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Etiology of Anemia in Patients With Advanced Heart Failure

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OBJECTIVES We prospectively investigated the causes of anemia in patients with advanced congestive heart failure (CHF).

BACKGROUND Anemia is common in patients with advanced CHF, and its etiology is generally considered to be multifactorial. However, despite its importance, precise information is lacking regarding the prevalence of putative etiologic factors.

METHODS Patients who were hospitalized for decompensated advanced CHF and who were stabilized after their initial treatment underwent evaluation of "clinically significant" anemia, defined as a hemoglobin content <12 g/dl for men and <11.5 g/dl for women. Patients with a serum creatinine concentration >3 mg/dl or patients with concurrent diseases that are known to cause anemia were not included. The initial evaluation included measurements of vitamin B_{12}, folic acid, thyroid-stimulating hormone, erythropoietin, lactate dehydrogenase, Coombs test, multiple fecal occult tests, and bone marrow aspiration. Patients without diagnosis by these methods underwent red cell mass measurement with ^{51}Cr assay.

RESULTS The mean age of the 37 patients was 57.9 ± 10.9 years and mean left ventricular ejection fraction 22.5 ± 5.9%. Iron deficiency anemia was confirmed by bone marrow aspiration in 27 patients (73%), 2 patients (5.4%) had dilutional anemia, and 1 patient (2.7%) had drug-induced anemia. No specific cause was identified in 7 patients (18.9%) who were considered to have "anemia of chronic disease." Serum ferritin for the iron-deficient patients was not a reliable marker of iron deficiency in this population.

CONCLUSIONS In this group of patients, iron deficiency was the most common cause of anemia. The iron status of patients with end-stage chronic CHF should be thoroughly evaluated and corrected before considering other therapeutic interventions. (J Am Coll Cardiol 2006;48:2485–9)

The 1-year death rate of patients suffering from congestive heart failure (CHF) refractory to standard medical treatment exceeds 50% (1). Furthermore, deaths attributed to CHF have increased 145% in the last 2 decades (2). This increased death rate, despite advances in medical treatment, points to the importance of identifying factors related to poor outcomes and developing new treatment and prevention modalities.

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In 2000, Silverberg et al. (3) published the first report of a decrease in blood hemoglobin content with increasing severity of CHF. Since then, several studies have documented both a greater mortality associated with anemia (4–12) and a high prevalence of anemia (3,5,13,14) in patients with advanced CHF. In small, randomized studies, the elimination of anemia significantly improved cardiac function, functional capacity, and quality of life of patients with advanced CHF (15,16).

Although the optimal treatment of anemia must target its underlying mechanisms, only a few studies have thoroughly investigated the causes of anemia in patients suffering from CHF, and almost none at all the causes in patients with advanced heart failure, intractable to standard medical treatment. The purpose of this study was to prospectively examine the etiology of anemia in patients presenting with end-stage CHF.

METHODS

Patient population and methods. This study included 37 consecutive patients suffering from end-stage CHF and anemia who had been treated with an optimal medical regimen and were hospitalized for management of acute cardiac decompensation, which did not respond to oral medical treatment and which required continuous intravenous infusions of dobutamine 10 μg/kg/min for not more than 72 h. This group of patients was selected by prospectively screening all patients who had been hospitalized for acute decompensated advanced heart failure and had re-

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Abbreviations and Acronyms
CHF = congestive heart failure
NYHA = New York Heart Association

sponded to intravenous dobutamine infusion. To guide their treatment, we submitted all patients to baseline right heart catheterization. The blood hemoglobin content, measured after the discontinuation of dobutamine, was ≤12 g/dl in men and ≤11.5 g/dl in women. Patients with chronic renal insufficiency and a serum creatinine concentration ≥3 mg/dl or a history of comorbid disorders known to cause anemia, such as hypothyroidism, hereditary anemia, hematological disease or known diseases that cause gastrointestinal bleeding, were excluded from the study.

After stabilization of their clinical status, all patients underwent a detailed evaluation including electrocardiogram, chest radiograph, echocardiogram, and baseline right heart catheterization. The creatinine clearance was estimated on the base of the Cockroff-Gault formula. Tests in search of an etiology of anemia included measurements of serum iron, ferritin, erythropoietin, folic acid, vitamin B_{12}, thyroid-stimulating hormone, lactate dehydrogenase, bilirubin, Coombs test, albumin, globulin, creatinine, C-reactive protein, fecal occult blood test repeated 3 times, and bone marrow aspiration. Iron deficiency on bone marrow biopsy was defined as absence of iron stores. When the etiology of anemia was not clarified by these investigations, the patients underwent red cell mass measurement by ^{51}Cr assay (17). At the conclusion of the evaluation, patients were classified into those having 1) iron deficiency anemia, 2) anemia of chronic disease, 3) drug-induced anemia, and 4) hemodilutional anemia. The ethical review board of our institution approved this study, and all patients had granted their written informed consent to participate.

Statistical analysis. Anemia was prespecified as a blood hemoglobin content <12 g/dl in men, and <11.5 g/dl in women, after clinical stabilization. Data are presented as mean values ± SD. Differences between patients with iron deficiency anemia versus patients with anemia not due to iron deficiency were examined by using the Student *t* test for unpaired observations, for continuous variables. Survival comparisons between patient subgroups were estimated by the Kaplan-Meier method and the log rank test. The concentrations of biochemical compounds were compared with standard normal values.

RESULTS

Clinical characteristics and hemodynamic measurements. The mean age of the 35 men and 2 women included in this study was 57.9 ± 10.9 years. All patients were in New York Heart Association (NYHA) functional class IV upon admission to the hospital. After stabilization by intravenous drug treatment, the mean NYHA functional class was 3.7 ± 0.5, mean pulmonary capillary wedge pressure 25.8 ± 7.5 mm Hg, and mean left ventricular ejection fraction 22.5 ± 5.9% (Table 1).

Table 1. Baseline Clinical Characteristics and Hemodynamic Measurements After Stabilization of 37 Patients With Advanced Congestive Heart Failure and Anemia

Age, yrs	57.9 ± 10.9
Men/women, n	35/2
Duration of heart failure, months (median)	60
Hemoglobin concentration, g/dl	10.1 ± 0.9
Hematocrit, %	32.1 ± 2.8
New York Heart Association functional class	3.7 ± 0.5
Heart rate, beats/min	76.1 ± 9.8
Systolic blood pressure, mm Hg	96.6 ± 9.2
Diastolic blood pressure, mm Hg	59.8 ± 10.8
Mean right atrial pressure, mm Hg	13.6 ± 6.9
Right ventricular systolic pressure, mm Hg	61.6 ± 15.5
Mean pulmonary artery pressure, mm Hg	40.4 ± 10.3
Pulmonary capillary wedge pressure, mm Hg	25.8 ± 7.5
Cardiac index, l/m^2/min	1.9 ± 0.5
Pulmonary vascular resistance, Wood units	4.3 ± 2.1
Left ventricular ejection fraction, %	22.5 ± 5.9
Left ventricular end-diastolic diameter, mm	70.9 ± 6.7
Serum creatinine, mg/dl	1.7 ± 0.6
Creatinine clearance, ml/min (Cockcroft)	51.7 ± 23.0
Serum sodium, mEq/l	136 ± 4
Body weight, kg	74.6 ± 11.6
Body mass index, kg/m^2	25 ± 4
Concomitant drug therapy, % of patients	
Furosemide	100
Digoxin	45.9
Angiotensin-converting enzyme inhibitors	56.8
Spironolactone	73
Metoprolol	10.8
Carvedilol	5.4
Amiodarone	89.2
Aspirin/clopidogrel	48.6
Warfarin	32.4
Daily furosemide dose, mg	450 ± 291

Unless specified otherwise, values are mean ± SD.

Hematological and biochemical observations. The results of the hematological and biochemical investigations in the 37 patients are shown in Table 2. The mean hemoglobin was 10.4 ± 0.8 g/dl on admission to the hospital and 10.1 ± 0.9 g/dl (range 8.8 to 12.0) after initial stabilization, the ferritin concentration was low (<17 ng/ml) in 2 patients and within normal limits (17 to 390 ng/ml) in the remainder of the population, and the mean erythropoietin concentration was 68.6 ± 54.7 μU/ml, more than double the upper normal limit (9 to 30 μU/ml) of our laboratory. The serum creatinine averaged 1.7 mg/dl and 56.7% were greater than the normal values of 1.4 mg/dl. Bone marrow aspirations confirmed the presence of iron deficiency in 27 of the 37 patients. In addition, 3 separate detection tests for occult fecal blood were negative in 89% of iron-deficient patients and in all non–iron-deficient patients.

The mean age, NYHA functional class, and indexes of cardiac and hemodynamic function in the 27 iron-deficient versus the 10 non–iron-deficient patients were similar. With

Table 2. Hematological and Biochemical Measurements After Clinical Stabilization in 37 Patients With End-Stage Heart Failure and Anemia

Hematocrit, %	32.1 ± 2.8
Hemoglobin, g/dl	10.1 ± 0.9
Mean corpuscular volume, fl	82.6 ± 8.5
Mean corpuscular hemoglobin, pg	26.3 ± 3.4
Serum iron, γ/dl	52.2 ± 23.6
Ferritin, ng/ml	113.2 ± 94.4
Erythropoietin, μU/ml	68.6 ± 54.7
Vitamin B_{12}, pg/ml	867 ± 443
Folic acid, ng/ml	10.2 ± 4.7
Thyroid-stimulating hormone, μIU/ml	4.4 ± 5.8
C-reactive protein, mg/dl	3.4 ± 3.8

Values are expressed as mean ± SD.

respect to hematological measurements, mean corpuscular volume, mean corpuscular hemoglobin, and ferritin concentration were significantly lower among the iron-deficient patients than among patients with anemia not due to iron deficiency (Table 3).

The 3-month mortality rate in the overall patient population was 46%. All deaths were due to worsening of CHF. The survival rates of iron-deficient and non–iron-deficient patients estimated by the Kaplan-Meier method were similar (44.4% vs. 50.0%, respectively, p = 0.83).

Etiology of anemia. In the studied group of 37 anemic patients, iron deficiency was confirmed in 27 (73%), as previously stated. The blood volume analysis with ^{51}Cr-labeled erythrocytes revealed that 2 patients (5.4%) had normal red blood cells volumes (>95% predicted, i.e., 31.8 ± 3.5 ml/kg body weight). Furthermore, 1 patient (2.7%) had enalapril-induced anemia, which resolved upon treatment discontinuation, and returned upon treatment rechallenge. No specific cause was identified in 7 patients (18.9%), who were classified as suffering from anemia of chronic disease (Fig. 1).

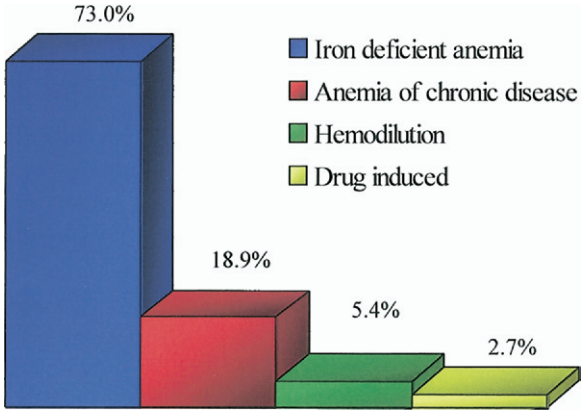

Figure 1. Distribution of various etiologies of anemia among 37 patients with advanced congestive heart failure.

DISCUSSION

In this group of patients with end-stage CHF and anemia, a high prevalence of iron deficiency was observed, accompanied by an inappropriately low erythropoietin and normal ferritin concentrations. Until recently, the role of anemia in patients with CHF has been underestimated. However, recent studies have shown that an increasing severity of anemia is associated with increasing mortality in patients with CHF (4–11,18).

The patients included in the present study had end-stage CHF and, despite all having been treated with maximally tolerated doses of oral medications, including high doses of furosemide, continued to have disabling dyspnea at rest. Therefore, they were all initially treated with additional continuous intravenous infusion of inotropes and, subsequently, intermittent infusions of inotropes and oral amiodarone (19). After their initial stabilization, they remained in NYHA functional classes III to IV, with markedly elevated pulmonary capillary wedge pressures. The 3-month

Table 3. Baseline Hematological and Biochemical Measurements in Iron-Deficient Versus Non–Iron-Deficient Patients

	Iron Deficient (n = 27)	Non–Iron Deficient (n = 10)	p Value
Hemoglobin, g/dl	10.2 ± 0.9	10.0 ± 0.9	0.61
Hematocrit, %	32.4 ± 2.8	31.1 ± 2.9	0.28
Mean corpuscular volume, fl	80.7 ± 8.8	87.7 ± 5.2	0.024
Mean corpuscular hemoglobin, pg	25.5 ± 3.4	28.5 ± 2.3	0.014
Iron, γ/dl	51.3 ± 23.3	54.6 ± 25.7	0.73
Ferritin, ng/ml	75.3 ± 59.1	211.9 ± 99.9	0.00001
Erythropoietin, μU/ml	74.8 ± 58.2	52.3 ± 42.3	0.27
Fibrinogen, g/l	349.8 ± 68.3	485.1 ± 124.1	0.0002
C-reactive protein, mg/dl	2.9 ± 3.5	4.7 ± 4.6	0.22
Erythrocyte sedimentation rate, mm/h	39.6 ± 21.9	65.9 ± 26.7	0.005
Serum sodium, mEq/l	135.1 ± 3.2	138.6 ± 4.9	0.0162
Daily dose of furosemide, mg	428.7 ± 288.1	510.5 ± 306.3	0.46
Brain natriuretic peptide, pg/ml	1,283.7 ± 1,260.0	1,670.0 ± 1,950.7	0.53
Serum creatinine, mg/dl	1.7 ± 0.6	1.7 ± 0.6	0.75
Creatinine clearance, ml/min	53.1 ± 25.1	47.9 ± 16.4	0.54
Thyroid-stimulating hormone, μIU/ml	3.9 ± 4.9	5.6 ± 8.0	0.46

Values are expressed as mean ± SD.

mortality rate in this population was inordinately high and comparable with that observed among patients requiring treatment with combined intravenous inotropes (20). This indicates that patients with cardiac decompensation and anemia are a population suffering from extremely severe CHF.

The high prevalence of iron deficiency anemia in these desperately ill patients, which probably plays a causative role in the progression of CHF, seems to be multifactorial, and at least partially the result of a defective release of iron from cells (21). Poor nutrition is common in advanced CHF (22), and both an insufficient dietary iron intake from acquired gastrointestinal malabsorption and chronic blood loss from the prophylactic use of aspirin and uremic gastritis may precipitate iron deficiency anemia (23). Iron deficiency has been observed in 21% of anemic patients suffering from CHF (7).

In contrast to other studies in which the type of anemia was diagnosed on the basis of hematological and biochemical testing, this study ascertained beyond doubt the diagnosis of iron deficiency anemia by verifying the absence of iron in the bone marrow. Iron deficiency anemia, in our patients, was not associated with the expected decrease in ferritin concentrations. This relative increase in ferritin concentrations might be the result of the inflammation that accompanies the CHF syndrome (24). Similarly the relatively low erythropoietin could be attributable to either cytokine inhibition of erythropoietin production on the kidney and/or to the associated renal failure. The increased C-reactive protein concentrations measured in our patients were a distinct indication of the presence of inflammation.

Role of hemodilution. A low hemoglobin concentration may be the consequence of an increased plasma volume and normal red blood cell volume (25). Androne et al. (26) have reported a 46% prevalence of hemodilution in anemic patients with advanced CHF. In our study, 5.4% of the patients had findings consistent with hemodilution and not true anemia. However, the presence of hypervolemia does not preclude the coexistence of true anemia. The discrepancy between the 2 studies has several potential explanations. First, in our study, measurements of the red blood cell volume were limited to 9 patients in whom the evaluation did not reveal the presence of iron deficiency or of another specific cause of anemia. Among these 9 patients, 2 had pseudo-anemia due to hemodilution, and 1 patient had anemia of chronic disease and hypervolemia. Therefore, among the patients whose red blood cell volume was measured, 33% were found to have hemodilution. Second, differences in techniques of blood volume measurements (^{51}Cr assay in our study versus radiolabeled albumin in the study by Androne et al. [26]) and the small number of patients included in both studies might have contributed to this discrepancy. Third, iron-deficient patients also might be hemodiluted. Considering all these factors, the prevalence of hemodilution in our study versus that of Androne et al. (26) seems similar.

Role of chronic disease. Anemia in patients with advanced CHF may be caused by bone marrow suppression (27). Interleukin-1 and tumor necrosis factor-α directly inhibit the in vitro production of erythropoietin in patients with inflammatory disorders who commonly exhibit a blunted response of erythropoietin to anemia (27,28). Elevated plasma concentrations of tumor necrosis factor-α interfere with the peripheral effects of erythropoietin (29,30). In our patients, the erythropoietin concentrations were elevated, although not to a level commensurate with their degree of anemia. This blunted elevation of erythropoietin may be a consequence of treatment with angiotensin-converting enzyme inhibitors (31), or of the chronic renal insufficiency that frequently complicates CHF, or both. In our study, 21 of 37 patients (57%) had a serum creatinine $\geq$1.5 mg/dl. In the study by Cromie et al. (32), 46% of anemic patients had renal insufficiency, whereas Ezekowitz et al. (7) reported that anemic patients were more likely to suffer from chronic renal insufficiency. Anemia is common in CHF despite elevated concentrations of erythropoietin, suggesting the existence of target organ resistance to its effects.

Study limitations. The observations of our study were made in, and should be limited to, a distinct population of patients with end-stage and recently decompensated CHF. Another limitation of the study was the small proportion of patients who underwent measurements of red cell volume. However, the high prevalence of hemodilution in anemic patients suffering from CHF warrants further investigations.

Conclusions. Our results suggest that the majority of anemic patients with advanced CHF are iron deficient, suggesting that a trial of iron-replacement therapy in patients presenting with advanced CHF and anemia is imperative.

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