Review

Anemia in Heart Failure—A Concise Review

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Summary: Heart failure affects 5 million persons in the United States, with 400,000 new cases occurring every year. Paradoxically, although advances in coronary angioplasty and effective drugs have increased survival post infarction, the myocardial damage and subsequent neurohormonal activation-induced remodeling causes significant morbidity years later in the form of heart failure. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) together with beta blockers modify the neurohormonal activation associated with heart failure and are key treatments for improving cardiac function and survival. Anemia is a significant risk factor predicting morbidity and mortality in heart failure. This article describes the various etiologies of anemia in heart failure. Of particular importance is the fact that recent stem cell studies have shown that the drugs acting on the renin-angiotensin system inhibit erythropoiesis in vivo and may cause anemia in patients with both normal renal function and end-stage renal disease (ESRD). The role of angiotensin-II as an erythropoietic growth factor and ACE in facilitating erythropoiesis is described in this article. Anemia has been shown to be a modifiable risk factor and its treatment correlates with improvement in clinical outcomes. Thus, anemia, its etiology (especially the contribution of ACEIs and ARBs), physiologic and prognostic impact, and treatment in the setting of heart failure are critical areas for investigation.

Key words: anemia, heart failure, angiotensin-II

Prevalence of Anemia Literature Review

The prevalence of anemia varies depending on the population studied (proportion of patients in class IV heart failure) and the definition of anemia used in the study. The strength of evidence illustrating the prognostic significance of anemia is good (level II—evidence is obtained from at least one well-designed randomized study). Tables I and II describe the study design and the varying prevalence of anemia depending on the definition of anemia used in the study. Table III describes anemia as a prognostic factor in predicting morbidity and mortality in heart failure and the strength of the observed association.^{1–6}

Consequences of Anemia

Anemia at levels between 10 and 12 g/dl causes an increase in exercise cardiac output. This results in an increased preload, wall stress, and left ventricular (LV) work, which in turn increases oxygen consumption and accelerates myocyte loss.⁷ The hypoxia at the tissue level and decreased blood viscosity cause arterial vasodilatation, which decreases afterload. A chronic volume-overload state induced by anemia causes the addition of myofibrils in series and the lengthening of myofibrils causing ventricular dilation and an increase in wall tension. This allows for an increase in stroke output by attaining a higher point in the Starling's curve. These processes might explain why anemia is deleterious to an ischemic or a failing heart.⁷

Etiologies of Anemia in Heart Failure

There have been a few studies of the etiologies of anemia in heart failure. Ezekowitz *et al.*⁵ used International Classification of Diseases (ICD) codes to identify anemia and reported that 58% of the anemic patients had anemia of chronic disease. Further data about the prevalence of other types of anemia are lacking in the literature.

Role of Cytokines

Tumor necrosis factor (TNF)- α has been implicated in the etiology of anemia of chronic disease. It blunts the erythropoietin (EPO) response to anemia by inhibiting the production

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TABLE I Trial designs of the various studies evaluating anemia in heart failure

Investigator	Study design
Al-Ahmad <i>et al.</i> ¹ SOLVD (Studies of Left Ventricular Dysfunction)	Retrospective analysis of 6,797 patients with an EF of $\leq 35\%$, enrolled in a multicenter randomized placebo-controlled double-blind trial
McClellan <i>et al.</i> ²	Retrospective study of randomly selected 665 Medicare patients with heart failure, recruited using ICD codes
Mozaffarian <i>et al.</i> ³ PRAISE (Prospective Randomized Amlodipine Survival Evaluation)	Prospective cohort analysis of 1,130 patients enrolled in a multicenter randomized trial of men and women with EF $< 30\%$ and NYHA class IIIB or IV heart failure
Horwich <i>et al.</i> ⁴	Prospective analysis of 1,061 patients in NYHA class III or IV and LVEF $< 40\%$ referred for heart transplantation in a single center
Ezekowitz <i>et al.</i> ⁵	Retrospective analysis of a population-based cohort of 12,065 patients with heart failure recently diagnosed and those who were hospitalized for heart failure for the first time; ICD codes were used to identify heart failure.
Kalra <i>et al.</i> ⁶	Prospective analysis of 93 heart failure patients, mostly men.

Abbreviations: EF = ejection fraction, ICD = implantable cardioverter defibrillator, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction.

TABLE II Varying prevalence depending upon the definition of anemia

Investigator	Definition	Prevalence
Al-Ahmad <i>et al.</i> ¹ SOLVD	Hct ≤ 39	Hct ≤ 39 : 22% Hct < 35 : 4.3%
McClellan <i>et al.</i> ²	Hct ≤ 39	Hct 36–39: 22.9% Hct 30–35: 33.2% Hct < 30 : 13.6%
Mozaffarian <i>et al.</i> ³ PRAISE	Lowest quintile—25.9–37.5% Highest quintile—46.1–58.8%	Prevalence was not studied
Horwich <i>et al.</i> ⁴	Hgb < 13 g/dl—men Hgb < 12 g/dl—women	30% were anemic
Ezekowitz <i>et al.</i> ⁵	ICD codes for anemia and anemia of chronic disease	17% had anemia, of whom 58% had anemia of chronic disease.
Kalra <i>et al.</i> ⁶	Hgb < 13 g/dl Hgb was analyzed in 4 quartiles	39% of patients were anemic

Abbreviations: Hgb = hemoglobin, Hct = hematocrit. Other abbreviations as in Table I.

and proliferation of erythroid progenitors. This has been studied in patients with cancer, rheumatoid arthritis, and other chronic infections. In a well-designed study, Iversen *et al.*⁸ have looked at the possible role of TNF- α in the anemia seen in mice with ischemic cardiomyopathy. Ligation of one of the coronary arteries was performed and ischemic cardiomyopathy was induced in a cohort of mice and studied in comparison with sham-operated mice. This was the first study to implicate TNF- α as contributing to anemia in heart failure and clearly outlines the pathogenesis of cytokine-induced anemia. In the mice with ischemic cardiomyopathy, both the circulating levels of TNF- α and the local expression of TNF- α /Fas protein in

the bone marrow were increased compared with sham-operated mice as demonstrated by increased TNF- α messenger ribonucleic acid (mRNA) in the T cells and natural killer cells of the bone marrow. The following observations in the heart failure mice were noted: decreased number of erythroid progenitor cells, inhibited proliferation of CD 34+ cells (which are early noncommitted progenitors), and enhanced Fas-induced apoptosis of CD 34+ cells. The T cells and natural killer cells from the mice with heart failure induced in vitro apoptosis of CD 34+ cells obtained from intact syngenic mice. These adverse effects were demonstrated exclusively in mice with ischemic cardiomyopathy.

TABLE III Studies about the profile of anemia in heart failure and its association with mortality and morbidity

Investigator	Profile	Association
Al-Ahmad <i>et al.</i> ¹ SOLVD	Anemic patients were more likely to be older, women, non-white, NYHA class III or IV, and diabetic	A 1% lower Hct was associated with a 1.027 (95% CI: 1.015, 1.038) higher relative risk for mortality; anemia and low GFR were found to be independent risk factors for predicting morbidity and mortality in heart failure
McClellan <i>et al.</i> ²	Anemic patients were more likely to be older	Compared with individuals with an Hct $\geq 40\%$, the RR (95% CI) at 1 year for anemic patients was 1.08 (.79–1.47) for Hct 36–39%; 1.17 (0.89–1.54) for Hct 30–35%; 1.60 (1.19–2.16) for Hct $\leq 30\%$
Mozaffarian <i>et al.</i> ³ PRAISE	Higher Hct was associated with younger age, male gender, more prevalent smoking, slightly lower EF, and higher blood pressure	Over a range of Hct between 25.4 and 37.5, each 1% decrease in Hct was associated with a 11% higher risk of death (HR 1.11, 95% CI: 1.02–1.20, $p < 0.01$) and an 8% higher risk of pump failure deaths (HR 1.08, 95% CI: 1.05–1.12) Compared with the highest quintile (46.1–58.8%), the patients in the lowest quintile (25.4–37.5%) had a 52% higher risk of death
Horwich <i>et al.</i> ⁴	Anemic patients were more likely to be women, in NYHA class IV, have lower albumin, lower BMI, impaired renal function, lower blood pressure, higher heart rate, and higher right-sided pressures	On univariate analysis, each 1 g/dl decrease in Hgb was associated with a 16% increased risk of death; on multivariate analysis, each 1 gm decrease in Hgb was associated with a 13% increased risk of mortality (RR 1.1, CI: 1.045–1.224)
Ezekowitz <i>et al.</i> ⁵	Anemia was more common in older patients, in women, and in patients who were hypertensive or had chronic renal insufficiency	1 and 5 year mortality was 38 and 59% in patients with anemia, respectively, compared with 27% and 50% for those without anemia ($p < 0.0001$); Cox proportional hazard ratios for mortality in anemic patients was 1.34 (1.24–1.46)
Kalra <i>et al.</i> ⁶	Anemic patients were more likely to be older, and have higher creatinine, lower peak VO ₂ , and severe symptoms; no significant difference in LVEF between the patients who were and were not anemic	Peak VO ₂ decreased significantly with decreasing Hgb levels; R: 0.41, $p < 0.014$; hemoglobin was an independent predictor of peak VO ₂ max, independent of age, EF, and serum creatinine

Abbreviations: CI = confidence interval, GFR = glomerular filtration rate, RR = relative risk, HR = high risk, VO₂ = peak oxygen consumption, BMI = body mass index. Other abbreviations as in Tables I and II.

Stem Cell Studies

Over the past 6 years, the possibility of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) causing anemia has been validated by stem cell studies (bone marrow and cord blood cells) which have unequivocally demonstrated that angiotensin II (AT II) actively stimulates erythropoiesis by increasing the proliferation of erythroid progenitors. This effect of AT II is receptor mediated as shown by the abolition of this EPO effect by losartan.^{9–11} Two studies^{10, 11} utilizing stem cells confirmed that a minimal concentration of EPO was required for the stimulatory effect of AT II on erythropoiesis. Rodgers *et al.*⁹ confirmed the role of AT II as a stimulator of the early stages of erythropoiesis and also demonstrated the presence of mRNA for AT II receptors in

erythroid progenitors. Naito *et al.*¹¹ reported that burst-forming unit-erythroid precursors had receptors for AT II. Another study in which AT II infusion significantly increased EPO levels also demonstrated that this increase was abolished by losartan.⁹ This suggests that the AT II effect on erythropoiesis is receptor mediated. Animal studies involving ACE knock-out mice showed that the anemia observed in these mice improved with the infusion of AT II, further confirming the role of AT-II as an EPO growth factor.¹² Stem cell studies have examined the role of ACEI in erythropoiesis. The endogenously produced physiologic inhibitor of erythropoiesis, Ac-SDKP (N-acetyl seryl-aspartyl-lysyl-proline) is degraded by ACE. Comte *et al.*¹³ showed that enalapril increased plasma and urinary AcSDKP levels 2–5 fold and decreased the number of erythroid progenitors (burst-forming units-erythroid).

Cross Talk between Renin-Angiotensin and Erythropoietin Systems

Activation of the renin-angiotensin system (RAS) may also cause an increase in EPO production.^{14, 15} Studies have also suggested that a local bone marrow angiotensin system exists and is inhibited by ACEIs and ARBs.^{16, 17}

Angiotensin-converting enzyme inhibitors can cause anemia by a variety of other mechanisms apart from the decreased production of AT II. This is important because of AT II escape with chronic ACE inhibition through CAGE (chymostatin-sensitive angiotensin-II generating enzyme) and chymase pathways.^{18, 19} These enzymes are an alternate pathway for generating angiotensin-II and are present in cardiac interstitium and vascular adventitium, whereas ACE is present in endothelial cells. The RAS and EPO production are closely linked to each other through common signal transduction pathways. Studies have shown that AT II and EPO have the same second messengers (Jak STAT signal transduction system) required for their effect on different stages of erythropoiesis and thus “cross talk” with each other.^{12, 14, 20}

Clinical Studies

The connection between RAS and erythropoiesis has been observed in animal studies¹² and has been confirmed in clinical studies involving patients on hemodialysis^{11, 21} and in renal transplant recipients.^{20, 21} These adverse hematopoietic effects of ACEIs/ARBs have been utilized successfully in the treatment of post kidney transplant erythrocytosis that is partly caused by the release of EPO from the native/transplanted kidneys and partly due to the increased expression of AT 1 receptors.^{20, 22, 23} Studies in patients undergoing dialysis have shown that the withdrawal of ACEIs caused a rebound increase in Hct to the extent of alleviating the need for EPO in several patients.²¹

Two case reports have shown that ARBs have reduced hematocrit in individual patients with polycythemia vera, secondary erythrocytosis of chronic obstructive pulmonary disease^{24, 25} and post renal transplant erythrocytosis. Researchers have disagreed as to whether ACEIs/ARBs decrease or increase EPO levels and whether they cause EPO resistance.^{14, 15} Although the data on the effect of ACEIs/ARBs on EPO levels are controversial, it is reasonable to assume that RAS affects erythropoiesis by EPO and non-EPO-related mechanisms in patients with normal renal function, renal replacement therapies, and renal transplants. The magnitude of reduction in the hematocrit was in the range of 6–10% and the treatment time needed to observe this effect was 3–6 months.

Hemodilution

In a study by Androne *et al.*²⁶ of 196 patients with advanced heart failure referred for heart transplantation, hypervolemia was observed in a group of patients with clinically euvolemic heart failure. The prevalence of hypervolemia was 33% in class II and 60% in class III patients. Hypervolemia was

assessed initially with plasma volume determinations, using radio-labeled albumin and was confirmed in one-third of the patients by right-sided cardiac catheterization. This study raises the possibility of volume overload causing anemia due to hemodilution. Volpe *et al.*²⁷ also confirmed this possibility by noting the elevated levels of plasma atrial natriuretic peptide and higher plasma volume in patients in New York Heart Association (NYHA) class IV. Volpe *et al.* studied the EPO levels in all classes of heart failure. The EPO levels in class I were normal and comparable with those of control subjects without any cardiac disease. However, the EPO levels rose with the class of heart failure, with patients in class IV showing 10 times greater EPO levels than those in class I. Plasma volume and red cell volume measured by a radioactive albumin-labeling technique were found to be increased in class IV compared with class I heart failure.

Adrenergic Activation

Renal sympathetic innervation has been shown to be closely related to EPO regulation. Patients afflicted with disorders of autonomic dysfunction have normochromic, normocytic anemia.²⁸ The mechanisms of anemia due to autonomic dysfunction have been examined by Ando *et al.*²⁹ in chemically sympathectomized rats with 6-hydroxydopamine, a neurotoxic agent (6-OHDA) in comparison with control rats. In this experiment, reversal of chemical sympathectomy was done by giving desipramine to 6-OHDA-treated rats. This study found that chemically sympathectomized rats had normochromic normocytic anemia, decreased EPO response to blood letting, and significant decrease in beta receptors on the surface of erythrocytes. Beta blockers are the standard of care in patients with heart failure. It is possible that there might be a cross talk between the adrenergic and the RAS systems via renin release. Lack of adrenergic activation due to use of beta blockers may have a negative effect on erythropoiesis and may contribute to the development of anemia in heart failure.

Anemia as a Modifiable Risk Factor

Silverberg *et al.*^{30, 31} and Mancini *et al.*³² have utilized erythropoietin in various classes of heart failure and have demonstrated favorable outcomes in randomized open-label studies. Silverberg *et al.* report that correction of anemia with subcutaneous EPO/intravenous (IV) iron from 10 to 12 g/dl in class IV patients was associated with a significant improvement in functional class and ejection fraction, and reduced the need for oral and IV diuretics. Silverberg *et al.* demonstrated this in diabetics with severe heart failure and mild anemia who were already on standard therapy (ACEI, diuretics). Mancini *et al.* showed that class IV patients given EPO with oral iron and folate to achieve a target hematocrit of 45% showed significant increase in peak oxygen uptake and exercise duration.

There is clearly a need for further trials studying the causes and consequences of anemia in heart failure, including the effects of beta blockers, ACEIs, and ARBs. Interventional stud-

ies clarifying and addressing the mechanisms of hypervolemia and suppression of erythropoiesis are needed to determine both the appropriateness of treatment of anemia in heart failure and the consequent improvement in outcomes.

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