REVIEW

CME CREDIT

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Anemia in chronic heart failure: Can EPO reduce deaths?

ABSTRACT

Many patients with chronic heart failure also have anemia, an association that has been increasingly recognized in recent years. Whether treating anemia will improve outcomes in patients with heart failure has yet to be determined, however. The decision to use an agent to treat anemia in heart failure should be made on a case-by-case basis.

KEY POINTS

Anemia in heart failure is likely multifactorial, with causes that include renal insufficiency, hemodilution, bone marrow suppression due to inflammation, and side effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Anemia can propagate and worsen heart failure by reducing oxygen-carrying capacity, forcing the heart to adapt by increasing its rate and stroke volume.

Treatment with recombinant human erythropoietin (EPO) has undergone trials with the intention of not only ameliorating the underlying anemia but also improving the signs and symptoms of heart failure. Though the results have been encouraging, EPO has side effects, and the initial studies were limited in size, thus leaving the question of potential treatments open for further study.

CAN WE REDUCE the mortality rate in heart failure by looking for and treating anemia?

Improvement is needed in treating heart failure. Eighty percent of men and 70% of women younger than 65 years who have heart failure die within 8 years. Angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, aldosterone antagonists, and angiotensin receptor blockers (ARBs) have become the foundation of maintenance therapy,[1–6] but even though they have attenuated the mortality rate to some degree, it remains high. Furthermore, the incidence of heart failure is increasing.

Thus, researchers are looking for alternative factors contributing to the underlying disease process that might be targets for therapy. One particular condition, anemia, has increasingly been found to be a comorbid condition in patients with heart failure and has emerged as a potential area for research.

NEUROHORMONES AREN'T EVERYTHING

The field of heart failure research is littered with trials of agents such as tumor necrosis factor and others that have not lived up to their initial billing.[7–10] These frustrating results have led to a reevaluation of our current understanding of the now-infamous neurohormonal cascade of heart failure, with the notion that alternative pathways may also need to be examined.[11]

The renin-angiotensin-aldosterone pathway is still integral to our understanding of the pathogenesis of heart failure, and effects of this pathway on other systemic processes are being investigated. However, it is also impor-

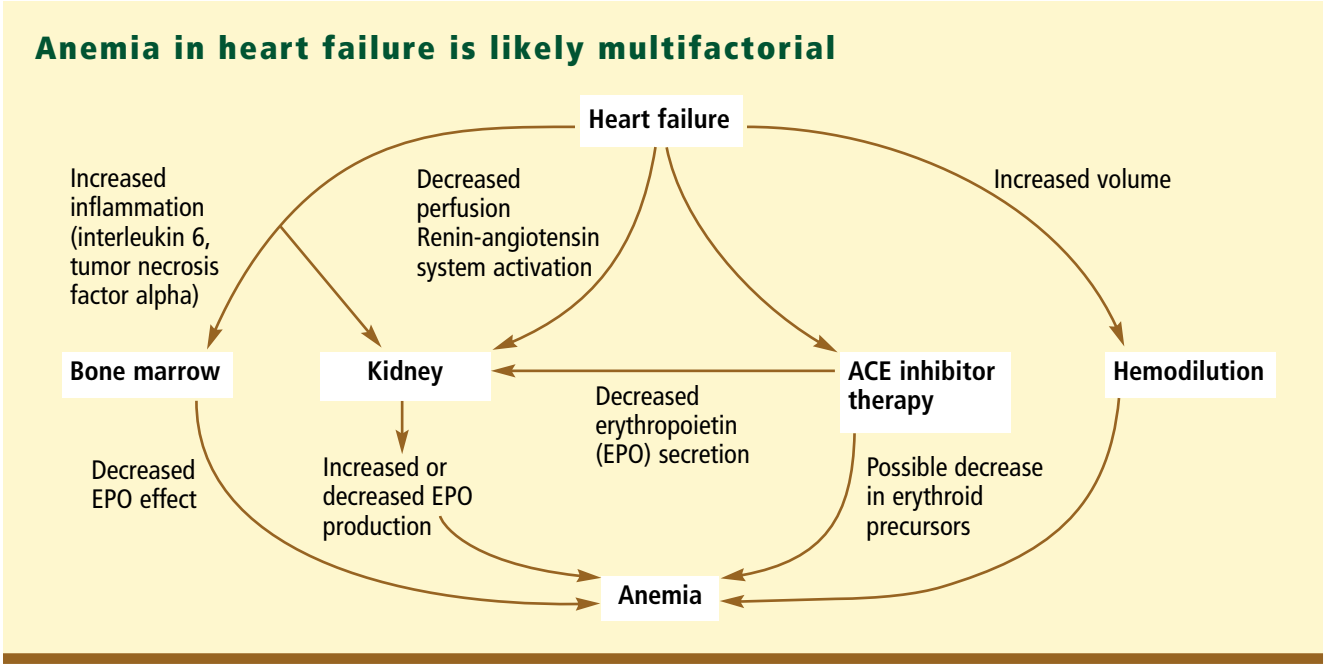

FIGURE 1

tant to study other comorbid conditions, such as anemia, and their relation to the pathophysiology of heart failure.

The exact prevalence of anemia in patients with heart failure is still open to debate, with reports ranging from 10% to 50%, but there is substantial evidence that these two disease processes tend to coexist.[12,13] Indeed, not only has anemia been linked to chronic heart failure, it has emerged as an independent risk factor portending poorer outcomes and decreased functional class.[14–18]

EPO levels can be low or high in anemic patients with heart failure

Anand et al[19] retrospectively analyzed data from the RENAISSANCE trial, which included 912 patients with heart failure. They found an inverse correlation between hemoglobin levels and left ventricular mass and mortality, corroborating the findings of previous studies.[14–18]

SEVERAL MECHANISMS OF ANEMIA

Anemia in heart failure is most likely multifactorial (FIGURE 1), involving renal insufficiency, chronic systemic inflammation with subsequent bone marrow dysfunction, side effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and hemodilution.

Renal insufficiency due to chronic hypoperfusion has been closely linked to the development of anemia in patients with heart failure.[20]

Of interest is that erythropoietin (EPO) levels can be either low or elevated in patients with chronic heart failure.[21] One would expect EPO levels to be low in a patient with anemia. The kidneys might be able to compensate for decreased oxygen delivery and thereby attenuate EPO production through intrinsic mechanisms (with a resultant increase in medullary oxygen supply), but this mechanism may have only a transient effect.[22] Persistently low renal perfusion induced by heart failure can stimulate the peritubular fibroblasts of the renal cortex to increase activation of hypoxia-inducible factor-1 and EPO gene expression.[23] Continuing anemia despite high EPO levels suggests a possible resistance to the effect of this growth factor.

Inflammation leading to bone marrow dysfunction. Heart failure is often thought of as a state of chronic inflammation.[24] Inflammatory cytokines such as tumor necrosis factor alpha and interleukin 6 have been associated with the pathogenesis of heart failure and are also thought to have a major deleterious impact on other systemic processes.[25]

The inflammatory state in heart failure can eventually lead to reduced EPO production in the kidneys and interfere with its activity in the bone marrow. In addition, use of iron stores for hemoglobin production is also hampered.[26] This in turn can lead to further deterioration of cardiac function, as the heart tries to compensate for the worsening anemia. Silverberg et al[27] coined this downward spiral "the cardio-renal-anemia syndrome" as a testament to the varied systemic interactions that produce these pathologic changes.

ACE inhibitors and ARBs. ACE inhibitors, the leading medications implicated in causing anemia in heart failure, have been linked to anemia in a variety of clinical conditions, from healthy people to those with renal insufficiency and heart failure.[28–30] Although the mechanism is still not clearly understood, current explanations revolve around the possible inhibition of erythroid precursor growth by both ACE inhibitors and ARBs.[31]

Ishani et al[32] recently found that patients with heart failure and normal hematocrits who received enalapril had an increased incidence of anemia in 1 year. Nevertheless, enalapril recipients had a higher overall survival rate, even if they developed anemia.

The subject of ACE inhibitor use and anemia, as well as the clinical significance of this possible relationship, is controversial and warrants further analysis before any definitive conclusions can be made.

Hemodilution can also produce the clinical scenario of anemia. Although one might think that a dilutional effect in heart failure would cause an anemia with normal red blood cell indices, there is clinical evidence that a decrease in red blood cell mass is just as likely (if not more so) in patients with heart failure and anemia.[33] Both scenarios, however, are still associated with a poor prognosis.

Other factors that can cause or contribute to anemia in heart failure include blood loss from the gastrointestinal tract, iron deficiency, and hemolysis. Patients should undergo a thorough evaluation for these potentially reversible conditions.

CONSEQUENCES OF ANEMIA

Anemia can propagate and worsen heart failure by reducing oxygen-carrying capacity, forcing the heart to adapt by increasing its rate and stroke volume. These compensatory responses can provide only so much hemodynamic support, and are even more limited in a heart that is already failing.[34] The exact mechanism by which anemia contributes to the pathogenesis of heart failure needs further clarification.

TREATING ANEMIA: FURTHER STUDY NEEDED

With the aforementioned evidence associating anemia and heart failure with poor survival outcomes, a logical approach would be to correct the anemia.

Transfusions: Not practical in the long term

Transfusion of packed red blood cells, the most common method of correcting anemia in the hospital, is fraught with problems that could further complicate a heart failure patient's clinical course. Although packed red blood cells can temporarily raise the hematocrit and are appropriate temporizing measures, they are rarely practical for long-term management in this population because they increase the intravascular volume, can cause infections, and are costly.

The issue of ACE inhibitor-associated anemia remains controversial and needs more study

Erythropoietin

Recombinant human EPO acts by inhibiting the apoptotic process of erythroid precursors in the bone marrow, resulting in increased formation and proliferation of erythroid cell lines.[35] It has been in clinical use for nearly 20 years, initially in patients with chronic kidney disease,[36] in whom it has been proven not only to boost the hematocrit but also to improve cardiac structure and function, including reducing left ventricular hypertrophy and increasing ejection fraction.[37]

Studies of EPO use in heart failure have been encouraging, but have been limited by size and design.

Silverberg et al[38] tested the effects of subcutaneous EPO and intravenous iron sucrose in a trial in patients with severe, chronic heart

TABLE 1

Advantages and disadvantages of erythropoietin treatment

Advantages
- Increases hemoglobin level
- Increases peak oxygen consumption max
- Improves functional class
- Decreases ventricular remodeling

Disadvantages
- Increases hypertension
- Increases thrombosis
- Increases endothelin activation
- Is expensive

failure, renal insufficiency (mean creatinine 2.1–2.4 mg/dL), and anemia (hemoglobin 9.5–11.5 g/dL). Patients improved significantly in New York Heart Association (NYHA) functional class, their ejection fractions increased, and they needed fewer hospitalizations. The changes were more profound in the patients with diabetes.

The same investigators also reported results from two earlier trials of EPO and iron therapy in patients with heart failure and anemia; both studies involved patients in NYHA classes III and IV with anemia (hemoglobin < 12 g/dL in the first and < 11.5 g/dL in the second).[39,40] Although the treated patients improved in functional class, hemoglobin levels, and ejection fraction and needed fewer hospitalizations in each study, the studies were limited by their relatively small size (n = 26 and 32, respectively) and design.

The ideal target hemoglobin level for patients with heart failure is not yet known

Mancini et al[41] performed a single-blind, randomized, placebo-controlled study to examine the effects of EPO treatment and oral iron supplementation on exercise capacity in patients with chronic heart failure. The hemoglobin concentration increased from 11 ± 0.5 g/dL at baseline to 14.3 ± 1.0 g/dL in the treatment group but not in the placebo group ($P < .05$). Peak oxygen consumption also increased in the treatment group but not in the placebo group, and the increases in the two variables were significantly correlated ($P < .02$).

Although this study supports the use of EPO in heart failure and was designed appropriately, the sample size, like those in the previously mentioned trials, was small, thus limiting any major conclusions about therapeutic changes in this population.

Darbepoietin alfa, a newer EPO analogue, is being investigated for its effectiveness and safety in treating anemia in heart failure. It has a long half-life (48 hours), and can be given at less-frequent intervals than recombinant human EPO.[42]

Caveats

Although correcting any underlying anemia in patients with heart failure would seem to be a worthwhile goal, caution is needed before fully embracing this concept. EPO can have adverse side effects and is expensive, costing about $6,000 per year (TABLE 1). Indeed, it has been associated with worsening hypertension,[43] thrombotic events,[44] and endothelin activation[45] in patients with end-stage renal disease.

Besarab et al[46] examined the use of EPO and iron dextran in patients with end-stage renal disease and heart disease. The patients who received doses of EPO to maintain a hematocrit of 42% had a trend of higher mortality rates compared with the patients who received a lower dose (with a goal of maintaining a hematocrit of 10%). Nevertheless, overall mortality rates for patients in each group decreased with increasing hematocrit levels. The authors explained this paradox as possibly being due to the increased amount of iron dextran infused to the patients in the "normal" hematocrit group, and the resultant side effects of iron therapy.

The ideal target hemoglobin level for patients with heart failure is not currently known. Inconclusive studies, as previously discussed, have drawn into question the validity of pharmacologically normalizing the hematocrit of a patient with heart disease.

The decision to use an agent to treat anemia in patients with heart failure should be made on a case-by-case basis, recognizing concomitant disease processes that might confound the clinical picture (eg, hemodilution). Until further large-scale investigations are completed, it would be rash and potentially detrimental to patient care to deem any new therapy as a primary choice of treatment.

Trials of therapies aimed at ameliorating both anemia and cardiac disease have been

promising but small. In addition, these medications are costly and can cause their own side effects. With the evident plateau of effective new remedies targeting the currently accepted pathways of heart failure, the potential of approaching this deleterious disease process from an alternate route can be viewed as an exciting, albeit investigational, option for the future.

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