

### Anemia in COPD: The Role of Blood Transfusion

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#### **INTRODUCTION**

Anemia occurs in 8-17% of patients with chronic obstructive pulmonary disease (COPD). The type of anemia is classified as an anemia of chronic disease due to the inflammatory state that exists in COPD patients.

It has been proposed that anemia, depending on its severity, due to either COPD itself or other medical conditions affecting these patients may contribute to increased work of breathing and reduced exercise tolerance. However, it is not clear if patients would benefit from a higher hemoglobin threshold for transfusion compared to non-COPD patients. The following is a brief review of the literature on anemia and RBC transfusion in COPD.

#### **ANEMIA IN COPD**

Paradoxically, anemia appears to be more common than polycythemia in patients with COPD. A 2005 retrospective observational study of 2,524 severe COPD patients found that 12.6% of men and 8.2% of women were anemic (hematocrit < 39% in men and < 36% in women), compared to 8.9% of men and 5.9% of women who were polycythemic (Hgb  $\geq$  55%)<sup>1</sup>. In a 2007 retrospective analysis of 677 patients with COPD, anemia (Hgb <13 g/dL) was present in 17.1 % of patients, and polycythemia (Hgb  $\geq$  17 g/dL in males, and  $\geq$  15 g/dL in females) was present in 5.9% of patients<sup>2</sup>. These findings challenge the commonly held view that COPD patients are more likely to become polycythemic due to chronic hypoxia during the course of their disease.

In chronic inflammatory disease states, anemia results from several factors, including a slightly shortened RBC survival, reduced iron utilization, and an impaired bone marrow erythropoietic response. There is good evidence that anemia of

chronic disease occurs in COPD. Patients with COPD have increased peripheral blood CRP, fibrinogen, leukocytes, TNF- $\alpha$ , IL-1 $\beta$  and IL-6, IL-8, MCP (monocyte chemotactic protein)- $\alpha$ <sup>3</sup>. In a 2005 prospective study of 101 patients, in which patients with other causes of anemia were excluded, 13 individuals were anemic and their serum CRP was higher than the non-anemic patients and control subjects<sup>4</sup>. This study showed an inverse correlation between hemoglobin level and the inflammatory markers CRP and IL-6. The same study also showed that the erythropoietin level was higher in the anemic patients, suggesting erythropoietin resistance, a characteristic feature of anemia of chronic disease.

#### **DISEASE SEVERITY**

COPD is a common co-morbidity in hospitalized patients, and the anemia in COPD patients is relatively mild. Most studies have shown an association between anemia and disease severity in COPD. One study of severe COPD patients found that hematocrit negatively correlated with forced expiratory volume at one second (FEV<sub>1</sub>)/vital capacity (VC) and FEV<sub>1</sub> percentage of predicted<sup>1</sup>. Another study showed a linear relationship between declining hemoglobin level in COPD patients compared with dyspnea score and six-minute walk distance (6MWD)<sup>2</sup>. However, a third study did not find a difference in pulmonary function between anemic and non-anemic COPD patients<sup>4</sup>.

#### **CLINICAL OUTCOMES**

Few studies have looked at clinical outcomes in COPD patients with anemia. One retrospective study showed that the hematocrit negatively correlated with rate and duration of hospitalizations. In this study, the 3-year survival ranged from 24% for patients with hematocrit of <35%

to 70% in patients with a hematocrit  $\geq 55\%$ <sup>1</sup>. Another retrospective study showed that anemic patients had a significantly shorter survival (49 mo.) compared to non-anemic patients (74 mo.) using the Cox statistical model; however, anemia was not a significant independent predictor of mortality by multivariate analysis<sup>2</sup>.

### **RBC TRANSFUSION**

There is very limited data regarding RBC transfusion in COPD patients with anemia, however one German group has looked at this question. They published a small, prospective study in 1998, including 20 patients with anemia ( $<11.0$  g/dL), 10 of which had severe COPD, and 10 without lung disease<sup>5</sup>. The transfusion protocol was comprised of transfusing one unit of RBCs per gram of hemoglobin  $< 11.0$  to  $12.0$  g/dL, with no more than three units given over 24 hours, with a goal hemoglobin of  $\geq 12.0$  g/dL. They found that in COPD patients, there were significant post-transfusion improvements compared to baseline for minute ventilation ( $V_E$ ) (9.9 to 8.2 L/min) and work of breathing (WOB) (1.03 to 0.85 WOB/L). Anemic patients without lung disease showed no changes in  $V_E$  or WOB after transfusion. A second study performed by the same group in 1997, available in English only in abstract form, examined 21 patients with anemia (Hgb  $< 11.0$  g/dL), including 15 patients with pulmonary disease and six patients without pulmonary disease, all receiving two to three RBC units within 8 hours<sup>6</sup>. They found that the patients with lung disease developed a 20% post-transfusion reduction of  $V_E$  and an unspecified reduction in WOB. Although the findings in these two studies are intriguing, the sample sizes are small and other institutions have not replicated these findings. The multicenter, randomized, controlled trial by Hebert, et al., where critically ill patients were randomized to "conservative" or "liberal" RBC transfusion thresholds of 7.0 g/dL or 9.0 g/dL, found that mechanical ventilation use was not different between the two groups ( $p=0.77$ )<sup>7</sup>. Although this study did not analyze COPD patients specifically, the majority of their patients required mechanical ventilation. They found that anemic patients with acute respiratory failure transfused using the lower hemoglobin threshold did not require more mechanical ventilation (outcome measures included duration of mechanical ventilation, the number of ventilator-free days, or time necessary to

successfully wean patients from ventilator support)<sup>8</sup>.

### **SUMMARY**

Anemia of chronic disease is relatively common in COPD. There is emerging data suggesting that anemia may be associated with increased disease severity, and perhaps mortality, in COPD. Although the findings in these retrospective analyses are intriguing, additional prospective studies need to be performed before the clinical impact of anemia in COPD can be fully established. There is very limited data regarding RBC transfusion in COPD patients with anemia. Whether a more aggressive hemoglobin threshold for RBC transfusion in COPD patients provides clinical benefit, should be looked at in larger, prospective studies. However, there does not appear to be evidence that warrants a change in the transfusion "trigger" for these patients at the present time.

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