemic patients in the general population and according to sex.

**Table II – Clinical characteristics of survivors and nonsurvivors**

Variables	Survivors n = 123	Nonsurvivors n = 19	P value
Age (years)	66.5±13.2	71±14.2	0.11
Male sex	62 (50.4%)	10 (52.6%)	0.85
(NYHA) FC IV	79.6%	94.7%	0.02
Ischemic etiology	76 (61.7%)	12 (63.1%)	0.58
Serum creatinine (mg/dL)	1.4±0.7	1.3±0.6	0.22
Serum sodium (mEq/L)	136±42	130±38	0.01
Hemoglobin (g/dL)	12.8±1.3	11.6±1.4	0.06
Systolic dysfunction	95(77.2%)	15 (79%)	0.54
Use of ASA	57 (46.3)	9 (47.3%)	0.87
Use of ACEI	88 (71.5%)	13 (68.4%)	0.68

ASA - acetylsalicylic acid; ACEI - angiotensin-converting enzyme inhibitor; (NYHA) FC IV - New York Heart Association functional class IV.

Table III - Multivariate analysis through logistic regression

Variable	Beta coefficient	Standard error	P value
Hyponatremia	4.5793	1.1596	0.0001
Anemia	2.5743	1.1479	0.0240
(NYHA) FC IV	2.2167	1.1206	0.0470

(NYHA) FC IV - New York Heart Association functional class IV.

converting enzyme inhibitors. Analyzing all this information, one may conclude that anemia may have a cause and effect relation with prognosis.

In heart failure, the cause of anemia seems to be multifactorial. Several mechanisms have been proposed, such as the presence

of alteration in renal function due to its severity and aggravated by the use of diuretics, the use of acetylsalicylic acid, the inhibition of the production of erythropoietin by the angiotensin-converting enzyme inhibitor, and hemodilution. Another possible cause that has been gaining attention is the suppression of erythropoietin and erythropoiesis by inflammatory cytokines, which are increased in heart failure.

Our study has a significant clinical implication. As anemia is an independent prognostic factor, one may influence its evolution through its correction. Some studies with a limited number of patients have shown that the correction of anemia with erythropoietin and intravenous iron has improved the functional class, reduced hospitalizations, and improved ejection fraction^{10,11}. In another study¹², treatment with erythropoietin improved the functional capacity of the patients with heart failure and anemia. A prospective, randomized, double-blind, multicenter study (STAMINA-HeFT) is going on, and it will assess the impact of darbepoietin-alpha in the exercise capacity of patients with heart failure and anemia.

An important limitation of our study is the fact that it is a retrospective analysis, which limits the control of some variables whose data were not available. Therefore, the type of anemia of those patients could not be established. It is worth noting, however, that this study was developed using a database, whose information was collected prospectively. In addition, it reproduces the same results already reported by other authors.

In conclusion, the presence of anemia was a prognostic factor independent of events, and this association was important, particularly in the male sex.

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