Managing anemia in patients with chronic heart failure; Is there a new pathway?

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Introduction

HF continues to be one of the most important problems of public health with significant morbidity and mortality. Currently, there are at least 15 million patients with heart failure in Europe. The prevalence of HF is 2-3% overall and rises sharply at age 75 and above, it is counted between 10-20% in 70-80-year-old people. This prevalence is increasing because of the ageing of the population and the success in prolonging survival in patients suffering coronary events. Coronary artery disease (CAD) and hypertension are the two of the most prevalent risk factors for the development of HF in population. Other common etiologies include diabetes mellitus, valvular heart disease and cardiomyopathies. Frequently, HF in older persons is multifactorial. During the last ten years both the mortality and re-hospitalization due to heart failure have increased despite remarkable advances in diagnosis and therapy in HF have been made over the past decade. There are not more than 50% of patients with symptomatic HF can survive within 5 year since diagnose has been made. Because many trials and experiences show that complex neurohormonal blocking is of limited use in the treatment of HF, some attempts have been made to find new approaches and treatment strategies that may further improve outcomes and cut down the mortality and morbidity in patients with this clinical syndrome. Identification of factors that affect quality of life or survival in HF may not only improve prognosis but also potentially provide new opportunities for novel therapeutic strategies in these patients. One of the factor that attracting interests to be a potential approach to improve treatment of patients with HF is the correction of concomitant anemia.

It is widely known that prolonged anemia can lead to heart failure even in the absence of underlying heart disorders. But there is less attention has been given to the fact that many patients with HF often have anemia, and that HF itself may contribute to causing it. Prevalence of anemia in HF ranges widely from 4%-70% due to lack of a consistent definition of anemia in HF setting. This prevalence increases with the severity of clinical symptoms of HF, older age, female gender, renal disease, and other co-morbidities. Ezekowitz et al analyzed a population-based cohort of patients with new-onset CHF from a database of patients discharged from 138 acute-care hospitals in Alberta, Canada, between April 1993 and March 2001. Among the 12,065 patients with CHF (median age 78 years), 17% had anemia. After adjustment for clinical and
demographic variables, patients with anemia were more likely to be older (odds ratio [OR] 1.01 per year) and female (OR 1.2 [95% confidence interval 1.1 to 1.3]) and to have a history of chronic renal insufficiency (OR 3.2 [95% confidence interval 2.8 to 3.6]), or hypertension (OR 1.3 [95% confidence interval 1.2 to 1.5]). One study reported that prevalence of anemia in patients with NYHA class IV was as high as 79%. Other study has reported that the prevalence of anemia was 4% in clinical trial participants (n=6797) with asymptomatic or mild left ventricular dysfunction, whereas 30% of participants (n=1061) with advanced heart failure had anemia. Some trials reported that coexistence of anemia and HF correlates with poorer clinical outcomes. Anemia in patients with HF is considered as vicious circle set in motion, whereby HF causes anemia, which in turn exacerbates to more advanced HF, and so on. However, there have been no current guidelines state to treat anemia in patients with HF specifically. There are still many controversies about the time when we should begin the treatment of anemia in HF, or what the target of hematocrit is, or about the recommended agent and its dose to be used in treating of HF patients with anemia.

Anemia and chronic heart failure; a complex interaction

The mechanism of the anemia in patients with heart failure and its role in the pathophysiology of heart failure has been elusive. Although anemia is common in heart failure, controversy remains about whether its prevalence in HF patients is directly related to heart failure itself or other co-morbid conditions. Multiple co-morbid conditions are common in HF patients, particularly renal insufficiency that is closely related with the development of anemia. Meanwhile, both anemia and HF are diseases of the elderly, and HF is more common in elderly population. This complex interactions lead to the consideration that etiology of anemia in HF patients is multifactorial. Some potential mechanistic links between anemia and HF are iron deficiency and loss, malnutrition, proinflammatory cytokines related to chronic disease, renal dysfunction, hemodilution, urinary losses of serum erythropoietin and transferring, adverse effect of medicine such as ACE inhibitors, disturbances of the autonomic nervous system (involved in the secretion of erythropoietin by the kidneys), and reduced blood supply to the bone marrow. Therefore anemia in HF is the result of complex interaction between cardiac performance, neurohormonal, inflammatory activation, renal function and bone marrow responsiveness. This relationship has been termed as the cardio-renal-anemia syndrome.

An expansion in plasma volume is often seen in heart failure and could cause a reduction in haemoglobin concentration through dilution rather than any real decrease in the mass of red blood cells. Therefore, some anemia may be dilutional rather than due to a true decrease in red blood cell mass. Androne et al reviewed 196 advanced heart failure patients and reported that in a subset of 37 ambulatory HF patients with anemia, 46% experienced anemia from hemodilution and only 54% experiencing “true anemia”. It is worth noting that both patients with hemodilution and true anemia in this study were associated with poorer outcomes, with the worst survival rates seen in patients with hemodilution anemia, which suggests that volume overload may be an important mechanism contributing to worse outcome in anemic HF patients. These findings make clinical sense, and suggest that diuretics should be optimized before accurate assessment and treatment of anemia is performed. Dilutional anemia may play a larger role in acute heart failure because significant volume overload is commonly found in acute heart failure hospitalization.

Other study of 37 patients with CHF, iron-deficiency anemia was confirmed by bone marrow aspiration in 27 patients (73%), 2 patients (5.4%) had dilutional anemia, and 1 patient
(2.7%) had drug induced anemia. No specific cause was identified in 7 patients (18.9%) who were considered to have “anemia of chronic disease.” Serum ferritin for the iron-deficient patients was not a reliable marker of iron deficiency in this population. Thus, the authors concluded that in this group of patients, iron deficiency was the most common cause of anemia. The iron status of patients with end-stage chronic CHF should be thoroughly evaluated and corrected before considering any other therapeutic interventions. Iron deficiency anemia may be due to low intake diet or to malabsorption because of nausea and loss of appetite which is common finding in HF patients related to gut and liver congestion caused by right heart failure. Occult gastrointestinal blood losses caused by chronic aspirin use, uraemic gastritis and proteinuria in patients with concomitant renal failure also contribute to iron deficiency anemia.

HF can be considered to cause chronic inflammatory activation as reflected by persistently elevated cytokine levels such as interleukins 1,6,18 and tumor necrosis factor alpha (TNF-a) in circulation and in myocardium. Anemia of inflammation is common in patients with congestive heart failure. In one study, 85 of 148 (57%) anemic outpatients with congestive heart failure had this kind of anemia. Higher levels of circulating proinflammatory cytokines are known to be associated with the severity of symptoms and worsened clinical outcomes. Cytokine-mediated responses include reduced red blood cell progenitor proliferation, with erythropoietin resistance , hepcidin elevation with resultant stunted iron absorption at the level of the intestine and the blockade of iron release from macrophages. Hepcidin is a small (20-25 amino acids) antimicrobial peptide that is expressed and secreted into the circulation by the liver in response to chronic inflammation. Hepcidin inhibits iron excretion in macrophages and enterocytes by binding to a key iron export protein, ferroportin. Elevated levels of circulating proinflammatory cytokines lead to a reduction in erythropoietin production and a weakening of the response of bone marrow to its effects. Therefore, anemia in heart failure may be a state of relative resistance to the effects of erythropoietin, with persistent anemia despite elevated erythropoietin levels. The concept of erythropoietin resistance is further supported by recent observations in HF patients, where elevated plasma erythropoietin levels are associated with an impaired prognosis and worse LV function independent of hemoglobin levels and other established markers of HF severity. Because patients with NYHA class IV symptoms, those with cardiac cachexia and those with edematous decompensation of their disease have the highest proinflammatory cytokines activation and more tendency to anemia, it can be hypothesized that inflammatory activation is the major contributor to anemia in this population.

Although ACE inhibitors is a mainstay in HF therapy, some data have shown that therapeutic doses of ACE inhibitors might decrease renal secretion of erythropoietin which would reduce hemoglobin concentration further in patients with HF, as well as in patients with hypertension, renal insufficiency and polycythemia. According to data from the Valsartan in Heart Failure Trial (Val-HeFT), valsartan use was associated with a significant decrease in hemoglobin concentration. Angiotensin II stimulates the proliferation of erythroid progenitor cells, whereas ACEs are needed to cleave N-acetylseryl-aspartyl-lysyl-proline (Ac-SDKP), a strong inhibitor of erythropoiesis. Therefore, using ACE inhibitors will deter the proliferation of the erythroid progenitor cells and markedly increase Ac-SDKP levels 5 to 6 fold and then reduce hematopoietic activity, which in turn it will reduce hemoglobin concentration.

Renal insufficiency is common in HF patients, presents in about half of the patients, and existence of both conditions often brings patients into end-stage disease, even with optimum
therapy. 24 One factor that is common to both conditions is anemia. Some studies indicate that the prevalence of anemia is higher in HF patients who also have kidney disease as a co-morbid. 12 Progressive renal dysfunction leads to decreased production of erythropoietin, with a subsequent impairment of erythrocyte production in bone marrow and lower hemoglobin levels. 11,12,24 It is also already known that anemia in patients with advanced renal insufficiency is associated with a variety of adverse cardiac consequences such as left ventricular hypertrophy or dilatation, and clinical symptoms of heart failure. Anemia could be considered as the connection between chronic heart failure and renal insufficiency.

Anemia of whatever underlying mechanisms may contribute directly to clinical deterioration of HF symptoms. Anemia relates with decreased oxygen carrying capacity and it will aggravate tissue hypoxia which has been persisted in HF patients. 11 This tissue hypoxia along with reduced blood viscosity related to anemia causes reduction in peripheral vascular resistance, leading to activation of the sympathetic nervous system in order to maintain the blood pressure. Vasoconstriction also occurs at renal vessels then triggers the renin-angiotensin-aldosterone (RAA) system, which in turn it will intensify renal and peripheral vasoconstriction. This destructive compensation cause renal ischemia, leads to further renal failure. 11,25 At that time, anemia will become worsened because of reduction in renal production of erythropoietin. Increased circulating aldosterone leads to extracellular fluid and sodium retention that can cause deteriorated clinical symptoms of HF. Persistent anemia also gives bad impact to the heart. Increased heart rate caused by sympathetic nervous system activation, and increased stroke volume related to fluid retention can cause additional load to heart work, while on the other hand oxygen carrying capacity in the blood is reduced by the anemia. This ambience will aggravate myocardial ischemia, then leads to myocardial cells death and fibrosis, ventricular dilatation or hypertrophy, and deterioration of functional class of HF as the later consequence. 25

Anemia as an independent prognostic factor in heart failure

Some observational studies have found that anemia is associated with adverse clinical outcomes in HF patients. Anemia is associated with worsening symptoms, reduced exercise tolerance, increased diuretics use, increased hospitalization and re-hospitalization, and long term survival in HF patients. It is considered as an independent factor of clinical outcomes in HF, out of other conventional factors such as left ventricular ejection fraction and concomitant renal insufficiency. 11,12,25 These findings persisted after adjustment of gender, heart failure etiology, and age. One study in HF patients with NYHA class III or IV demonstrated that hemoglobin was an important prognostic factor, independent of pulmonary capillary wedge pressure, body mass index, serum albumin, or serum creatinine. 10 Furthermore, this study also identified an increased risk even in HF patients with relatively mild anemia. Anemia has been also associated with worsening structural heart disease; diastolic dysfunction, LVH, increased left ventricular mass index and higher pulmonary heart pressures. 12 Other published study of 93 men with HF found that hemoglobin was a significant independent predictor of maximal exercise tolerance as measured by peak oxygen consumption, independent of ejection fraction, age, and renal function. 26
Several studies have noted that low hemoglobin was related to independent predictor of mortality in patients with HF. Horwich et al. evaluated a cohort of 1061 patients with advanced HF, with an EF below 40%. They divided patients into 4 groups: those with a hemoglobin below 12.3 g/dL, hemoglobin 12.3 to 13.6 g/dL, hemoglobin 13.7 to 14.8 g/dL and with hemoglobin above 14.8 g/dL. They reported that patients with the lower hemoglobin quartiles were more likely to have HF class IV ($P = 0.0001$); better survival was found in the higher hemoglobin quartile. They concluded that hemoglobin acts as an independent predictor for 1-year mortality with mortality increasing as hemoglobin decreased below 14 g/dL. Furthermore, these survival rates steadily declined with each decrease in hemoglobin deciles, with no evidence of a U-shaped relationship. Silverberg and colleagues have also confirmed that anemia is associated with increased mortality in HF. A study performed by Ezekowitz et al. showed that an absolute difference of survival within 1 year between non-anemic and anemic patients was 15% points (75% vs 60%). This difference persisted for the next 4 years. Analysis from PRAISE Study, a prospective multi-center study that evaluated 1130 HF patients with NYHA class III-IV and EF<30%, reported that patients with hematocrit of 25.4% to 37.5% had worse mortality and every 1% decrease in hematocrit was associated with a 11% higher risk of mortality. In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, hemoglobin levels were noted to be an independent risk factor for death and re-hospitalization with every 1 g/dL drop in hemoglobin. There is no significant difference between mortality risk of anemia in systolic or diastolic HF. And it is also interesting to note that clinical outcomes and mortality are found higher in HF patients with anemia caused by hemodilution.

Although there are lots of studies reported lower hemoglobin as an independent predictor of mortality in advanced HF patients, there are still some controversies whether or not anemia causes direct effect on that outcomes. Other co-morbid factors that are common related to advanced HF can create pitfalls in interpreting data from those studies so that proper adjustment should be made to overcome this problem. Reduced hemoglobin may merely be a marker for the epiphenomena of conditions in advanced HF, such as hemodilution due to volume overload, malnutrition from cardiac cachexia, renal insufficiency and higher dose of ACE inhibitors use. All of these factors can contribute to deterioration of clinical outcomes and mortality risk in those patients with advanced HF.

A study from National Heart Care Project performed by Kosiborod et al gave an important note about this limbo. They analyzed 50,405 patients with age 65 years and older admitted to acute care hospitals with a principal discharge diagnosis of HF between April 1, 1998, and March 31, 1999, or between July 1, 2000, and June 30, 2001. From analysis of 50,405 patients with age 65 years and older, they reported in unadjusted analysis that lower hematocrit levels were associated with increased 1-year mortality and hospital re-admission for HF. Compared with patients with a hematocrit greater than 40% to 44%, those with a hematocrit of 24% or less had a 51% higher risk of death (relative risk [RR], 1.51; 95% confidence interval [CI], 1.35 - 1.68; $P_{.001}$) and a 17% higher risk of HF-related re-admission (RR, 1.17; 95% CI, 1.01-1.34; $P_{.04}$). However, after adjustment for multiple co-morbidities and other clinical factors, the association between lower hematocrit levels and increased 1-year mortality was markedly attenuated, even in those patients with the most severe anemia (hematocrit 24% vs 40%–44%: RR, 1.02; 95% CI, 0.86-1.19; $P_{.85}$). The association between lower hematocrit values and HF-related readmission persisted after multivariable adjustment (hematocrit 24% vs 40%-44%: RR, 1.21; 95% CI, 1.04-1.38; $P_{.01}$). This finding may consider lower hematocrit
levels as an independent predictor of hospital readmission, but its relationship with increased mortality in HF patients is largely explained by the greater severity and burden of other co-morbid illness. Hematocrit was not independently associated with 1-year mortality in HF patients. As conclusion, they suggested that anemia may be predominantly a marker rather than a mediator of increased mortality risk in older patients with HF. This result was also supported by a study by Karla et al. of 552 patients with new-onset heart failure that reported no association between hemoglobin levels and survival after adjustment for other variables, although they found a significant incidence of anemia in that cohort (18% with hemoglobin < 11.5 g/dL). The authors concluded that anemia early in the HF was likely related to other co-morbid factors.

Advanced HF patients with anemia are more likely to have concomitant renal insufficiency, and both conditions have been considered as independent predictors of subsequent risk of death as well as worsened clinical outcomes. McClellan et al. noted the 1-yr death rates among HF patients with and without CKD were 44.9% and 31.4%, respectively (relative risk [RR], 1.43; 95% confidence interval [CI], 1.17 to 1.75). The mortality at 1 yr was 31.2% for individuals with a hematocrit above 40%; 33.8% (RR, 1.08; 95% CI. 0.79 to 1.47) for hematocrit 36 to 39%; 36.7% (RR, 1.17; 95% CI. 0.89 to 1.54) for hematocrit between 30 and 35%; and 50.0% (RR, 1.60; 95% CI, 1.19 to 2.16) for those with a hematocrit below 30%. Furthermore, they reported that anemia was a predictor of mortality in HF patients independent of serum creatinine. A cohort study in Medicare population noted that mortality risk of patients with both HF and chronic kidney disease (CKD) were 3.3 time higher than the reference population, and this relative risk increased to 4 times higher in patients with HF, CKD and anemia together. Both anemia and CKD were considered as independent mortality risk factors in the elderly population.

Serum erythropoietin levels as a promising predictor in advanced heart failure

There is a complex interaction between heart failure, renal insufficiency, and erythropoietin production by kidney. Because there is high prevalence of renal insufficiency in patients with advanced HF, circulating levels of erythropoietin are generally normal to elevated in this population. Increased plasma erythropoietin levels have been correlated with worsening NYHA classification, although the exact mechanism has not been fully understood. Erythropoietin is a glycoprotein produced primarily in the kidneys that stimulates the proliferation and differentiation of committed erythroid progenitors in the bone marrow. Because some previous studies showed that anemia in HF may be correlated with chronic inflammation states, recent interest in the role of erythropoietin, which is a cytokine, in advanced HF has increased. Currently, there is more understanding of additional mechanisms of action and other potential implementations of this pleiotropic cytokine. Erythropoietin has been reported to have anti-apoptotic and antioxidant properties, and recent findings suggest that it promotes endothelial precursor cell mobilization, thereby potentially contributing to tissue angiogenesis and vasculogenesis. In view of these diverse properties, it may be assumed that EPO could represent a form of a stress hormone that is up-regulated in advanced HF patients as their clinical status deteriorates. Increased renal production of erythropoietin may be triggered by prolonged renal hypoperfusion and hypoxia related to impaired cardiac performance in HF. In this condition with elevation of erythropoietin levels in advanced HF, prevalence of anemia in this population is higher. The effect of increased circulating inflammatory cytokines in HF, including erythropoietin, together with erythropoietin resistance in the bone marrow, interferes with the
normal operation of the feedback system so that it may produce an inverse relationship of hemoglobin to erythropoietin levels.\textsuperscript{12}

A large prospective study of 188 outpatients with HF performed by Jacob G et al. confirmed the findings of elevated erythropoietin serum levels in congestive heart failure (CHF) patients.\textsuperscript{37} Moreover, they have found the correlation between the NYHA classification of HF and the elevation of serum erythropoietin. The cutoff of 23 U/mL of serum erythropoietin levels could be used as a predictor of re-hospitalization or mortality of patients with CHF. They also noted that erythropoietin levels are correlated with NT-proBNP and CRP levels, but not with left ventricular ejection fraction. Collectively, these findings suggest that activation hormonal and inflammatory processes are reactive to the progression toward more advanced CHF.\textsuperscript{37} From this cohort study, erythropoietin levels can be considered as a prognostic value to mortality and to an acceptable end point of quality of life and hospitalizations due to CHF exacerbation.

**Strategy to treat anemia; Controversies and the role of erythropoietin**

Current understanding of the role of anemia in the outcomes of patients with HF has led to interest in anemia as a potential therapeutic target. But there are still some controversies and limbos in treatment of anemia in HF, partly because anemia is under recognized in this kind of population. No guidelines yet recommend clearly about when we should begin treating anemia in HF patients, what the proper rate of correction should be performed, which agents to use, and what the optimal Hb or Ht level is. Even, the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008 did not recommend that correction of anemia as a routine therapy in HF.\textsuperscript{1} Moreover, most studies related management of anemia in HF patients are small, non-randomized, and using subjective endpoints such as NYHA class or exercise capacity so that limiting their validity. Potential treatment strategies for anemia include the use of red blood cell transfusions, erythropoietin-stimulating agents (ESAs) or EPO therapy, and iron infusions. In view of the risks (transmission of infections and potential immunosuppressive effects), costs, and uncertain benefit of red blood transfusion, this procedure has been left behind as a therapeutic strategy for the routine treatment of anemia in patients with HF. However, ESAs or EPO therapy has become a mainstay in the treatment of anemia in patients with HF, especially if chronic kidney disease persists.\textsuperscript{11,12,25}

Irrespective of the cause of anemia in patients with HF, some current data report that ESAs or EPO therapy when given over several months might improve cardiac performance as well as exercise tolerance.\textsuperscript{38-39} A randomized, single-blind, placebo-controlled study by Mancini et al evaluated the effect of 3 months of EPO therapy on exercise tolerance in 26 patients with anemia and NYHA class III-IV heart failure. They reported significant improvement in peak oxygen consumption (VO\textsubscript{2} max) in the EPO treated patients compared with placebo. There was also significant correlation between elevations in Hb with EPO therapy and increased VO\textsubscript{2} max.\textsuperscript{38} Unfortunately, this study is limited by its small sample size so that larger confirmatory studies are needed to complement its validity and applicability. Some studies used combination of ESAs and iron infusion to evaluate the benefits in correcting anemia in severe HF patients.\textsuperscript{8,27,42} Marked improvements in NYHA class and LVEF, and also significant reduction of re-hospitalization were found in a study after anemia correction.\textsuperscript{42} Whereas other study using this combination regimen noted that there were reduction of diuretics doses and hospital stay, and improvements in ejection fraction and serum creatinine after achieving Hb > 12.5 g/dL.\textsuperscript{8} ESAs and IV iron might be considered as promising treatment of anemia in patients with advanced HF.
These potential beneficial effects of EPO in HF might be caused by reduced apoptosis of myocytes, reduced cardiac fibrosis, anti-oxidant effect, mitogenic, suppression of inflammatory mediators, and angiogenesis. These mechanisms are out of hematopoetic effects of EPO.11,12

Different results were reported by other 2 studies about the efficacy ESAs in clinical outcomes of HF patients with anemia. A randomized, double-blind, placebo controlled study performed by Van Veldhuisen et al evaluated the use of subcutaneous darbepoetin alfa every 2 weeks for 26 weeks at a starting weight-adjusted dose of 0.75 mcg/kg (n=56) or a fixed dose of 50 mcg (n=54) to achieve target Hb of 14.0 ± 1.0 g/dL in patients with CHF and Hb 9.0-12.4 g/dL. They reported that although there was a significant improvement in Kansas City Cardiomyopathy Questionnaire total symptom score (8.2 vs. 1.5 points; P = 0.027), there were non-significant improvements for 6 minutes walk distances, NYHA class, LVEF, and Minnesota Living With Heart Failure Questionnaire score.40 The STAMINA-HeFT study, a 8-month double-blind randomized, placebo controlled, and multi-center trial, also showed that darbepoetin alfa did not significantly improve NYHA class, exercise capacity or quality of life score compared with placebo (HR 0.68; 95% CI 0.43, 1.08; P=0.10).41

Controversy has also been arisen over whether the long term EPO therapy or ESAs is safe or not. Several harmful effects could theoretically happen from using this agents, although some data from several trials showed inconsequent results. EPO therapy or ESAs is associated with worsening hypertension, especially in anemic HF patients with ESRD.8,11 Increased risk of thrombosis also is considered because EPO could increase platelet activation, blood viscosity, and effect on the levels of C proteins. Eventually, EPO may cause endothelial activation and endothelin release, a circulating peptide that has been associated to harmful impact in HF.11 Further confirmatory data about the efficacy and safety of long term use of darbopoetin alfa in anemic HF patients are awaited from ongoing Reduction of Events with Darbopoetin alfa in Heart Failure (RED-HF) trial. This double-blinded, multi-centered, placebo controlled now enters phase III of clinical trial, with estimated completion date in April 2012.

These uncertainties about the efficacy, safety, and how to use EPO therapy or ESAs to treat anemia in patients with HF have led to 2 small studies using intravenous iron alone as a treatment strategy. Bolger et al used 1 g IV iron sucrose over a 12-day treatment phase to treat 16 anemic outpatients with HF. This procedure improved Hb levels followed by reduced symptoms and improvement in exercise capacity. There were no significant adverse effect in the IV iron group.43 They also noted that although using IV iron was previously considered dangerous for HF, current iron sucrose preparations are much safer than the older high-molecular-weight dextran infusion. With a more sample size, Tobli et al studied IV iron sucrose 200 mg weekly for 5 week in 40 anemic patients with chronic heart failure and chronic renal insufficiency. This randomized, placebo controlled study used NT-proBNP and C-reactive protein, along with clinical and functional status, as comparative parameters between the treatment group and placebo. After 6 months follow-up, the treatment group improved in all measured parameters, including the NT-pro BNP, NYHA class, Minnesota Living with Heart Failure Quality of Life Score, 6-min walk test, LVEF, reduced creatinine clearance, lower C-reactive protein, less diuretic use and less re-hospitalization.44 The long term reduction of NT-pro BNP with IV iron treatment and tight correlation between NT-proBNP levels and Hb are important points to note from this study. However, anemia itself is associated with elevated plasma NT-proBNP with or without HF, and correcting Hb might lead directly to reduced NT-proBNP level.45 Because NT-proBNP levels are correlated with clinical outcomes and prognosis of CHF, IV iron sucrose might become a promising strategy to improve morbidity and mortality of patients with CHF.
Another recently interesting trial using IV iron in patients with HF is Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency (FAIR-HF) Trial. This randomized, placebo-controlled study enrolled 459 patients with CHF class II-III and iron deficiency (ferritin level < 100 mcg/L or between 100 and 299 mcg/L if the transferrin saturation was <20%), either with or without anemia. Patients were randomly assigned, in a 2:1 ratio, to receive 200 mg of IV iron (ferric carboxymaltose) or saline (placebo). As the results, the FAIR-HF Investigators reported significant improvements of symptoms, NYHA class, 6-min walk test, and quality of life in the treatment group, without any prominent adverse effects. However, mortality rate was similar in two groups.

These clinical studies using IV iron to patients with HF are important because they give a promising alternative strategy different than using EPO or ESAs to treat anemia in patients with HF. Using IV iron sucrose complex might prove to be more efficacious, safer and less costly than applying long term ESAs or EPO therapy. However, additional larger and more reliable clinical trials using IV iron are still needed to confirm these data. Clinical trials using EPO therapy or ESAs also should be continued to give more reliable information about efficacy and safety of this procedure. Another approach using combination of ESAs and IV iron is also deserved to go on. Because to achieve target Hb levels with ESAs requires sufficient body iron stores, it is sensible that combining ESAs treatment with IV iron would give better outcomes. Supplementation iron should be administered to maintain a transferring saturation of 20% and a serum ferritin level of 100 ng/mL.

There are insufficient data on routine treatment of anemia in HF. However, the Canadian Cardiovascular Society in 2007 suggested that ESAs may be considered for severe symptomatic HF if Hb level is less than 9 g/dL and after iron, vitamin B12 and folate replacement. The National Kidney Foundation KDOQI clinical practice guideline recommended the range of 11.0-12.00 g/dL as the Hb target in treatment with ESAs of anemic patients with CKD and CHF.

Conclusion

Anemia is a common problem in patients with advanced heart failure and it has been recognized as an important co-morbid condition which might cause a negative effect on prognosis and clinical outcomes of those patients. EPO therapy or ESAs has become a mainstay in treatment of anemia in heart failure patients, although it is just supported by some small sample size studies. Controversy also has been developed about some theoretically adverse effects of long term use of ESAs or EPO therapy. A long term trial of darbepoeitin alfa (RED-HF) is still ongoing, and until more data are forthcoming, there are still in limbo about efficacy and long term safety of this strategy in patients with heart failure. Several other preliminary studies, supported by FAIR-HF study, reported that IV iron sucrose alone contributed to some positive results on clinical outcomes of anemic heart failure patients without any significant adverse effects, so that it might become a promising alternative strategy to treat anemia in patients with heart failure. However, current guidelines have not recommended yet treating anemia as a routine management in patients with heart failure because of limitation of reliable clinical trials supported it. We still look forward to additional larger and more carefully controlled clinical trials using ESAs or IV iron to make such procedures be considered as the proper treatment of anemia in patients with chronic heart failure.
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