SEMINARS IN
NEPHROLOGY

Erythropoietin in Heart Failure

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The incidence of both congestive heart failure (CHF) and end-stage renal disease both are increasing. Anemia is common in both conditions and is associated with a marked increase in mortality and morbidity in both CHF and chronic kidney insufficiency (CKI). Each of these 3 conditions can cause or worsen the other 2. In other words, a vicious circle frequently is present in which CHF can cause or worsen both anemia and CKI, in which CKI can cause or worsen both anemia and CHF, and in which anemia can cause or worsen both CHF and CKI. We have called this vicious circle the *cardio renal anemia syndrome*. Optimal treatment of CHF with all the recommended CHF medications at their recommended doses will, in our experience, frequently fail to improve the CHF and CKI if anemia is present and is not corrected. On the other hand, correction of the anemia with subcutaneous erythropoietin and intravenous iron has caused a great improvement in the CHF including a marked improvement in patient and cardiac function and a marked reduction in the need for hospitalization and for high-dose diuretics. It also frequently has caused renal function to improve or at least stabilize. In addition, patients' quality of life and exercise capacity also have improved with the correction of the anemia. In CKI patients, anemia also may play an important role in increasing the risk for death, coronary heart disease, stroke, and progression to end-stage renal disease. Erythropoietin may have a direct positive effect on the heart and brain unrelated to correction of the anemia by reducing cell apoptosis and by increasing neovascularization, both of which could prevent tissue damage. This could have profound therapeutic implications not only in CHF but in the future treatment of myocardial infarction, coronary heart disease, strokes, and renal failure.
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Congestive heart failure (CHF) is a major challenge in medicine. The prevalence of CHF is increasing rapidly,[1-3] perhaps because people are living longer as medical care improves, and in a decade it likely will exceed greatly the current prevalence of about 2% of the population (≈5 million people in America).[1] Despite the great progress that has been made in CHF treatment, many patients, even when adequately treated with the currently recommended therapies (angiotensin-converting enzyme inhibitors, β-blockers, angiotensin receptor blockers, and aldospirone or epleronone),[4] still have severe progressive CHF, a high mortality rate, frequent hospitalizations, and a low quality of life,[1-3,5] suffering especially from severe fatigue and shortness of breath. Why does CHF treatment fail in so many cases?

Anemia is seen commonly in patients with CHF[6-9] and has been shown to be an independent risk factor for the severity of CHF, mortality, rehospitalization,[6-9] and for progression of the often-associated chronic kidney insufficiency (CKI).[10] Could the lack of correction of this anemia be an important cause of the frequent failure of CHF treatment and the increasing prevalence of end-stage renal disease (ESRD)?

CHF is an important contributor to the progression of CKI to ESRD.[11] In a recent US study of 755 patients hospitalized with CHF, 32.1% required readmission within 1 month, 37% were dead within 1 year, and 2% developed ESRD within 1 year.[11] In those patients who already had a reduction in renal function to a creatinine clearance of less than 60 mL/min/1.73 m^2, the chance of progressing to ESRD in the first year was 3.5% and over a 4-year period was 6.1%. As stated previously, anemia may play a role in the progression to ESRD because anemia in CHF patients is an independent predictor of progression of CKI[10] and treatment of anemia in

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Table 1 Characteristics of CHF Patients Who Are Anemic Compared With Those Who Are Not Anemic

Clinical Findings
Higher mortality
More hospitalizations
Longer hospitalization stays
Higher hospital costs
More severe CKI
Lower LVEF
More frequent and more severe systolic heart failure
More frequent and more severe diastolic heart failure
Worse NYHA class
Higher brain natriuretic peptide (BNP)
Higher C-reactive protein
More resistant to medical therapy
More likely to require dialysis
Lower quality of life
Higher percentage requiring intravenous diuretics
Higher oral diuretic dose
Higher percentage requiring digoxin
A higher percentage taking aspirin and angiotensin-converting enzyme inhibitors
Older age
Less likely to be smokers
Higher prevalence of diabetes
Abnormal laboratory findings
Higher serum creatinine level
Lower creatinine clearance
More rapid decrease of GFR
Hyponatremia
Lymphopenia
Hyperuricemia
Increased Signs of Malnutrition and Inflammation
Lower caloric intake
Reduced serum albumin
Reduced serum total protein
Reduced serum cholesterol
Reduced body mass index
Evidence of iron deficiency
Higher C-reactive protein
Higher serum tumor necrosis factorα
Higher interleukin 6
Increased cortisol/decreased androgens (ie, signs of increased catabolism)
Blunted serum EPO response to anemia
Abnormal red blood cell plasma and body volume
Lower red cell mass
Higher plasma volume
Higher total body water
Higher extracellular body water
More serious cardiovascular abnormalities
Higher right and left ventricular filling pressures
Higher pulmonary artery pressure
Increased pulmonary capillary wedge pressure
Greater LV hypertrophy and left ventricular mass index
Greater atrial dimensions
Lower oxygen utilization during maximal exercise (MVO2)
Poor peripheral perfusion
Lower blood pressure
Higher heart rate

CKI slows down the rate of progression of CKI and thus reduces the need for dialysis.[12]

The mean serum creatinine level in patients with CHF is approximately 1.5 mg/dL.[6-9,11] By using this as the definition for moderate to severe CKI, about half of patients with CHF therefore have moderate to severe CKI. The same is true if the creatinine clearance is measured directly or derived from an equation. In CHF it averages approximately 60 mL/min/1.73 m^2 in CHF[6-9,11,13] so that about half of patients with CHF have levels below this—that is, they already have moderate to severe CKI when CHF is first diagnosed. In a study of CHF patients,[13] the glomerular filtration rate (GFR) decreased to a rate of approximately 1 mL/min/mo, equivalent to the decrease in GFR in severe diabetic nephropathy. Perhaps this is not surprising when one considers that CHF can cause a profound reduction in renal blood flow,[14] leading to renal ischemia, which is known to increase renal cell death and interstitial fibrosis.[15] About 25% of CKI patients with a serum creatinine level of 1.5 to 6 mg/dL have CHF.[16] This increases to up to 64% in patients starting dialysis.[17] That CHF may be an important contributor to the progression of ESRD also is suggested by a long-term study of patients with essential hypertension. The presence of CHF was a major predictor of which hypertensive patients eventually progressed to ESRD.[18] The presence of cardiovascular disease[19] as well as CHF[11] are both independent predictors of time to dialysis. The possibility therefore exists that CHF itself may be an important contributor to progressive CKI.

Anemia in CHF

The mean hemoglobin (Hb) level in CHF patients is approximately 12 to 12.5 g/dL.[6-9] If this is considered to be the lower limit of normal in men and women, it suggests that almost half of all CHF patients are anemic. The characteristics of anemic CHF patients compared with those CHF patients who are not anemic are seen in Table 1.[7-9]

Approximately 30 studies have shown that anemia in CHF patients is an independent risk factor for mortality and 8 other CHF studies have shown anemia to be an independent risk factor for rehospitalization.[7-9] The number of hospitalizations, the number of days in the hospital, and the cost of hospitalization all are higher in the anemic CHF patients, even taking into consideration other contributing factors.[7-9] Many recent studies of patients with CHF show that it is much more severe in the presence of anemia in terms of the severity of systolic and diastolic dysfunction, severity of CHF as judged by degree of shortness of breath and fatigue (New York Heart Association [NYHA] functional class), reduced exercise tolerance, higher serum beta natriuretic level, lower peak oxygen consumption with exercise, lower blood pressure, higher heart rate, and a higher pulmonary artery wedge

pressure. The anemia also is associated with a lower renal function and more rapid deterioration of renal function. Signs of malnutrition and inflammation, such as a low serum albumin level, iron level, cholesterol level, body mass index, and high C-reactive protein and tumor necrosis factor α are also more common in CHF patients who are anemic.[7-9]

The Variable Presence of Anemia in CHF

The prevalence of anemia in patients with CHF is very variable and has been reported to be present in from 2.5% to 61% of CHF cases, the average being around 40%.[6-9] This enormous variation between studies seems to be related to several factors.

Age

Although the mean age of patients with CHF in the community is approximately 74, many studies of CHF include only younger people because these may be the only patients being seen for possible heart transplantation or who are considered more suitable for controlled studies. The Hb level in these younger patients tends to be higher than in the elderly, so that anemia is less common in the younger group.

Severity of Renal Failure

Many studies of patients with CHF specifically excluded patients with CKI in whom the serum creatinine level would have been higher and the Hb level lower. Even taking the serum creatinine level into consideration grossly may underestimate the renal function because a calculated or actual creatinine clearance is a much more accurate indicator of GFR than a serum creatinine level alone.

Severity of CHF

Patients seen in out-patient clinics clearly would have a milder form of CHF at that moment than patients who are hospitalized with CHF and are in pulmonary edema. Because the prevalence and severity of anemia have been found to be greater the more severe the CHF, the prevalence and severity of anemia therefore would be worse in in-hospital patients.

Definition of Anemia

Some studies do not even define what anemia is but depend on a doctor writing it as a diagnosis in the summary. Clearly this has several problems. Doctors may not recognize a low Hb level as a problem and may ignore it. In addition, there are different criteria for what constitutes anemia. Clearly if a Hb level of 11 g/dL is taken as the definition, the prevalence of anemia will be a lot less than if 12 or 13 g/dL are taken as the criteria. However, in studies of large populations in which all types of patients are included at all ages and degrees of renal function, approximately 40% of patients have a Hb level of 12g/dL or less and the mean Hb level is approximately 12 to 12.5 g/dL.[7-9]

The Effect of Anemia in Animals With Damaged Hearts

The sensitivity of the damaged heart to anemia has been shown in many animal studies—CHF develops at much milder degrees of anemia in those animals with damaged hearts than in those with normal hearts.[20-22] The cardiac stress could be caused by a partial blockage of 1 or more of the coronaries, induced hypertensive heart disease, induced myocardial infarction (MI), or other causes.[20-22] In all these studies CHF developed at a higher Hb level than it did in anemic controls without heart disease. In 1 study of rats in whom a MI was induced and who then were subjected to a decrease in hematocrit (HCT) to 20%[23] they could only increase their cardiac output by 14% in response to the anemia compared with an increase of 45% in the anemic sham-operated control rats with normal hearts. As a result, there was a 50% decrease in oxygen delivery to the tissues in the anemic MI group compared with only a 28% decrease in the anemic sham-operated rats. In addition, the left ventricular end-diastolic pressure, an early sign of heart failure, increased twice as much in the anemic MI group than in the anemic controls, a clear sign of more severe heart failure. All this suggests that the damaged heart tolerates anemia very poorly.

How Could Anemia Cause or Worsen the CHF and CKI?

As mentioned earlier, damage to the heart from any cause can increase the chances of developing CHF if anemia is present. But anemia of any cause even without basic heart disease can cause renal and cardiac damage.[24] Anemia causes peripheral ischemia, which causes peripheral arteriolar vasodilatation and a decrease in blood pressure. This activates both the sympathetic and renin angiotensin, aldosterone, and vasopressin activity, resulting in both reduced renal blood flow, reduced GFR, and increased sodium and water absorption.[24] The expanded extracellular volume causes hemodilution and a further decrease of the Hb concentration. The increased plasma volume causes ventricular dilation, which puts an additional stress on the heart already stressed by the tachycardia and increased stroke volume caused by the increased sympathetic activity. Eventually left ventricular hypertrophy occurs, which can lead to myocardial cell death from necrosis and apoptosis. All these factors can contribute to the production of CHF. Put simply, anemia can cause or worsen edema and CHF. There are additional mechanisms whereby anemia can cause CHF. The lack of oxygen supply to the heart caused by the anemia in the face of the increased heart rate and stroke volume may cause ischemia and lead to myocardial cell death. In addition, the red blood cells contain many antioxidants and therefore, not surprisingly, anemia is associated with an increase in oxidative stress,[25,26] which could cause damage to the myocardial cells.

Does Correction of the Anemia With Erythropoietin and Iron Improve the CHF and the Associated CKI?

Is the anemia in CHF a cause of these cardiac and renal abnormalities or just an innocent bystander? Only by interventional studies in which the anemia is treated in CHF patients can this question be answered. In a joint nephrology-cardiology CHF program we found in 142 CHF out-patients that the more severe the anemia the worse the CHF.[6] In an uncontrolled prospective study of 26 anemic CHF patients resistant to a CHF medication regimen,[6] we found that correction of the associated anemia with subcutaneous erythropoietin (EPO) and intravenous iron [ferric sucrose, venofer (Venofer-Vifor Internat, St. Gallen, Switzerland)] (ferric sucrose, Venofer) improved the left ventricular ejection fraction (LVEF) and NYHA functional class, reduced hospitalization (compared with the period before anemia treatment), and allowed the dose of oral and intravenous furosemide to be reduced markedly. The correction of the anemia also prevented further deterioration of the GFR in most patients. The mean GFR, which had been decreasing before correction of the anemia, stabilized once the anemia was controlled.

In a subsequent controlled study in 32 resistant anemic CHF patients[27] we found that the mean serum creatinine level remained stable in those 16 patients in whom the anemia was corrected and increased significantly in the 16 patients in the control group in whom the anemia was not corrected. We also found, as in the previous study, that in the group in whom the anemia was corrected the LVEF, NYHA class, and diuretic dose were improved and hospitalizations were reduced compared with the period before anemia treatment. In contrast, in the 16 patients in the control group in whom anemia was not treated, 4 died of CHF-related causes, the LVEF and NYHA class worsened, and the dose of diuretics and the number of days of hospitalization increased.

Working in cooperation with our cardiologists we now jointly have treated 179 patients with anemia and resistant CHF.[28] A total of 47% were diabetic and the mean age was 73.5 ± 9.5 years. The mean serum creatinine level was 2.3 ± 1.3 mg/dL. The results were similar to our 2 previous intervention studies,[6,27] including the stabilization of the renal function. By using a visual analog scale to assess fatigue and/or shortness of breath, in which the patients themselves judge their own status and in which 10 is the worst the patient could feel and 0 the best, the patients' scores decreased from 8.8 ± 1.4 to 2.8 ± 1.9 after the anemia was corrected. This improvement is particularly striking when compared with the usual quality-of-life scores in patients with severe CHF, which usually are very poor and worsen with time.[29] All this suggests that aggressive medical treatment of CHF and control of the associated anemia may prevent the deterioration of both CHF and CKI.

In a placebo-controlled trial, Mancini et al[29] found that patients with severe CHF who received EPO for 3 months had a significant improvement in maximum oxygen utilization during peak exercise (MVO_2), in exercise duration in seconds, and distance walked in 6 minutes. In the control group none of these changed significantly. In the treated group the quality of life based on a questionnaire showed improvement in the treated group and a deterioration in the placebo group. A significant positive linear correction was observed between the change in Hb level and the change in peak VO_2. In those patients who had excessive plasma volume, correction of the anemia reduced the plasma volume to normal.

In a recent preliminary study of 84 patients with CHF and anemia, correction of the anemia over a period of 15 months with EPO and intravenous iron was associated with fewer hospitalizations and fewer hospital days, an improvement in renal function, and a reduction in diuretic dose.[30] In another preliminary study of 81 patients with CHF and anemia treated with EPO and orally administered iron, the treatment was associated with a reduction in the number of hospitalizations and an improvement in renal function.[31]

The Effect of Anemia in Other Cardiac Conditions

Even patients with heart disease but without CHF may be very sensitive to the damaging effects of anemia. Anemia has been found to be associated with markedly reduced survival in patients 1 month[32,33] and 1 year[33,34] after a MI. In addition, 2 years after elective percutaneous coronary interventions in male patients with proven coronary heart disease (CHD),[35] patients in the lowest Hb quintile showed, in a Cox regression analysis, a markedly higher risk for death (adjusted hazard rate ratio, 4.09). Indeed, in those CHD patients with an initial Hb level of 10.9 g/dL or less the mortality rate at 2 years was 55% compared with only 3% in those with a Hb level of 14 to 14.9 g/dL. Remarkably, 48% of all deaths occurred in the lowest Hb quintile, which included only 21% of all percutaneous coronary intervention patients. In several other recent similar studies of patients with CHD who underwent coronary angiography, anemia also was found to be an independent risk factor for adverse outcomes including death and cardiovascular complications.[36-39] In 1 of these studies, the anemia and CKI were found to have an additive effect on the incidence of adverse events.[37] This suggests that anemia may be a common and important contributor to death and morbidity in patients with CHD unrelated to CHF. One study suggests that this anemia actually may be causative of the mortality in CHD and not merely a casual association.[32] In that study the correction of anemia by blood transfusion during hospitalization for an acute MI was associated with a marked reduction in the mortality rate over a 1-month period compared with those anemic patients not transfused. Clearly, randomized controlled intervention trials on the role of EPO in correction of anemia in patients with CHD are indicated.

The Association Between Anemia, CHF, and Mortality in Kidney Disease

Another method to prove causality of anemia in patients with CHF would be to study the role of anemia on mortality and morbidity in other conditions. In patients with CKI the level of anemia is an independent predictor of death.[40,41] In patients with CKI not on dialysis the risk for cardiovascular events[42] including stroke[43] is increased greatly when anemia is present. In studies both in the United States[44,45] and in Europe,[46] in patients with CKI in the predialysis period, when compared with those anemic CKI patients not taking EPO, the regular use of EPO caused an increase in Hb level. This was associated with a reduction in hospitalizations including hospitalizations for CHF. Mortality and morbidity and CHF also were less when these EPO-treated patients eventually were placed on dialysis.[44,45,47,48] In patients already on dialysis the higher the level of Hb, up to 12 g/dL, the lower the mortality and hospitalization rate.[49,50]

Anemia and Progressive Renal Failure in Patients With CKI

Anemia also may increase the rate of deterioration of renal function in patients with CKI[41,51] and therefore the rate of progression of renal failure to dialysis. In a study of more than 1 million US elderly in the Medicare system,[41] patients with CHF alone, CKI alone, or those with a combination of CHF and CKI were more likely to die or to progress to dialysis if they were anemic than if they were not. This is consistent with our own findings[6] that anemic CHF patients lose GFR at a rate of about 1 mL/min/mo and that this decrease in GFR can be stabilized in most of the patients if the anemia is corrected and the CHF is well treated.[6,27,28]

The Cause of the Anemia in Patients With CHF

The main cause of the anemia is most likely CKI produced by the renal vasoconstriction leading to prolonged renal ischemia.[14] This causes renal damage[14,15] and reduced production of EPO in the kidneys.[52] In diabetic patients the anemia may be more common and more severe. For every level of renal function the Hb level of diabetic patients is lower than in nondiabetic patients.[53] This likely is caused by early damage of the EPO producing cells in the interstitium of the kidneys in diabetic patients. The degree of anemia in diabetes is proportional to the degree of microalbuminuria, macroalbuminuria, and the degree of renal insufficiency.[53] As a result, EPO levels in the blood of diabetic patients fail to increase to the same levels as they do in nondiabetic patients with the same level of renal function.[54]

Studies in animals have shown that CHF itself may cause anemia independent of CKI.[55] The damaged heart may secrete cytokines such as tumor necrosis factor α,[55] which can cause anemia in 4 ways:[56] by reducing EPO production in the kidneys, by interfering with EPO activity at the level of the bone marrow, by inhibiting the release of iron from the reticuloendothelial system so that it cannot get to the bone marrow to be used in Hb production, and by inhibiting iron absorption through the gut. This is done through cytokine production of the protein hepcidin in the liver which inhibits iron absorption in the small bowel.[57] Indeed, it has been shown that the higher the tumor necrosis factor α level in patients with CHF, the lower the Hb level.[58] EPO production and use also can be inhibited by angiotensin-converting enzyme inhibitors, which can cause anemia.[59] Iron deficiency also is common in anemic CHF patients. There is some preliminary work to show that the bone marrow in anemic CHF patients frequently is depleted of iron,[60] as it is in many anemic patients with CKI.[61,62] This iron deficiency may be caused partly by the fact that many CHF patients have a reduced appetite.[63] Aspirin, which often is used in CHF patients, may cause blood loss in the gut. Another reason for iron deficiency is that CHF patients often have proteinuria, and EPO, iron, and transferrin all can be lost in significant amounts in the urine with protein,[64] contributing to the anemia. CKI, as mentioned previously, is very common in patients with CHF, also is associated with reduced absorption of iron in the gut.[65] CHF alone also may cause malabsorption—probably because of edema in the gut[63] and, as mentioned above, through hepcidin production in the liver. Giving iron pills[66] or intravenous iron[60] to patients with CHF can improve the anemia. We[67,68] have shown that the anemia of CKI also often will respond well to intravenous iron. Finally, part of the anemia in CHF may be caused by hemodilution, but recent studies show that the majority of anemic CHF patients actually have a reduced red cell volume.[69]

Could EPO Alone Be Affecting the Heart Without Relationship to Anemia?

Besides its role on hematopoietic cells, EPO recently has been found to have several nonhematopoietic effects as well. There are large reductions in infarct size after EPO therapy in the hearts and brains of rats after exposure to ischemia and reperfusion and other forms of tissue damage.[70,71] This improvement may be caused partially by the antiapoptotic effects of EPO and partly by its proangiotic effects causing neovascularization.[70,71] In a randomized double-blind study of 40 patients with an ischemic stroke who received either EPO or saline for 3 days after a stroke, no adverse effects were seen from EPO.[72] One month later the investigators observed an improvement in clinical outcome and a trend toward reduction in infarct size in the EPO-treated group.

The Vicious Circle of CHF, CKI, and Anemia: The Cardiorenal Anemia Syndrome

A vicious circle appears to be present in CHF, in which CHF itself causes both anemia and CKI. The CKI causes more anemia and the anemia and CKI act back to further worsen the CHF, which then further worsens the anemia and CKI, and so on. In other words, each of the 3 can cause or be caused by the other. We suggest calling this relationship the *cardiorenal anemia syndrome*.[7-9]

heart failure
↕ ↕
anemia ↔ renal failure

The importance of this concept is that if the anemia is not treated in CHF patients there likely will be resistance to any other form of CHF therapy and there will be progression of both the CHF and the CKI. Thus, correction of anemia may be crucial in the prevention of the progression of both CHF and CKI. It also follows that the failing heart needs maximal protection with all the CHF medications in the recommended doses.

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