Hemodilution Is Common in Patients With Advanced Heart Failure

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Background—Anemia frequently occurs in chronic heart failure (CHF) patients and is associated with a poor prognosis. A low hematocrit may result from an increased plasma volume (hemodilution) or from reduced red blood cell volume (true anemia). The prevalence and clinical outcome of CHF patients with hemodilution is unknown.

Methods and Results—The prevalence of anemia and its effect on outcome was examined in 196 patients with CHF. The prevalence of hemodilution was assessed in a subset of 37 ambulatory anemic patients with I^{131}-tagged albumin to measure red blood cell and plasma volume. Clinical outcome was monitored. Sixty-one percent of the CHF patients were anemic. The prevalence of anemia increased from 33% in patients with New York Heart Association class II heart failure to 68% in class IV CHF patients. Survival was reduced in anemic patients compared with patients with a normal hematocrit ($P<0.05$). In the subset of 37 anemic patients, 17 patients (46%) had hemodilution and 20 patients (54%) had a true anemia. Nine patients with hemodilution died or underwent urgent transplant compared with 4 patients in the true anemia group ($P<0.04$).

Conclusion—Hemodilution is common in CHF patients. Anemia is associated with a poor prognosis in CHF. Patients with hemodilution tend to do worse than patients with true anemia, which suggests that volume overload may be an important mechanism contributing to the poor outcome in anemic CHF patients. (***Circulation***. 2003;107:226-229.)

Key Words: heart failure ■ anemia ■ blood volume

Anemia is common in patients with chronic heart failure (CHF) and is associated with a poor prognosis.[1–3] Anemia in CHF may be due to chronic disease, bone marrow depression from excessive cytokine production,[4] malnutrition, concomitant renal disease, and/or drug therapy.[5] A reduced hematocrit can result not only from a reduced red blood cell (RBC) volume but also from an increased plasma volume.[6] Hemodilution may occur in edematous, hypervolemic patients and patients appearing euvolemic on clinical examination.[7] Estimation of plasma and RBC volume with I^{131}-tagged albumin techniques can identify patients with CHF who have hemodilution. Identification of these patients is clinically important because patients with true anemia need further diagnostic workup, whereas those with hemodilution do not. Whether hemodilution carries the same poor prognosis as true anemia is unknown. The purpose of our study was to assess the prevalence and clinical outcome of hemodilution in patients with CHF.

Methods

Hematocrit levels for 196 consecutive patients with CHF referred for heart transplantation in the year 2000 were determined to assess anemia prevalence. Anemia was defined as a hematocrit <38% in females and <41% in males. The prevalence of hemodilution was determined prospectively in a subgroup of 37 ambulatory anemic patients with blood volume analysis as described below. The volume status of each patient was assessed by physical examination and compared with the blood volume analysis results. Clinical outcome was assessed by review of medical records and/or telephone follow-up.

Blood Volume Analysis

Twenty-five μCi of I^{131} serum albumin (Megatope, Iso-Tex Diagnostics, Inc) were injected in a peripheral vein from a prefilled syringe. Twelve minutes after injection, 5cc of venous blood was collected at 6-minute intervals for 36 minutes. Spun hematocrit was determined from each sample, and plasma radioactivity was measured in an automated counter (BVA-100 Blood Volume Analyzer, Daxor Corp). Plasma volume was determined as the volume of distribution of albumin.[8] Blood and RBC volume were estimated from spun hematocrit and then compared with normal values for sex, height, and weight. Volumes are expressed in absolute numbers and as percent deviation from predicted values. Anemic patients were considered to have hemodilution if the percent predicted RBC volume was >95%.

Statistical Analysis

Intra- and intergroup differences were compared by paired and non-paired *t* testing, respectively. A $P<0.05$ was considered significant. Results are reported as mean±standard deviation. Time to event (death or urgent transplant) was analyzed using Kaplan Meier curves and log-rank analysis. Patients who underwent elective

TABLE 1.   Clinical Characteristics

	All (n=196)		Anemic (n=120)		Non-Anemic (n=76)	
	Men	Women	Men	Women	Men	Women
No.	152	44	97	23	55	21
Age, y	52±11	51±11	53±11	52±11	52±11	51±11
BMI, kg/m^2	27±4	24±5	27±4	24±4	27±4	25±7
LVEF, %	23±9	29±11	24±10	30±12	21±7	29±11
VO$_{2max}$, mL · kg^{-1} · min^{-1}	13.4±4	11.1±3.7	13±3	10±2	14±4.5	11.7±4.3
Hemoglobin, mg/dL	12.4±2.5	11.9±1.7	11±1.7	10.7±1.4	14.9±1.1	13.3±1
Hematocrit, %	38±7	37.1±5	33.5±5	33.2±4	45.5±3.3	41.4±2
Ferritin, ng/mL	221±152	153±117	243±167	157±110	187±124	149±122
Creatinine, mg/dL	1.65±1.4	1.17±0.6	1.8±1.7	1.26±0.7	1.38±0.4	1.07±0.5

Values are expressed as mean±SD. BMI indicates body mass index; and LVEF, left ventricular ejection fraction.

transplant were censored at transplant. We also performed χ^2 analysis on outcomes.

Results

Patients Characteristics

Sixty-one percent of the patients were anemic. No significant differences in the clinical characteristics of patients with normal and reduced hematocrits were observed (Table 1).

Blood Volume Analysis With I^{131}-Tagged Albumin

The clinical characteristics of the 37 anemic patients who underwent blood volume analysis were comparable to the entire anemic patient cohort. In this subset, 17 patients (46%) had normal RBC volume (>95% of predicted) with excess plasma volume, resulting in hemodilution. Plasma volume excess was more common in men than women (39% versus 16%, $P=0.01$). Patients with hemodilution had a higher hematocrit than those in the anemia group (Table 2) and a

TABLE 2.   Clinical Characteristics of Patients With Hemodilution Versus True Anemia

	Hemodilution (n=17)	True Anemia (n=20)
Hematocrit, %	35.4±4*	32.8±4
Ferritin, ng/mL	173±108	210±160
BMI, kg/m^2	26±3	27±5
PCW, mm Hg	26±4†	18±7
LVEF, %	22±6	27±7
Peak VO$_2$, mL · kg^{-1} · min^{-1}	12.6±3.5	13.7±4.3
Diuretic dose, n (%)		
None	2 (12%)	1 (5%)
Low-dose‡	9 (53%)	12 (60%)
High-dose¶	6 (35%)	7 (35%)

Values are expressed as mean±SD or n (%). BMI indicates body mass index; PCW, pulmonary capillary wedge; and LVEF, left ventricular ejection fraction.

*$P<0.05$; †$P<0.01$.

‡Low-dose diuretic indicates furosemide (or equivalent) <100 mg/day.

¶High-dose diuretic indicates furosemide (or equivalent) ≥100 mg/day.

mean plasma volume excess of 1460 cc (149% of predicted). Patients with anemia had a 23% deficit in RBC volume and a 20% plasma volume excess. Pulmonary capillary wedge was significantly higher in the hemodilution group compared with the anemia group ($P<0.01$, Table 2) but left ventricular ejection fraction, peak oxygen consumption, and diuretic dosage did not differ between the 2 groups. Clinical fluid status assessments and blood volume analysis were concordant in 50% of cases, with 56% of patients with hemodilution appearing euvolemic.

Clinical Outcome

Nine patients were lost to follow-up. One-year survival of the 114 anemic patients was less than the survival of the 74 patients with normal hematocrits (41% versus 63%, $P<0.05$; Figure 1). None of the 37 ambulatory anemic patients were lost to follow-up. The clinical outcomes of the patients with anemia and hemodilution were compared. Follow-up duration was 417±229 days. Four patients in the anemia group died or underwent urgent transplant compared with 9 patients in the hemodilution group. Kaplan Meier survival curves were not statistically different between the groups (Figure 2), although patients with hemodilution tended to do worse ($P=0.08$). As shown by χ^2 analysis, a significant difference in adverse
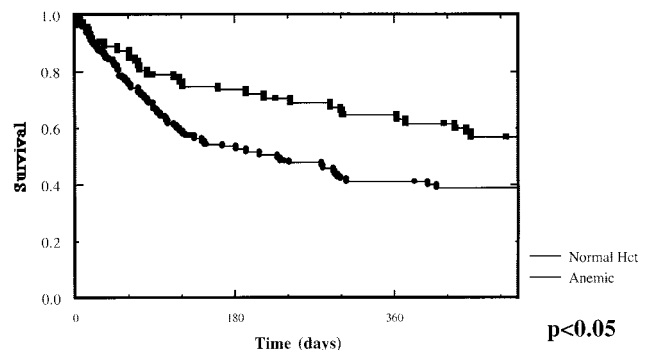

p<0.05

Figure 1. Survival curves of patients with and without anemia. Hct indicates hematocrit.
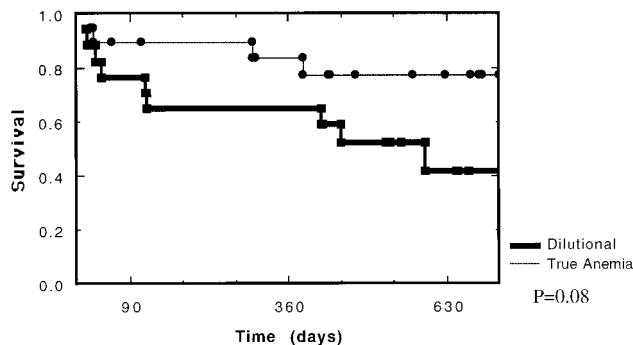
Figure 2. Survival curves of the patients with true anemia versus hemodilution.

events (ie, death or urgent transplant) was observed between the groups ($P<0.04$).

Discussion

This is the first study to examine the prevalence of hemodilution in CHF and its impact on clinical outcome. Our study demonstrated that hemodilution is common and that clinical outcomes in these patients tended to be worse than in CHF patients with true anemia.

Prevalence of Anemia

Previous investigators have shown that anemia is common in CHF, and its prevalence increases with disease severity. Silverberg et al[2] reported a 9% prevalence of anemia in New York Heart Association functional class I patients that increased to 79% in class IV CHF patients. Horwich et al[3] showed that hemoglobin levels were significantly associated with symptoms, exercise capacity, and prognosis in 1061 patients with class III to IV CHF. Our findings are consistent with these prior reports.

Hemodilution in CHF

The pathogenesis of anemia in CHF is multifactorial. In our study, the incidence of hemodilution was extremely common, occurring in 46% of the anemic patients. Identification of patients with true anemia selects patients who require further diagnostic work-up and treatment of their anemia. CHF patients with hemodilution may simply require an adjustment in diuretic dosage. Hemodilution can have a deleterious effect on patients with CHF, however, as it results in impaired peripheral oxygen delivery. Compensatory mechanisms to circumvent tissue hypoxia include an increase in cardiac output via sympathetic stimulation, redistribution of blood flow, an increase in whole body oxygen extraction ratio,[9] and activation of aortic chemoreceptors with an increase in venomotor tone.[10]

Although volume assessment on physical examination has a firm basis for acute CHF,[11] in the chronic state, compensatory mechanisms may mask signs of volume overload. Physical findings of congestion are detected in only 50% of patients found to be hypervolemic by use of invasive hemodynamic monitoring.[7,12] In our study, congestion was de-

tected in only 50% of patients with plasma volume excess as determined by the I^{131}-tagged albumin technique.

Prognosis

Anemia is associated with an increased mortality in patients with asymptomatic left ventricular dysfunction to advanced CHF.[1–3] Anemia is an independent risk factor for the development of CHF[13] and could contribute to the worsening of CHF.[14] Our data also demonstrate a worse outcome in anemic CHF patients. Anemia could exacerbate CHF by increasing myocardial and peripheral hypoxia, promoting left ventricular hypertrophy,[15] and activating neurohormonal and cytokine systems.[16]

Volume overload that occurs with hemodilution could also contribute to worse outcome. The higher pulmonary capillary wedge pressure in the hemodiluted versus anemic groups is consistent with greater volume overload. Hypervolemia may be linked to increased mortality risk since B-type natruretic peptide, a cardiac-derived hormone closely correlated to left ventricular end-diastolic pressure, has been shown to be an independent predictor of survival in CHF patients.[17] Our data support this hypothesis, as there is evidence for worse survival in the patients with hemodilution versus true anemia. Despite the small number of patients in our study, our data imply that volume overload may be a key mechanism contributing to the increased mortality in CHF patients with anemia.

Study Limitations

Our study population of patients with advanced CHF may not reflect the characteristics of CHF patients in the general population. Hematocrit levels were assessed at a single time point. Only a subgroup of patients underwent administration of I^{131}-tagged albumin to measure plasma and RBC volume. The estimated RBC volume reported may be less accurate than direct measurement with 51-chromium labeling technique. The causes of anemia in our CHF population were not discussed, nor were the specific treatments provided.

Conclusion

There is a high prevalence of anemia in patients with CHF. Many of these patients have hemodilution. The clinical outcome of CHF patients with true anemia and hemodilution is poor, and both conditions should be actively corrected.

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