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
transplant were censored at transplant. We also performed χ² 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 I¹³¹-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 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 euvoletic.

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 χ² analysis, a significant difference in adverse

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**TABLE 1. Clinical Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All (n=196)</th>
<th>Anemic (n=120)</th>
<th>Non-Anemic (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>No.</td>
<td>152</td>
<td>44</td>
<td>97</td>
</tr>
<tr>
<td>Age, y</td>
<td>52±11</td>
<td>51±11</td>
<td>53±11</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27±4</td>
<td>24±5</td>
<td>27±4</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23±9</td>
<td>29±11</td>
<td>24±10</td>
</tr>
<tr>
<td>VO₂max, mL·kg⁻¹·min⁻¹</td>
<td>13.4±4</td>
<td>11.1±3.7</td>
<td>13±3</td>
</tr>
<tr>
<td>Hemoglobin, mg/dL</td>
<td>12.4±2.5</td>
<td>11.9±1.7</td>
<td>11±1.7</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>38±7</td>
<td>37.1±5</td>
<td>33.5±5</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>221±152</td>
<td>153±117</td>
<td>243±167</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.65±1.4</td>
<td>1.17±0.6</td>
<td>1.8±1.7</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. BMI indicates body mass index; and LVEF, left ventricular ejection fraction. *P<0.05; †P<0.01.

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

<table>
<thead>
<tr>
<th></th>
<th>Hemodilution (n=17)</th>
<th>True Anemia (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, %</td>
<td>35.4±4*</td>
<td>32.8±4</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>173±108</td>
<td>210±160</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±3</td>
<td>27±5</td>
</tr>
<tr>
<td>PCW, mm Hg</td>
<td>26±4†</td>
<td>18±7</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>22±6</td>
<td>27±7</td>
</tr>
<tr>
<td>Peak VO₂, mL·kg⁻¹·min⁻¹</td>
<td>12.6±3.5</td>
<td>13.7±4.3</td>
</tr>
<tr>
<td>Diuretic dose, n (%)</td>
<td>None 2 (12%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td></td>
<td>Low-dose‡ 9 (53%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td></td>
<td>High-dose¶ 6 (35%)</td>
<td>7 (35%)</td>
</tr>
</tbody>
</table>

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.

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**Figure 1.** Survival curves of patients with and without anemia. Hct indicates hematocrit.
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 detected in only 50% of patients with plasma volume excess as determined by the $^{113}$-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 natriuretic 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 $^{113}$-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.

**References**


