Article published online: 2022-05-23

MINIREVIEW

Anemia In Chronic Heart Failure: A Review

[1*]A. E. Faraj, [2]M. Houmsse

1. Department of Medicine, Gradiot Medical Center, MI, USA
2. Department of Medicine, The Ohio State University, Columbus, Ohio, USA

*Corresponding author: A. E. Faraj Email: adrissq@yahoo.co.uk
Published: 01 January 2010
Ibnosina Journal of Medicine and Biomedical Sciences 2010, 2(1):32-37
Received: 10 October 2009
Accepted: 12 December 2009
This article is available from: http://www.ijmbs.org
This is an Open Access article distributed under the terms of the Creative Commons Attribution 3.0 License
which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract
Despite advances in chronic heart failure (CHF) medical and device therapy in recent years, CHF continues to be a syndrome associated with significant morbidity and mortality. Abundance of data suggests that anemia is prevalent in CHF. The pathophysiology of CHF-related anemia is complex and poorly understood. Earlier small trials demonstrated improvement in morbidity with use of erythropoietin stimulating agents (ESA) and parenteral iron but that was not supported by more recent large randomized trials. There is a concern regarding the safety of ESA. Small studies showed benefits from parenteral iron alone or combination with ESA. This was promising since parenteral iron is a relatively cheap therapeutic intervention to treat anemia in CHF patients. So far there are no clear recommendations regarding the treatment of CHF related anemia. The purpose of this article is to review the most recent epidemiology, pathophysiology, and therapeutic options for anemia in CHF.

Key Words: Chronic heart failure, anemia, erythropoietin and iron

Introduction

CHF is a complex clinical syndrome resulting from structural or functional heart disorders, which impair the ventricular filling and contractility. CHF results in multiple neurohormonal changes that adversely remodel ventricular function and subsequently lead to deterioration of cardiac function, as well as, significant increases in morbidity and mortality (1-3). Anemia is not an outcome of these neurohormonal changes since erythropoietin is usually elevated in CHF and possibly is a marker of chronic disease. Anemia is well recognized as an independent predictor of poor outcomes in CHF (3,7-11). Anemia treatment as shown in multiple studies improves CHF symptoms, functional capacity, and mortality. Therefore, it becomes a new target for treatment in CHF patients who continue to be symptomatic despite receiving optimal medical therapy

(1-6). The authors in this concise review will summarize the current understanding of anemia in heart failure and provide an overview of possible therapeutic options.

Epidemiology

The World Health Organization (WHO) defines anemia as any hemoglobin level < 13.0 g/dl in men and < 12.0 g/dl in women (2,3,7,8). The prevalence of anemia in heart failure syndrome has been well established (2,3,7,8). Anemia affects up to 61% of heart failure patients with systolic dysfunction (2,3,7-9). The hemoglobin levels in those patients tend to be mildly reduced with levels ranging between 10 to 11.5 g/dl. The more advanced the functional class (FC) of heart failure (as adopted by New York Heart Association, (NYHA) FC I (mild) through FC IV (severe and advanced)), the higher the incidence of anemia. Other factors associated with a high prevalence of anemia in CHF include older patients, impaired kidney function, low body weight, female gender, and use of ACE inhibitors (12). Anemia is also common in heart failure with normal ejection fraction (EF is a surrogate for ventricular systolic function). Brucks et al reported anemia in 42% of 137 patients with CHF and normal EF (13).

Pathophysiology of Anemia in CHF

Kidney oxygen sensors usually regulate erythropoietin (EPO) in response to various forms of hypoxia including but not restricted to anemia and low blood oxygen capacity. In these conditions, the kidney will release EPO, which will stimulate bone marrow erythropoiesis (14-16). The majority of anemia in CHF patients is of the normocytic, normochromic type and is classified as anemia of chronic disease (11,13). The exact mechanism of anemia and its role in the pathophysiology of CHF has not been established. Conversely, CHF-related mechanisms contribute to the pathogenesis of anemia. Inflammatory immune activation occurs as part of the neurohormonal changes of HF syndrome, which has been associated with increased levels of pro-inflammatory cytokines (17-19). Recent studies have demonstrated that cytokines including TNF-α, interleukin-1 and interleukin-2 play a major role in the suppression of erythropoietin mediated hemoglobin synthesis mainly by increasing the bone marrow resistance to EPO (19). Furthermore, cytokines appear to also enhance the hepatic synthesis of the peptide hepcidin which inhibits the small bowel absorption of iron by binding Ferroportin, an iron transport protein in small intestine enterocytes which leads to depleted iron stores (20, 21). Interestingly, ACE inhibitors, which are routinely implemented in CHF medical management, may also contribute to CHF-related anemia (12). These agents inhibit angiotensin-2 synthesis, which plays a regulatory role in erythropoietin production, (22). In addition, ACE inhibitors lead to increased levels of Ac-SDKP, which is normally broken-down by an ACE-mediated process (23). Ac-SDKP inhibits erythropoiesis leading to anemia. Finally, it is important to be aware of the role of hemodilution on anemia in heart failure patients (24). These patients often have a large plasma volume with normal red cell mass (25,26).

Anemia as an Independent Predictor of Chronic Heart Failure Outcomes

An abundance of data has demonstrated the role of anemia as an independent predictor of hospitalization, NYHA functional class, and all cause mortality in CHF patients (27,28). An analysis of the Studies of Left Ventricular Dysfunction (SOLVD) showed that the level of hematocrit was an independent predictor of mortality in patients with left ventricular dysfunction. At 33 months the mortality was 22%, 27%, and 34% for those with a hematocrit of > 40, 35 to 40 and < 35 respectively. In a cohort of 1,060 patients with advanced CHF and LVEF < 40 %, Horwich, et al, revealed that mild anemia was associated with worsened symptoms, functional status, and survival (8). In The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial, anemia was found to be a powerful independent predictor of survival among 1,130 patients with CHF and low ejection fraction. Furthermore, there was a linear relationship between the level of hemoglobin and poor outcomes in the PRAISE trial. Hematocrit (Hct) levels remain an important predictor of outcomes. When Hct decreased by 1%, there will be an 8% increase in pump failure death (HR 1.08, 95% CI 1.05 to 1.12, p< 0.001) (10). There also appears to be an inverse relationship between hemoglobin level and serum brain natriuretic peptide (BNP, a biomarker that increases during worsening of NYHA functional class of CHF) levels. The underlying mechanism of this relationship is poorly understood but anemia may simply reflect a severe cardiac pathology. Other possible mechanisms of the inverse relationship of BNP and hemoglobin levels, which abnormally activate the neurohormonal system, are altered ventricular loading conditions, increased free radicals, and elevated plasma cytokines (28). It remains unclear whether anemia plays a major part in the pathophysiology of CHF or if it primarily represents a marker of poor outcome. Additional randomized controlled trials are required to arrive at a conclusion regarding this point.

Therapeutic Options of Anemia in Chronic Heart Failure

Treatment of anemia in CHF remains is a therapeutic option in addition to traditional optimal medical and device therapies for desperately ill CHF patients. Optimal anemia management in CHF could include erythropoietin stimulating agents, parenteral iron therapy, blood transfusions or a combination of these.

Erythropoietin Stimulating Agents

As mentioned earlier, erythropoietin (EPO)-mediated erythropoiesis is impaired in anemic CHF patients because of inadequate EPO secretion as well as bone marrow resistance. Therefore erythropoietin stimulating agents (ESA) such as recombinant human erythropoietin--namely epoetin-α and epoetin-β and darbepoetin-α-- may have a role in treating anemia in CHF (30). The use of these agents in patients with anemia of chronic kidney disease is well documented. EPO and its analogues tend to improve functional capacity and left ventricular function (31). Previous small single center studies suggest that EPO and parenteral iron therapy administered to CHF patients with anemia over several months resulted in an improvement of functional capacity and left ventricular function. These reports also indicated that these patients had reduced renal dysfunction, hospitalizations and diuretics use. (4-6,32). This improvement was noticed despite of modest improvement in hemoglobin level. These benefits need to be evaluated carefully since they could be attributed to the parenteral iron therapy. This has been supported with similar positive results in a recently published study of intravenous iron replacement in CHF known as the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial (33). However, negative results of EPO-like replacement therapy was shown in another trial, the Study of Anemia in Heart Failure Trial (STAMINA-HeFT). The later study was the largest randomized placebo controlled trial utilizing ESA. The outcome did not support the role of ESA in improving exercise capacity in CHF patients as reported by Ghali, et al. They enrolled 319 patients with symptomatic systolic CHF (EF < 40%) and mild anemia (hemoglobin between 9.0 to 12.5 gm/dl) and randomized them to a placebo group (N=157) or a darbepoetin alfa group (N=162). These patients were given the medication subcutaneously every two weeks for one year. There was a significant improvement in hemoglobin levels but not in exercise duration, functional class, or quality of life as compared to the placebo group (34). It was obvious there is a need for large trials to address the impact of such an intervention on the morbidity and mortality of heart failure patients, but most of the worker in the field of ESA has not been optimistic. The results of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) will add to the pool of data regarding the safety and potential role of anemia treatment with darbepoetin alfa in CHF (35, 36). In addition to the lack of current supporting data of ESA utilization in CHF, there is a concern for its unwanted adverse effects which include an increased incidence of both venous thrombosis and hypertension (26, 37) therefore, ESA is not yet the standard of care in heart failure patients with anemia.

Parenteral Iron Administration

Because of the concerns regarding ESA unwanted side effects and lack of supporting data for their therapeutic use, iron administration was studied as an alternative therapeutic interventions in HF-related anemia. Frank iron deficiency occurs in a small number of CHF patients but functional iron deficiency is common. Parenteral iron administration becomes more attractive since iron saccharate, also known as iron sucrose complex, comes with less adverse side effects than the large-weight dextran forms.

Two small recent studies have demonstrated that parenteral sucrose iron, given over several weeks to CHF patients, demonstrated some benefit. Bolger, et al, treated 16 anemic CHF patients with one gram of IV iron sucrose over 12 days with mean follow up of 92 ± 6 days. Following iron sucrose injection, improvement in Hemoglobin levels, heart failure symptoms, and functional class capacity was concluded. Further, Bolger, et al, reported no adverse effects associated with the use of iron sucrose (38). Another small, randomized control trial including 40 CHF patients randomized to parenteral iron sucrose or normal saline administered over five weeks was and followed up for five months. Patients included in the active arm of the study showed improvement in NYHA functional class, Minnesota Living with Heart Failure Quality of Life Score, NT-proBNP (N terminal – Pro BNP) level, six-minute walk test, and left ventricular function. Further, investigators documented decreased use of diuretics; lower C-reactive protein, improved creatinine clearance, and shorter hospital stay (39).

Recently during the 2009 annual American Heart Association (AHA) scientific meeting, Akers and colleagues presented their findings of the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial, which was designed as a double-blinded randomized study to determine whether intravenous iron replacement (ferric carboxymaltose) therapy benefits patients with CHF and iron deficiency. The FAIR-HF trial

reported that in patients with systolic heart failure and iron deficiency anemia treated with injectable iron preparation (ferric carboxymaltose), they responded over 24 weeks with significantly improved symptoms, NYHA functional class, six-minute-walk distance, and quality of life, regardless of whether or not they had anemia (33).

Blood Transfusion in Heart Failure Related Anemia

The role of blood transfusions in mildly or moderately anemic CHF patients is debatable. Wen-Chih Wu and colleagues demonstrated that blood transfusion increased the 30-day mortality with an odds ratio of 1.38, CI (1.05-1.80) in elderly patients admitted with myocardial infarction who are found to be mildly anemic with hematocrit level above 36% (40). Vincent, et al, demonstrated increased adverse outcomes in critically ill patients who received blood transfusions (41). This data raised concern regarding the safety of blood transfusions in patients with cardiovascular system disease, including but not restricted to the risk of iron overload and increased risks for infection. Thus, blood transfusions should be avoided in heart failure patients unless there is sever anemia (42). The recommendations based on these data do not support the overzealous correction of mild anemia with blood transfusions in heart failure patients.

Conclusion

Anemia is prevalent in CHF patients and associated with significant morbidity and mortality. The underlying etiology of the anemia is multifactorial including functional iron deficiency, renal dysfunction, and pro-inflammatory cytokines mediated erythropoiesis suppression. While the results of small studies suggest combination therapy of EPO like analogues and parenteral iron have shown some benefit, the data from large controlled trials do not support the routine use of EPO-like agents in heart failure.

The results of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) are pending. This large randomized study will give us much more information about the safety and efficacy of long acting ESA darbepoetin alfa on morbidity and mortality (as well as quality of life) in patients with anemia in CHF. Current and recent (FAIR-HF) clinical studies showed promising outcomes when we administer IV iron to treat heart failure for CHF patients with iron deficiency with or without anemia

References

1. Jessup M, Abraham W.T, Casey D.E, Feldman A.M, Francis G.S, Ganiat T.G, ||Konstam M.A, Mancini D.M, Rahko P.S, Silver M.A, Stevenson L.W, Yancy C.W. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. J Am Coll Cardiol. 2009; 53:1-90. doi: 10.1016.
2. Wexler D, Silverberg D, Sheps D, Blum M, Keren G, Iaina A, Schwartz D. Prevalence of anemia in patients admitted to hospital with a primary diagnosis of congestive heart failure. Int J Cardiol. 2004;96:79-87.
3. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, Tavazzi L, Latini R, Cohn J. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trail and in clinical practice. J Card Fail. 2005;11:91-8.
4. Silverberg DS, Wexler D, Blum M, Tchebiner JZ, Sheps D, Keren G, Schwartz D, Baruch R, Yachnin T, Shaked M, Schwartz I, Steinbruch S, Iaina A. 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;18:141-6.
5. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, 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;37:1775-80.
6. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, 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 reduces hospitalizations J Am Coll Cardiol. 2000;35:1737-44.
7. Ezekowitz JA. McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insight from a cohort of 12065 patients with new-onset heart failure. Circulation. 2003;107:223-5.
8. Horwich TB, Fonarow GC, Hamilton MA, Maclellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol. 2002;39:1780-86.
9. Al-Ahmad A, Rand WM, Manjunath G, Konstam

MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001; 38:955-62.
10. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure; the prospective randomized amlodipine survival evaluation (PRAISE). J Am Coll Cardiol. 2003;1933-39.
11. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, Chiang YT, Aknay N, Maggioni AP, Opasisch C, Latini R, Cohn JN. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from ValoHeft. Circulation. 2005;112:1121-27.
12. Ishani A, Weinhandl E, Zhao Z, Gilbertson DT, Collins AJ, Yusuf S, Herzog CA. 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;45:391–99.
13. Brucks S, Little W, Chao T, Rideman RL, Upadhya B,Wesley-farrington D, et al. Relation of Anemia to Diastolic Heart Failure and the Effect on Outcome. Am J Cardiol. 2004;93(8):1055-7.
14. Bauer C, Kurtz A. Oxygen sensing in the kidney and its relation to erythropoietin production. Annual. Rev. Physiol. 1989; 51:845-56
15. Cheung JY, Miller BA. Molecular mechanisms of erythropoietin signaling. Nephron. 2001;87:215–22.
16. Fisher JW. Erythropoietin: physiology and pharmacology update. Exp Biol Med (Maywood). 2003;228:1–14.
17. Deswal A, Peterson NJ, Feldman AM, White BG, Mann DL. Effects of Vesnarinone on peripheral circulating Cytokines and cytokine receptors in patients with heart failure: A Report from Vesnarinone Trial. Chest. 2001; 120(2):453-59.
18. Torre-Amione G,Bozkurt B, Deswal A, Mann DL. An overview of TNF alpha and the failing human heart. Curr. Opin. Cardiol. 1999;14:206-10
19. Macdougall IC, Cooper AC. Erythropoietin resistance: the role of inflammation and pro-inflammatory cytokines. Nephrol Dial Transplant. 2002;17(Suppl 11):39–43.
20. Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, Kaplan J. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science. 2004;306:2090–3.
21. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood. 2003;102:783-8.
22. Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. J Clin Invest. 1997;100:2310–4.
23. Van der Meer P, Lipsic E, Westenbrink BD, van de Wal RM, Schoemaker RG, Vellenga E, van Veldhuisen DJ, Voors AA, van Gilst WH. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. Circulation. 2005;112:1743–7.
24. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, Mancini DM. Hemodilution is common in patients with advanced heart failure. Circulation. 2003;107:226–9.
25. Anand IS, Chandrashekhar Y, Ferrari R, and Poole-Wilson PA, Harris PC. Pathogenesis of edema in chronic severe anemia: studies of body water and sodium, renal function, hemodynamic variables, and plasma hormones. Br Heart J. 1993;70:357–62.
26. Mann JF. Hypertension and cardiovascular effects–long-term safety and potential long-term benefits of r-HuEPO. Nephrol Dial Transplant. 1995;10(Suppl 2):80-4.
27. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, Burton PB. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004;110:149–54.
28. Karla PR, Bolger AP, Francis DP, Genth-Zotz S, Sharma R, Ponikowski PP, Poole-Wilson PA, Coats AJ, Anker SD. Effect of anemia on exercise tolerance in chronic heart failure in men. Am J Cardiol. 2003;91:888–91.
29. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, Niebauer J, Hooper J, Volk HD, Coats AJ, Anker SD. Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation. 2000;102:3060–7.
30. Cleland JG, Sullivan JT, Ball S, Horowitz JD, Agoram B, Rosser D, Yates W, Tin L, Fuentealba P, Burton PB. Once-monthly administration of darbepoetin alfa for the treatment of patients with chronic heart failure and anemia: a pharmacokinetic and pharmacodynamic investigation. J Cardiovasc

Pharmacol. 2005;46:155–61.
31. 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;107:294-9.
32. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A. 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;37:1775-80.
33. Anker SD, Colet JC, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency. N Engl J Med. 2009;361:2436-48.
34. Jalal K, Ghali I, S.Anand, W.T.Abraham, G.C.Fonarow, B.Greenberg, H.Krum, B.M.Massie, S.M.Wasserman, M.Trotman, Y.Sun, B.Knusel, P.Armstrong. Study of Anemia in Heart Failure Trial (STAMINA-HeFT). Circulation. 2008;117;526-35.
35. Young JB AI, Diaz R, Maggioni AP.McMurrar JJV, O'Connor C, Pfeffer MA, Solomon S, Tendera M, Va, Veldhuisen DJ, Wasserman SM, Swednerg K. Reduction of Events With Darbepoetin alfa in Heart Failure (RED-HF) trial. J Card Fail. 2006;6(suppl 1): S77.Abstract.
36. McMurray JJV, Annd IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, Plu AP, Solomon SD, Sun Y, Swedberg K, Tendera M, Van Veldhuisen DJ, Wasserman SM, Young J. The Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): Phase III Trial. Eur J Heart Fail. 2009; 11(8): 795-801.
37. Churchill DN, Muirhead N, Goldstein M, Posen G, Fay W, Beecroft ML, Gorman J, Taylor DW. Probability of thrombosis of vascular access among hemodialysis patients treated with recombinant human erythropoietin. J Am Soc Nephrol. 1994;4:1809-13.
38. Bolger AP, Bartlett FR, Penston HS, O'leary J, Pollock N, Kaprielian R, Chapman CM. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. J Am Coll Cardiol. 2006;1225-27.
39. Toblli JE, Lombrana A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-PRO-Brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. J Am Coll Cardiol. 2007;50:1657-65.
40. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med. 2001;345:1230–6.
41. 41.Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D. Anemia and blood transfusion in critically ill patients. JAMA. 2002;288:1499–507.
42. Goodnough LT, Brecher ME,Kanter MH, AuBuchon JP.Transfusion medicine: first of two parts–blood transfusion. N Engl J Med. 1999;340:438-47.