Anemia and Inflammation in COPD*

Matthias John, MD, PhD; Soeren Hoernig, MD; Wolfram Doehner, MD; Darlington D. Okonko, MD; Christian Witt, MD, PhD; and Stefan D. Anker, MD, PhD

Background: Anemia in patients with COPD and its pathophysiology is an understudied issue.

Methods: In a group of 101 COPD patients (FEV1 percentage of predicted, 37 ± 2% [mean ± SEM]; mean age, 61 ± 1 years; 35% female gender), the prevalence of anemia and its relationship to body mass and weight loss, inflammatory parameters, and erythropoietin levels was determined. Data were compared to a control group (healthy persons with matched age) in order to identify potential factors that may influence the development of anemia in patients with COPD.

Results: Anemia was diagnosed in 13 patients (hemoglobin levels < 13.5 mg/dL in male patients and < 12.0 mg/dL in female patients), which represents a prevalence of 13%. Anemic COPD patients showed elevated erythropoietin levels (41.8 ± 25.4 U/L vs 16.3 ± 2.9 U/L) and an increased inflammatory response compared to nonanemic patients. A significant inverse correlation of hemoglobin vs erythropoietin (r = - 0.84, p < 0.01) was observed in anemic COPD patients, but not in the nonanemic group.

Conclusion: Anemic COPD patients show high erythropoietin levels, which may indicate presence of erythropoietin resistance. The latter may be mediated through inflammatory mechanisms, which is typical for anemia of chronic illness.

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Key words: anemia; COPD; inflammation

Abbreviations: CRP = C-reactive protein; IL = interleukin; IQR = interquartile range

Anemia is commonly associated with chronic illnesses such as heart failure and inflammatory diseases such as rheumatoid arthritis, with chronic infectious disorders, and with cancer. Anemia in chronic illness is characterized by weakness, fatigue, cachexia, nutritional state, and impaired mood, cognitive functions, and quality of life. The clinical symptoms of anemia often do not stand in the foreground in patients with chronic diseases. It has been suggested that anemia to some extent contributes to exercise limitation and dyspnea in chronic illness. It has been extensively studied that metabolic alterations, systemic inflammation, and neurohormonal activation frequently occur in patients with COPD.

The occurrence and prevalence of anemia in patients with COPD has rarely been studied. Anemia is such a common and simple clinical finding that we may underestimate its physiologic relevance in COPD.

Under the assumption that anemia frequently occurs in patients with COPD, we hypothesized that inflammatory responses and relative erythropoietin resistance would be associated with anemia or at least suboptimal hemoglobin concentrations. We also aimed to study whether anemia in COPD is related to presence of cachexia. To test this, we determined in a group of COPD patients the prevalence of anemia and its relationship to body weight, weight loss history, inflammatory parameters, and erythropoietin in comparison to a control group in order to identify potential factors that may influence the appearance of anemia in COPD.

Materials and Methods

Patient Population

We recruited 101 patients (mean age [± SEM], 60.8 ± 1.2 years; 35 women and 66 men) with COPD diagnosed according
to the guidelines of the American Thoracic Society. All patients showed an FEV₁ reversibility of < 9% in response to inhaled bronchodilators. In this population, 21 were smokers, 75 were ex-smokers, and 5 were nonsmokers (> 5 years of smoking cessation). Grading the disease severity revealed that 23 patients had mild COPD, 36 patients had moderate COPD, and 42 patients had severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines. At time of investigation, all patients were clinically stable without signs of acute exacerbation. No patients required hospital admission or treatment changes during the preceding 3 months. Treatment included long-acting β₂ agonists (88%), ipratropium bromide (20%), oxitropium bromide (30%), tiotropium bromide (11%), theophylline (69%), and/or inhaled steroids (32%) in varying combinations. Exclusion criteria were current or past diagnosis of asthma and a respiratory tract infection in the previous 3 months. Patients with cancer, thyroid disease, severe liver disease, and chronic heart failure were also excluded. Patients with a history of GI hemorrhage or blood loss of any other cause and patients with a known vitamin B₁₂ or folic acid deficiency were also not enrolled.

Anemia was defined by hemoglobin levels < 13.5 mg/dL in male patients and < 12.0 mg/dL in female patients. Weight loss was defined by involuntary loss of > 7.5% of body mass in 6 months. For comparison, healthy control subjects of similar age and gender distribution were recruited.

The study was approved by the local ethics committee of the University Hospital Charité, Berlin. All patients gave informed consent.

**Pulmonary Function Testing**

FVC and FEV₁ were measured with standard spirometric techniques (Masterlab; Jaeger; Wurzburg, Germany). All values obtained were related to age and gender and were expressed as a percentage of their predicted values.

**Biochemical Analysis**

The inflammatory parameters interleukin (IL)-6 (sensitivity, 5 pg/mL), IL-8 (sensitivity, 5 pg/mL), and IL-10 (sensitivity, 5 pg/mL) were analyzed by enzyme-linked immunoassay using commercially available kits (R&D Systems; Minneapolis, MN). Erythropoietin was quantified by a chemiluminescence assay (sensitivity, 0.24 U/L) [DPC; Bad Nauheim, Germany].

Blood cell counts, hemoglobin, and C-reactive protein (CRP) were measured in automated systems in the routine hospital laboratory.

**Blood Sampling**

Peripheral venous blood samples were collected between 9 AM and 10 AM, after a fasting period of ≥ 12 h and a ≥ 10-min supine rest. After immediate centrifugation, aliquots were stored at −70°C until analysis.

**Statistical Analysis**

Results are given as mean ± SEM. To analyze relationships between variables, Student t test and simple regression analyses were performed (StatView 4.5; Abacus Concepts; Berkeley, CA). Variables that are not normally distributed were log-transformed for statistical analyses (median and interquartile range [IQR] are reported for these variables); p < 0.05 was considered significant.

**RESULTS**

**Prevalence and Characteristics of Anemia**

According to the definition of anemia in this study (hemoglobin concentration in men < 13.5 mg/dL; hemoglobin concentration in women < 12.0 mg/dL), 13 of 101 COPD patients were anemic, which represents a prevalence of anemia of 13%. Anemia appeared as normochromic and normocytic. In a subgroup of nine anemic patients, erythropoietin was measured and appeared to be higher in the anemic group compared to nonanemic COPD patients and normal control subjects (p < 0.05) [Table 1].

**Characteristic of Anemic and Nonanemic COPD Patients in Comparison to Normal Control Subjects**

The main characteristics of the study population are shown in Tables 1, 2. Compared to nonanemic patients, COPD patients with anemia did not show a

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**Table 1—Prevalence and Characteristics of Anemia in COPD Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>All COPD (n = 101)</th>
<th>Control Subjects (n = 15)</th>
<th>p Value, Control vs All COPD</th>
<th>Nonanemic COPD (n = 88)</th>
<th>Anemic COPD (n = 13)</th>
<th>p Value, Anemic vs Nonanemic COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.4 ± 0.2</td>
<td>13.7 ± 0.2</td>
<td>0.2</td>
<td>14.7 ± 0.2</td>
<td>11.9 ± 0.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.43 ± 0.01</td>
<td>0.41 ± 0.01</td>
<td>0.1</td>
<td>0.44 ± 0.01</td>
<td>0.36 ± 0.01</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Erythrocytes/μl/dL</td>
<td>4.76 ± 0.05</td>
<td>4.61 ± 0.08</td>
<td>0.3</td>
<td>4.85 ± 0.05</td>
<td>4.09 ± 0.11</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Erythropoietin, U/L</td>
<td>19.6 ± 4.2 (n = 69)</td>
<td>11.3 ± 1.6</td>
<td>0.4</td>
<td>16.3 ± 2.9 (n = 60)</td>
<td>41.8 ± 25.4 (n = 9)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Log CRP, mg/dL</td>
<td>−0.119 ± 0.069 (n = 91)</td>
<td>−0.804 ± 0.088 &lt; 0.0001</td>
<td>−0.199 ± 0.067 (n = 80)</td>
<td>0.465 ± 0.225 (n = 11)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Median; IQR</td>
<td>−0.097; 1.041</td>
<td>−0.886; 0.355</td>
<td>−0.154; 0.916</td>
<td>0.398; 1.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log IL-6, pg/mL</td>
<td>0.876 ± 0.043 (n = 74)</td>
<td>2.000 ± 0.00 &lt; 0.0001</td>
<td>0.854 ± 0.041 (n = 66)</td>
<td>1.061 ± 0.215 (n = 8)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Median; IQR</td>
<td>0.699; 0.255</td>
<td>0.301; 0.00</td>
<td>0.699; 0.255</td>
<td>0.699; 0.764</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>5.3 ± 0.1 (n = 52)</td>
<td>5.1 ± 0.1</td>
<td>0.4</td>
<td>5.3 ± 0.1 (n = 46)</td>
<td>5.4 ± 0.4 (n = 6)</td>
<td>0.9</td>
</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>4.4 ± 0.4 (n = 64)</td>
<td>5.0 ± 0.0</td>
<td>0.5</td>
<td>4.3 ± 0.4 (n = 54)</td>
<td>5.2 ± 1.6 (n = 10)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Data are shown as mean ± SEM.
decreased appetite score or weight loss. Compared to normal control subjects, COPD patients (anemic and nonanemic) showed decreased appetite ($p < 0.02$) and weight loss ($p < 0.001$). Parameters of pulmonary function (FEV1, FVC, and FEV1/FVC) did not differ between the anemic and nonanemic COPD patients. The parameters of systemic inflammation, IL-6 ($p < 0.0001$) and CRP ($p < 0.001$), were elevated in anemic COPD patients compared to control subjects. Compared to nonanemic patients, CRP was significantly higher in the anemic group ($p < 0.001$), whereas IL-6 did not differ between both groups. Other inflammatory parameters (IL-8 and IL-10) did not show any differences between the groups. Erythropoietin was significantly elevated in the anemic group compared to nonanemic patients (41.8 $\pm$ 25.4U vs 16.3 $\pm$ 2.9L) and normal subjects (41.8 $\pm$ 25.4U vs 11.3 $\pm$ 1.6L) [$p < 0.05$]. No difference in erythropoietin was found between normal subjects and nonanemic patients. The analysis of the disease severity showed no differences in the distribution of COPD severity between the two COPD groups (Table 3). Age, height, and drug therapy were similar between groups ($p > 0.05$; Table 2).

Correlation Analysis

A significant inverse correlation of hemoglobin vs erythropoietin was observed in anemic COPD patients ($r = -0.54; p < 0.01; n = 9$). This correlation was not present in nonanemic COPD patients ($r = -0.14; p > 0.2; n = 60$) [Fig 1]. In the group of all COPD patients, significant inverse correlations were observed between hemoglobin and inflammatory parameters CRP ($r = -0.28; p < 0.01; n = 91$) and IL-6 ($r = -0.23; p = 0.05; n = 74$).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Anemic COPD Patients</th>
<th>Nonanemic COPD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD stage I</td>
<td>3 (23)</td>
<td>20 (23)</td>
</tr>
<tr>
<td>COPD stage II</td>
<td>5 (38)</td>
<td>31 (35)</td>
</tr>
<tr>
<td>COPD stage III</td>
<td>5 (38)</td>
<td>37 (42)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).
Discussion

This study documents that anemia occurs relatively frequently in COPD patients and is related to the presence of inflammation. Anemia is an understudied issue in COPD but may be of great importance in this disease. In our cohort, anemia (with hemoglobin concentrations <12.0 g/dL in women and <13.5 g/dL in men) was present in as many as 13% of all COPD patients. This may be an underestimation of the anemia prevalence, as we have excluded patients with anemia related to bleeding and known folate or vitamin B12 deficiency. Furthermore, anemic COPD patients showed increased levels of erythropoietin compared to nonanemic patients and normal control subjects.

Anemia of chronic illness is typically a normocytic anemia and is most commonly observed in patients with concurrent infectious, and inflammatory or neoplastic diseases. COPD fulfills the criteria of a chronic, inflammatory, multisystemic disease leading to the expectation of anemia. While anemia in chronic heart failure or renal insufficiency has been frequently investigated, it is understudied in COPD.

The mechanism of anemia development in COPD might be similar to that in other chronic diseases. It has been shown that mediators of the immune and inflammatory response, such as tumor necrosis factor-α, IL-6, and interferon-γ are potentially involved in the development of anemia in chronic illness. The increased levels of inflammatory cytokines lead to a shortened RBC survival, with a demand for a slight increase in RBC production. The bone marrow cannot adequately respond to the increased demand for RBCs. This is caused by a relative erythropoietin resistance due to an impaired ability of RBC progenitors to respond to erythropoietin. An impaired mobilization of reticuloendothelial iron stores is an additional pathophysiologic factor.

The observed increased inflammatory response in anemic patients confirms the pathophysiologic understanding of anemia in chronic disease, in that anemia is at least partially due to excessive production of inflammatory cytokines such as IL-6, which inhibit the production and the effect of erythropoietin and iron at the level of the bone marrow. Once anemia has developed, an autoregulatory up-regulation of erythropoietin occurs to maintain the homeostasis. However anemic COPD patients do not respond to increased levels of erythropoietin. The increased levels indicate a relative peripheral erythropoietin resistance in COPD. This is similar to other diseases and fits into the pathophysiology of anemia in chronic disease. The hypothesized relationship of anemia to weight loss and cachexia was not observed in our cohort, indicating that the development of anemia is independent from nutritional factors.

In chronic heart failure, it was demonstrated that the mortality rate correlated with the severity of anemia and that anemia is an independent risk factor for increased mortality. Furthermore, it has been shown that a hemoglobin concentration below the physiologic range is a predictor of exercise limitation and mortality in chronic heart failure. Whether anemia contributes to symptoms or exercise limitations in COPD is presently unknown. However, in our study overall COPD severity according to standard criteria of lung function was not related to frequency of anemia and hemoglobin levels (Tables 1, 3). More studies are needed to study these issues.

The present study is limited by a relative small number of patients. For future investigations, larger study populations are needed. This would allow investigating whether anemia is related to the primary disease process per se or to secondary systemic manifestations such as weight loss, loss of lean tissue mass, hypoxia, or systemic inflammation.

Anemia in COPD is understudied. There are no previous reports on anemia frequency and pathophysiology in COPD. More detailed investigations on hematologic and clinical parameters (ie, prevalence of anemia in COPD and its gender relatedness, exercise capacity, 6-min walk test) and prognosis are required to provide indications whether anemia is merely a marker or a mediator of pathophysiologic processes that may impair physical functioning in COPD. Interventions with erythropoietin and iron supplementation would then seem very promising in order to improve the poor health status and prognosis of patients with COPD.

References

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