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-

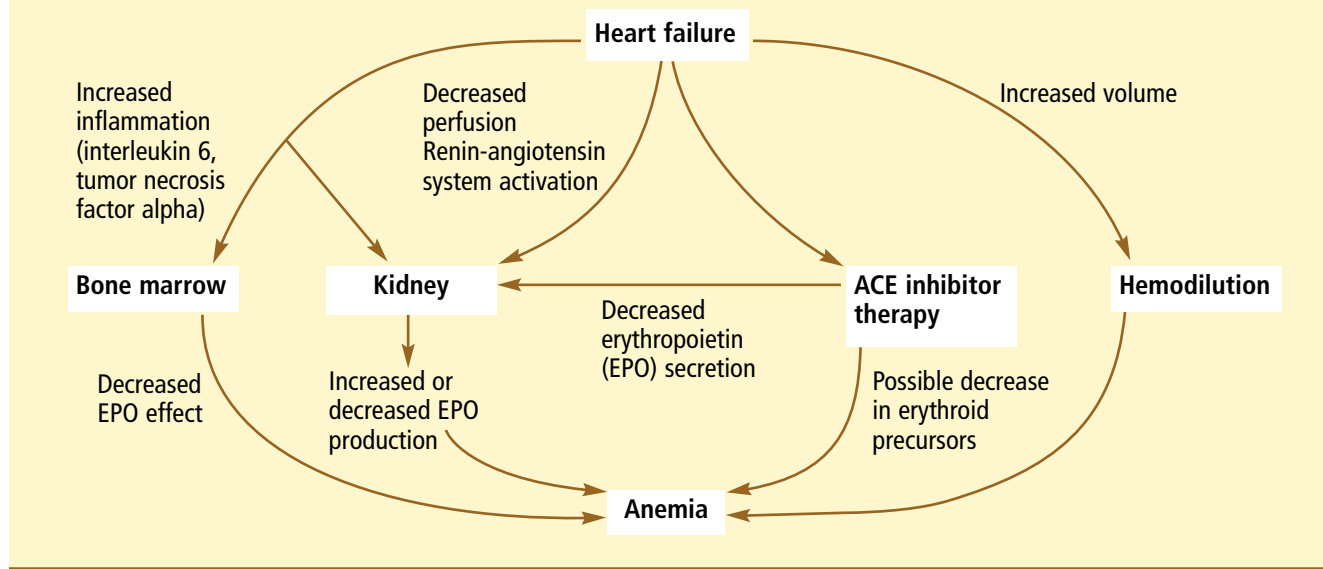**Anemia in heart failure is likely multifactorial**

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]

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.

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

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

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

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

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.

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 pre-

viously 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. ◼

◼ REFERENCES

1. **Cohn JN, Johnson G, Ziesche S, et al.** A comparison of enalapril with hydralazine isosorbide dinitrite in the treatment of chronic congestive heart failure. N Engl J Med 1991; 325:303–310.
2. **Packer M, Bristow MR, Cohn JN, et al.** The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996; 334:1349–1355.
3. **Packer M, Coats AJS, Fowler MB, et al.** Effect of carvedilol on survival in severe chronic heart failure. Carvedilol Prospective Randomized Cumulative Survival Study Group. N Engl J Med 2001; 344:1651–1658.
4. **Hjalmarson A, Goldstein S, Fagerberg B, et al.** effects of controlled release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). JAMA 2000; 283:1295–1302.
5. **Pitt B, Zannad F, Remme WJ, et al.** The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341:709–717.
6. **Cohn JN, Tognoni G.** A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001; 345:1667–1675.
7. **Packer M, Califf RM, Konstam MA, et al.** Comparison of omapatrilat and enalapril in patients with chronic heart failure. The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002; 106:920–926.
8. **Louis A, Cleland JG, Crabbe S, et al.** Clinical trials update: CAPRI-CORN, COPERNICUS, MIRACLE, STAF, RITZ-2, RECOVER, and RENAIS-SANCE and cachexia and cholesterol in heart failure: highlights of the Scientific Sessions of the American College of Cardiology, 2001. Eur J Heart Fail 2001; 3:381–387.
9. **Anand I, McMurray J, Cohn JN, et al.** Long term effects of darusentan on left-ventricular remodeling and clinical outcomes in the ET-A Receptor Antagonist Trial in Heart Failure (EARTH): randomized, double-blind, placebo-controlled trial. Lancet 2004; 364:347–354.
10. **O'Connor CM, Gattis WA, Adams KF, et al.** Tezosentan in patients with acute heart failure and acute coronary syndromes: results of the Randomized Intravenous Tezosentan Study (RITZ-4). J Am Coll Cardiol 2003; 41:1452–1457.
11. **Mehra MR, Uber PA, Francis GS.** Heart failure therapy at a crossroad: are there limits to the neurohormonal model? J Am Coll Cardiol 2003; 41:1606–1610.
12. **Al-Ahmad A, Rand WM, Manjunath GM, et al.** Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001; 38:955–962.
13. **Tanner H, Moschovitis G, Kuster GM, et al.** The prevalence of anemia in chronic heart failure. Int J Cardiol 2002; 86:115–121.
14. **Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J.** Anemia is associated with worse symptoms, greater impairment in functional capacity and significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 2002; 39:1780–1786.
15. **McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R.** Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population based study. J Am Soc Nephrol 2002; 13:1928–1936.
16. **Ezekowitz JA, McAllister FA, Armstrong PW.** Anemia is common in heart failure and is associated with poor outcomes. Circulation 2003; 107:223–225.
17. **Koshiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM.** The prognostic importance of anemia in patients with heart failure. Am J Med 2003; 114:112–119.

18. **Felker GM, Gattis WA, Leimberger JD, et al.** Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. Am J Cardiol 2003; 92:625–628.
19. **Anand I, McMurray JJV, Whitmore J, et al.** Anemia and its relationship to clinical outcome in heart failure. Circulation 2004; 110:149–154.
20. **Hillege HLM.** Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000; 102:203–210.
21. **Volpe M, Tritto C, Testa U, et al.** Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. Am J Cardiol 1994; 74:468–473.
22. **Donnelly S.** Why is erythropoietin made in the kidney? The kidney functions as a critmeter. Am J Kidney Dis 2001; 38:415–425.
23. **Ebert BL, Bunn HF.** Regulation of the erythropoietin gene. Blood 1999; 94:1864–1877.
24. **Levine B, Kalman J, Mayer L, Fillit HM, Packer M.** Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990; 323:236–241.
25. **Elgert KD, editor.** Immunology: Understanding the Immune System. New York: Wiley-Liss; 1996.
26. **Means RT.** Advances in the anemia of chronic disease. Int J Hematol 1999; 70:7–12.
27. **Silverberg DS, Wexler D, Blum M, Iaina A.** The cardio-renal-anemia syndrome: correcting anemia in patients with resistant congestive heart failure can improve both cardiac and renal function and reduces hospitalization. Clin Nephrol 2003; 60:S93–S102.
28. **Griffing GT, Melby JC.** Enalapril (MK-421) and the white cell count and hematocrit. Lancet 1982; 1:1361.
29. **Kamper AL, Nielsen OJ.** Effect of enalapril on hemoglobin and serum erythropoietin in patients with chronic nephropathy. Scan J Clin Lab Invest 1990; 50:611–618.
30. **Fyhrquist F, Karppinen K, Honkanen T, Saijonmaa O, Rosenlof K.** High serum erythropoietin levels are normalized during treatment of congestive heart failure with enalapril. J Intern Med 1989; 226:257–260.
31. **Glicklich D, Kapoian T, Mian H, Gilman J, Tellis V, Crizat H.** Effects of erythropoietin, angiotensin II, and angiotensin-converting enzyme inhibitor on erythroid precursors in patients with post-transplantation erythrocytosis. Transplantation 1999; 68:62–66.
32. **Ishani A, Weinhandl E, Zhao Z, et al.** Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2005; 45:391–399.
33. **Androne AS, Katz SD, Lund L, et al.** Hemodilution is common in patients with advanced heart failure. Circulation 2003; 107:226–229.
34. **McBride BF, White CM.** Acute decompensated heart failure: a contemporary approach to pharmacotherapeutic management. Pharmacotherapy 2003; 23:997–1020.
35. **Winearls CG.** Recombinant human erythropoietin: 10 years of clinical experience. Nephrol Dial Transplant 1998; 13(suppl 2):23–27.
36. **Eschbach JW, Egrie JC, Downing MR, et al.** Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med 1987; 316:73–78.
37. **Goldberg N, Lundin AP, Delano B, et al.** Changes in left ventricular size, wall thickness, and function in anemic patients treated with recombinant human erythropoietin. Am Heart J 1992; 124:424–427.
38. **Silverberg DS, Wexler D, Blum M, et al.** The effect of correction of anemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrol Dial Transplant 2003; 18:141–146.

39. **Silverberg DS, Wexler D, Blum M, et al.** The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduced hospitalizations. J Am Coll Cardiol 2000; 35:1737–1744.

40. **Silverberg DS, Wexler D, Sheps D, et al.** The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 2001; 37:1775–1780.

41. **Mancini DM, Katz SD, Lang CC, Lamanca J, Hudaihed A, Androne AS.** Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 2003; 107:294–299.

42. **Locatelli F, Canaud B, Giacardy F, et al.** Treatment of anemia in dialysis patients with unit dosing of darbepoietin alfa at a reduced dose frequency relative to recombinant human erythropoietin (rHuEpo). Nephrol Dial Transplant 2003; 18:362–369.

43. **Mann JF.** Hypertension and cardiovascular effects—long term safety and potential long term benefits of rHuEpo. Nephrol Dial Transplant 1995; 10(suppl 2):80–84.

44. **Taylor JE, McLaren M, Henderson IS, Belch JJ, Stewart WK.** Prothrombotic effect of erythropoietin in dialysis patients. Nephrol Dial Transplant 1992; 7:235–239.

45. **Carlini RG, Dusso AS, Obialo CI, Alvarez UM, Rothstein M.** Recombinant human erythropoietin (rHuEpo) increases endothelin-1 release by endothelial cells. Kidney Int 1993; 43:1010–1014.

46. **Besarab A, Bolton WK, Browne JK, et al.** The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoietin. N Engl J Med 1998; 339:584–590.

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