Pathogenesis of Anemia in Cardiorenal Disease

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The link between chronic heart failure (CHF) and chronic kidney disease (CKD) is well known. Approximately 50% of patients with CHF have some renal dysfunction, and 25% of patients with CKD and serum creatinine levels ranging from 1.5 mg/dL to 6 mg/dL have CHF. The association of CHF with CKD is strong and may contribute to its long-term progression. Anemia is also common in patients with CKD and contributes to increased morbidity and mortality. More recently, anemia has been found to be frequently present in patients with CHF, and its presence is associated with worse long-term CHF outcomes. Thus, anemia, CHF, and CKD may be independently related to one another, and this relationship may have important implications for their management.

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The link between chronic heart failure (CHF) and chronic kidney disease (CKD) is well known. Serum creatinine is increased in patients with CHF, varies with the severity of CHF, and is an independent risk factor for adverse events.[1,2] Approximately 50% of patients with CHF have some renal dysfunction, and 25% of patients with CKD have CHF.[3] Many more CKD patients have asymptomatic left ventricular (LV) dysfunction. Thus, the association of CHF with CKD is strong and may contribute to its long-term progression.

Anemia is also common in patients with CKD and contributes to increased morbidity and mortality.[4] More recently, anemia has been found to be

frequently present in patients with CHF,[5,6] and its presence is associated with worse long-term CHF outcomes.[5,6] Thus, anemia, CHF, and CKD may be independently related to one another, and this relationship may have important implications for their management.

In this review, the magnitude of the problem of anemia in heart failure will be discussed. Factors that are associated with the development and worsening of anemia in CHF will be examined. The mechanisms that may be involved with worsening of CHF in patients with anemia will be outlined. Finally, the long-term adverse outcomes associated with anemia in CHF will be described.

Prevalence of Anemia in Heart Failure and Chronic Kidney Disease

The prevalence of anemia in CHF patients varies considerably, depending on the definition of anemia used and the population studied. The World Health Organization defines anemia in the general population as hemoglobin (Hb) concentration less than 13.0 g/dL in men and less than 12.0 g/dL in women.[7] Using this definition, investigators in the Atherosclerosis Risk in Communities (ARIC) study found that approximately 9% (5% of all men, 13% of all women) of a normal population (n = 15,792), aged 45 to 64 years, in 4 US communities, have anemia.[8] In hospitalized patients, the prevalence of anemia has varied from 14% to 70% in different studies. In the more stable and highly selected patients seen in CHF clinical trials, values of 15% to 56% are reported (Table 1).

A study by McClellan and colleagues[9] examined rates of anemia in 5222 predialysis CKD patients. Overall, anemia (Hb ≤ = 12 g/dL) was shown to be present in 47.7% of patients and prevalence of anemia increased as kidney function, as measured by GFR, decreased. Diabetes, female sex, and African-American, Hispanic, or Asian ethnicity were all factors that increased the likelihood of anemia.

Table 1
Prevalence of Anemia in Patients Randomized in CHF Trials and Hospitalized for Worsening CHF

Stable Patients in Heart Failure Clinical Trials

Study	N	Anemia Definition	Prevalence
Silverberg et al[42]	142	Hb < 12 g/dL	56%
STAMINA-HFP[48]	982	Hb < 12 g/dL F, < 13 g/dL M	33%
UCLA Study[12]	1061	Hb < 12 g/dL F, < 13 g/dL M	30%
Val-HeFT[11]	5010	Hb < 12 g/dL F, < 13 g/dL M	23%
PRAISE[39]	1130	Hct < 37.6%	20%
RENAISSANCE[13]	912	Hb ≤ 12 g/dL	20%
COPERNICUS[49]	2286	Hb < 12.5 g/dL	19%
ELITE II[50]	3044	Hb ≤ 12.4 g/dL	17%
Szachniewicz[51]	176	Hb < 12 g/dL	17%
IN-CHF[14]	2411	Hb < 11 g/dL F, < 12 g/dL M	16%
Tanner[52]	193	Hb < 12 g/dL	15%

Hospitalized Heart Failure Patients

Study	N	Anemia Definition	Prevalence
McClellan et al[3]	663	Hct < 40	70%
Wexler et al[53]	338	Hb < 12 g/dL	52%
OPTIME-CHF[54]	906	Hb < 13 g/dL M, < 12 g/dL F	49%
Kosiborod et al[41]	2281	Hct ≤ 37%	48%
Herzog et al[55]	152,584	ICD-9 codes	28%
EuroHeart Failure Survey[56]	9971	Hb < 11 g/dL	21%
Ezekowitz et al[40]	12065	ICD-9 codes	17%
Cromie et al[22]	269	Hb ≤ 11 g/dL	14%

CHF, chronic heart failure; Hb, hemoglobin; ICD, international classification of diseases; Hct, hematocrit; STAMINA-HFP, Study of Anemia in a Heart Failure Population; UCLA, University of California, Los Angeles; Val-HeFT, Valsartan in Heart Failure Trial; PRAISE, Prospective Randomized Amlodipine Survival Evaluation; RENAISSANCE, Randomized Etanercept North American Strategy to Study Antagonism of Cytokines; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; ELITE, Evaluation of Losartan In The Elderly; IN-CHF, In-Community Heart Failure; OPTIME-CHF, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure.

Incidence of Anemia and Changes in Hemoglobin Over Time

Although the high prevalence of anemia in patients with CHF is now well established, only a few studies have reported the incidence of developing anemia or changes in Hb over time in the same patient populations. In the Studies of Left Ventricular Dysfunction (SOLVD), the prevalence of anemia (hematocrit < 39 in men and < 36 in women) at baseline was 18.4%, and new anemia developed in 9.6% patients over 1 year.[10] In the Valsartan for Heart Failure Trial (Val-HeFT), the prevalence of anemia

(Hb < 13.0 g/dL in men and < 12.0 g/dL in women) at baseline was 23%, and new onset anemia developed in 16.9% of patients.[11] These studies illustrate that both prevalent and incident anemia are common in patients with CHF.

Clinical Characteristics of Anemic Patients With Heart Failure

When compared to CHF patients who do not have anemia, anemic patients are more likely to be older, female, and have diabetes and chronic renal failure. These patients are also more likely to have more severe CHF as indicated by higher New York Heart Association (NYHA) class, lower exercise capacity, worse quality-of-life scores, greater peripheral edema, lower blood pressure, higher use of diuretic and other cardiovascular medications, worse neurohormonal profiles, and higher C-reactive protein (CRP) levels.[1,5,11-14] However, anemic patients with CHF do not appear to have worse LV dysfunction as compared to non-anemic patients. In the Val-HeFT database, measures of ejection fraction and LV size were no different in patients with or without anemia.[11] Moreover, the prevalence of anemia is similar in patients with CHF due to LV dysfunction or preserved LV function.[15,16] These findings raise the interesting question of the nature of the association between anemia and CHF.

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Causes of Anemia in Heart Failure

Although the mechanisms of developing anemia in patients with CHF are not entirely clear, several factors may be involved in its pathogenesis. Impaired renal perfusion resulting in renal dysfunction and decreased erythropoietin (EPO) secretion has been considered an important factor. However, there is evidence that EPO levels are increased in CHF,[17,18] suggesting a relative EPO resistance in this condition. Inflammation has also been implicated: tumor necrosis factor-α (TNF-α) and several other pro-inflammatory cytokines,[19] as well as circulating neutrophils and CRP, are elevated in CHF patients.[20] TNF-α may cause anemia through a number of different mechanisms, including inhibition of EPO production in the kidney, preventing EPO from stimulating bone marrow production of erythrocytes, and preventing the release of iron from body stores. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers used in the treatment of CHF cause a modest reduction in Hb by inhibiting EPO synthesis, and may contribute to the development of anemia.[11,21] Although hematinic abnormalities are generally not seen in CHF,[22,23] iron deficiency may occur because of malabsorption or nutritional deficiencies due to CHF associated cachexia[24] and aspirin-induced gastrointestinal bleeding. Finally, in a recent study of patients with severe CHF awaiting heart transplantation, hemodilution due to expanded plasma volume was found to be the cause of anemia in nearly half the patients, who were clinically euvolemic.[25] Thus, multiple mechanisms could cause anemia in patients with CHF.

Does Anemia Worsen Heart Failure?

In chronic severe anemia, several physiologic adjustments compensate to maintain tissue oxygenation. These include an increase in EPO[26] production in patients with normal renal function that helps to increase Hb; a shift of the hemoglobin-oxygen dissociation curve to the left, which helps to unload oxygen to the peripheral tissues; and peripheral vasodilation that helps to increase cardiac output and blood flow to the tissues.[27] Although the exact mechanisms by which anemia causes or worsens CHF are not clear, peripheral vasodilation appears to play a central role in its pathogenesis.[28]

In order to understand the mechanisms of fluid retention in these patients, hemodynamics, body fluid compartments, and neurohormones were studied in a group of patients with untreated chronic, severe anemia. The findings were compared with those seen in patients with severe, untreated cardiomyopathy.[27,29] Table 2 compares the hemodynamics of patients with untreated chronic, severe anemia and untreated CHF. The anemic patients had a high cardiac output, low blood pressure, and low systemic vascular resistance (SVR) when compared to patients with untreated CHF, who had low

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Table 2
Hemodynamics of Untreated Chronic Severe Anemia and Untreated CHF

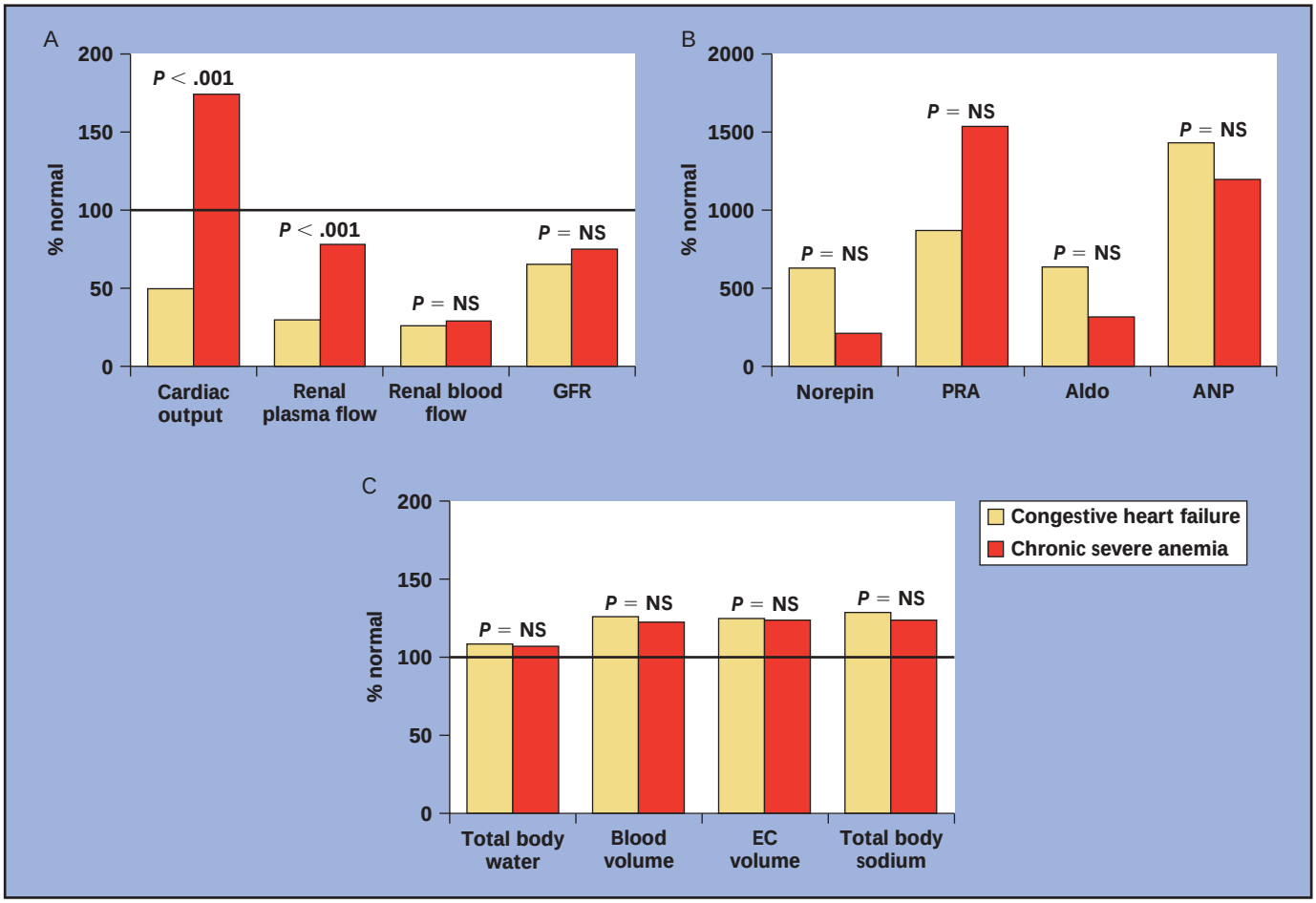
	HR beats/min	RAP mmHg	PAP mmHg	PAWP mmHg	AOP mmHg	CI L/min/m^2	SVR dynes.sec.cm^{-5}
Anemia[27]	92	9	22	15	77	6.6	629
CHF[29]	114	15	44	30	90	1.75	2495

CHF, chronic heart failure; HR, heart rate; RAP, mean right atrial pressure; PAP, mean pulmonary arterial pressure; PAWP, mean pulmonary arterial wedge pressure; AOP, mean systemic arterial pressure; CI, cardiac index; SVR, systemic vascular resistance.
Data from Anand et al.[27,29]

cardiac output, normal blood pressure, and high SVR.

Despite fundamental differences in hemodynamics, renal blood flow and glomerular filtration rates (GFR) were similarly reduced in the 2 groups (Fig 1A). A very similar neurohormonal response was seen in both conditions (Fig 1B) that resulted in an identical increase in body fluid compartments (Fig 1C). The mechanism responsible for similar hormonal response in low- and high-output CHF appears to be a tendency toward low arterial blood

Figure 1. *Comparison of* **(A)** *hemodynamics,* **(B)** *hormone levels, and* **(C)** *body fluid compartments in patients with untreated chronic, severe anemia versus those with severe, untreated cardiomyopathy. GFR, glomerular filtration rate; PRA, plasma renin activity; Norepin, norepinephrine; Aldo, aldosterone; ANP, atrial natriuretic peptide; EC, extracellular. Data from Anand et al.[27,29]*



pressure in both of these conditions. Blood pressure is low or is threatened in low-output states because of a low cardiac output and because of a decrease in SVR in high-output states.[28] The neurohormonal response evoked by the body is, however, similar. The origins of the response can probably be traced back in evolution, to the time when maintenance of arterial pressure during flight and fight were of paramount importance for the survival of the species. The same stereotyped response is seen whenever the blood pressure is "threatened," whatever the cause.

In patients with chronic severe anemia, SVR is reduced partly because of low blood viscosity, and in part due to enhanced basal activity of nitric oxide,[30] with up-regulation of renal and vascular nitric oxide synthase.[31] A decrease in SVR reduces blood pressure and sets in motion baroreceptor-mediated neurohormonal activation, which, as mentioned above, is identical to that seen in patients with severe low-output heart failure.[27-29] The increased sympathetic and renin-angiotensin-aldosterone activity results in peripheral vasoconstriction, tachycardia, and increased stroke volume. Renal blood flow is reduced, leading to a decrease in GFR, causing kidneys to retain salt and water. Extracellular and plasma volumes expand, leading to ventricular dilation. Pulmonary and systemic venous congestion follow, resulting in the clinical syndrome of heart failure. The increased cardiac workload coupled with neurohormonal activation may cause LV hypertrophy, a risk factor for worse cardiovascular outcomes.[32,33] Over the long term, these factors may result in necrosis and apoptosis of the cardiac myocytes, leading to cardiac fibrosis and progressive LV remodeling and dysfunction. Data from the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trial showed that a 1 g/dL increase in Hb level was associated with a 4.1 g/m^2 decrease in LV mass index over 24 weeks.[13] Anemia could also worsen myocardial ischemia and thereby contribute to LV dysfunction. The pathogenetic role of severe anemia in causing high-output failure is underscored by studies showing that correction of anemia promptly reverses fluid retention.[27] Figure 2 shows the possible sequence of events in the pathogenesis of heart failure in patients with anemia.

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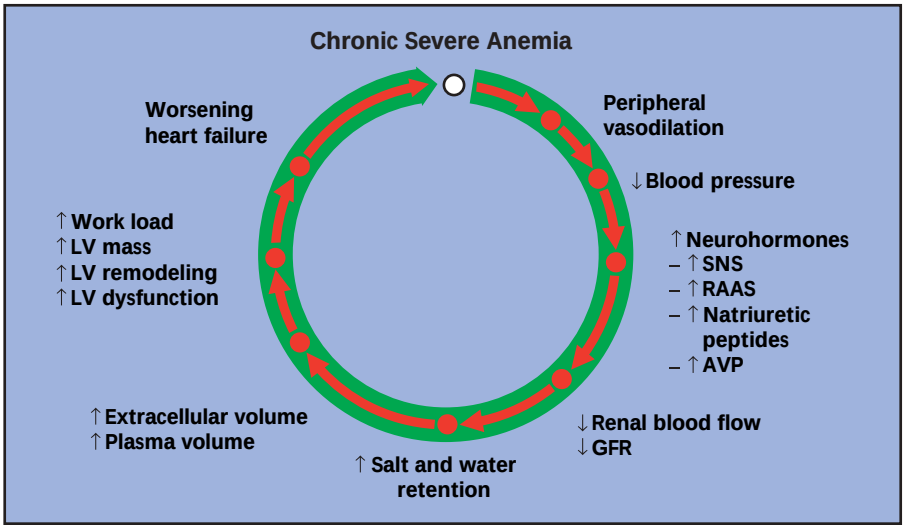
Interrelated Pathogenesis of Anemia, Diabetes, and Chronic Kidney Disease

Diabetes, renal failure, heart failure, and anemia are tightly linked conditions. Whether anemia is worsened or is caused, in part, by diabetes is not clear. In diabetic nephropathy (DN), anemia tends to be more severe, and occurs at an earlier stage than in nondiabetic renal disease. However, because most patients with DN may have little overt renal impairment, their first-line health care providers may not be aware of the critical importance of screening for anemia in this population and it may often go unrecognized and untreated.[34]

Normochromic, normocytic anemia of EPO deficiency is found in DN before the onset of advanced renal failure, but does not occur in nondiabetic renal disease of similar severity. Bosman and colleagues[35] postulated that EPO deficiency might be caused, at least in part, by efferent sympathetic denervation of the kidney, leading to the loss of appropriate EPO production. These

Figure 2. *Pathophysiology of fluid retention in chronic severe anemia. SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; AVP, arginine, vasopressin; GFR, glomerular filtration rate; LV, left ventricular. Data from Anand et al.[27]*



workers questioned whether anemia with EPO deficiency occurs in type 1 diabetic patients with DN, in the absence of advanced renal failure, compared with patients with nondiabetic renal disease of similar severity. A total of 27 type 1 diabetic patients with DN (defined as persistent proteinuria), were compared with 26 nondiabetic patients with glomerulonephritis and persistent proteinuria. Hb concentration, red cell indices, and serum EPO levels were measured, whereas other causes for anemia were excluded. An association was found between anemia and EPO deficiency early in DN, before the onset of advanced renal failure, which was not seen in nondiabetic renal disease of similar severity. The researchers speculated that in nephrotic syndrome, EPO deficiency results from the severity of proteinuria, leading to excessive loss of EPO in the urine.

EPO release by renal cells is modulated by kidney splanchnic innervation. Renal denervation in animal models leads to a loss of EPO production in response to hypoxic stimuli, and EPO deficiency has recently been observed in anemic type 1 diabetic patients with severe, symptomatic DN. In a small cohort, the serum EPO levels in anemic diabetic patients were found to be inappropriately low compared to the values observed in a control group of anemic subjects with iron deficiency. These findings led Winkler and associates[36] to conclude that efferent sympathetic denervation of the kidneys may contribute to EPO deficiency.

Moreover, a reduced number of specific EPO-synthesizing interstitial cells and impairment of the processes enabling oxygen sensing, secondary to interstitial fibrosis or vascular lesions, has also been considered to cause anemia prematurely in patients with type 1 diabetes and diabetic nephropathy, before the onset of advanced renal failure. Other mechanisms causing EPO deficiency include cytokine-induced inhibition of EPO synthesis, hyporeninemia, urinary loss of EPO, and glycation of the EPO receptor by, or secondary to, hyperglycemia. There is now considerable evidence that anemia worsens outcomes of peripheral small vessel disease in diabetic patients and that recombinant human EPO (epoetin) therapy may prevent or reverse these complications.[34]

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Weiner and colleagues[37] investigated the effects of anemia (hematocrit $< 36\%$ in women and $< 39\%$ in men) and left ventricular hypertrophy on cardiovascular outcomes in 2423 patients with CKD (GFR 15-60 mL/min /1.73 m^2). Electrocardiogram and anemia data was available in 96% of these patients. Left ventricular hypertrophy was found to be an independent risk factor for the composite of myocardial infarction, stroke, and death, as well as cardiac outcomes, whereas anemia was independently associated with increased risk for only the composite outcomes. The authors concluded the combination of anemia and LVH in CKD identifies a high-risk population.

The relation between anemia in CHF and renal dysfunction was reported by Philipp and associates in 2941 patients.[38] They found that whereas anemia was positively associated with symptoms of HF as median hemoglobin levels fell, anemia was not associated with any LV structure or function parameters. However, symptoms of HF were associated with renal dysfunction. The mean estimated GFR in patients with New York Heart Association class I HF was 82 mL/min/1.73 m^2 and 59 ml/min/1.73 m^2 in patients with class IV ($P < .05$). As expected, there was an association between impaired renal function and hemoglobin values, and even in patients with normal renal function (GFR $>$ 85 mL/min) there was an association of anemia and HF. These findings support the previously described Val-HeFT data.

Impact of Anemia and Lower Hemoglobin on Outcomes in Patients With Heart Failure

Several studies have reported that anemia and low Hb are independent predictors of mortality in patients with CHF,[1,10-13,39-41] and a few studies have shown that anemia and lower Hb concentrations are also independently associated with higher rates of hospitalizations for heart failure.[11,13] In the Val-HeFT trial, for example, anemia increased the unadjusted risk of mortality by 39% (RR 1.39, 95% CI 1.21-1.57), and of hospitalization for CHF by 55% (HR 1.55, 95% CI 1.34-1.81). Although the degree of anemia in these patients was mild (average Hb in anemic patients = 11.9 g/dL), the presence of anemia increased the risk of death by 21% and hospitalization for heart failure by 17%, independent of other important prognostic variables.[11] Hence, even modestly reduced Hb in patients with CHF could have important health care implications.

Although in Val-HeFT, 1 g/dL lower baseline Hb was associated

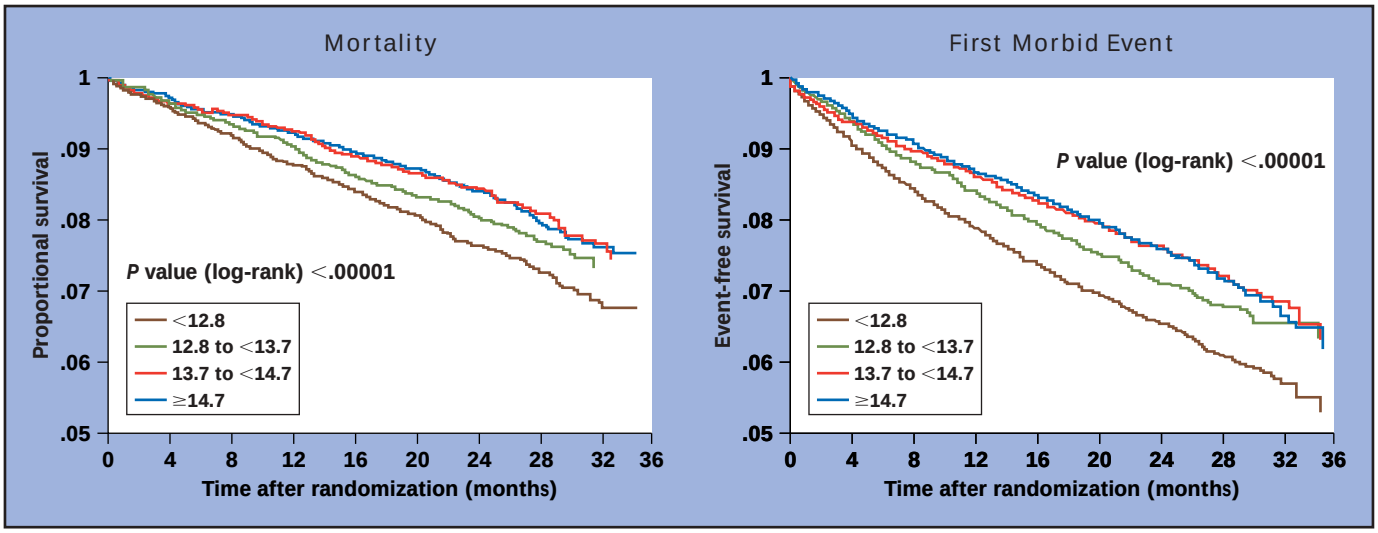
with a 12.6% increase in mortality risk and a 19.3% increase in hospitalizations for heart failure,[11] it should be emphasized that the association of Hb with adverse effects is not linear. Figure 3 shows the Kaplan-Meier curves for baseline Hb values in quartiles for mortality and morbidity. It is important to note that the risks are nearly identical in the 2 highest Hb quartiles (13.7-<14.7 g/dL; ≥14.7 g/dL) representing patients with normal Hb. Most of the increased risk of morbidity and mortality is seen in the lower 2 quartiles (<12.8 g/dL; 12.8-<13.7 g/dL), which together included all anemic patients. Moreover, a 1 g/dL decrease in Hb was associated with a significant increase in mortality (RR 1.148, 95% CI 1.06-1.25, $P < .001$) in patients with baseline Hb below the median (13.7 g/dL) (mean Hb = 12.51 g/dL) but not in patients with Hb above the median (mean Hb 14.8 g/dL, RR 1.016, 95% CI 0.91-1.14, $P = .78$).

Whereas several studies have confirmed the adverse effects of anemia and low baseline Hb, few have examined the effect of spontaneous changes in Hb over time with subsequent mortality and morbidity. In the SOLVD trial, prevalent anemia at baseline was associated with a 44% increase in mortality. New onset anemia was associated with a much greater (108%) increase in mortality.[10] In Val-HeFT, the quartile of patients who had the greatest decrease in Hb over 12 months (14.2 decreasing to 12.6 g/dL) had a significantly greater subsequent mortality (13.2%) than the quartile of patients with the smallest changes in Hb (13.7 to 13.8 g/dL, 8.5% mortality). Compared to this latter group, the quartile of patients who experienced an increase in Hb (13.3 to 14.4 g/dl) did not have a better prognosis (9.8% mortality).[11]

Because the baseline risks may be different in patients who spontaneously increase or decrease their Hb over time, the analyses were repeated separately in patients with or without anemia at baseline. There were 668 patients with anemia at baseline who survived 12 months and had a complete set of baseline covariates. Fifty-nine percent of the patients with anemia at baseline had an increase in Hb over 12 months, averaging 1.0 ± 1.0 g/dL. After adjustment for the differences in baseline risks, patients who had an increase in Hb of 1.0 g/dL had a significantly lower risk of mortality (HR 0.78, CI 0.65-0.93). In the much larger subgroup of 2424 patients who were not anemic at baseline, 43% had an increase in Hgb that averaged 0.6 ± 0.5 g/dL. In the non-anemic group, an increase in Hb of 1.0 g/dL was also associated with a significantly lower risk of mortality (HR 0.79, CI 0.71-0.89).[11]

Do these data, therefore, imply that treatment of anemia in patients with CHF may be beneficial? Several small clinical studies have shown that treatment of anemia with EPO in patients with CHF is clinically beneficial.[42-44] However, as shown above, therapeutic measures to increase Hb may increase systemic vascular resistance and decrease cardiac output, thereby worsening hemodynamics.[27,30] Also, raising hematocrit above 42% has been shown in a large randomized trial to increase cardiovascular mortality[45] and trials have been stopped early in Europe because

Figure 3. *Kaplan-Meier mortality and morbidity curves from the Valsartan in Heart Failure Trial (Val-HeFT). Data from Anand et al.[11]*



of excessive vascular events in the EPO-treated groups.[46,47] Fortunately, a number of trials are in progress and others are being designed to test the hypothesis of whether Hb should be raised and ideal levels achieved in patients with CHF. Please see Dr. Foley's article in this publication for a more in-depth discussion of this question.

Conclusion

In conclusion, the prevalence and incidence of anemia is high in patients with CHF. Both prevalent and incident anemia, lower baseline Hb, and decreases in Hb over time are associated with higher mortality and morbidity. However, whether an increase in Hb is associated with improved outcomes, and the ideal level of Hb to achieve in patients with CHF, both remain unknown. Several factors, including renal dysfunction, increase in proinflammatory cytokines, and hemodilution, may explain anemia and changes in Hb over time in these patients. However, LV dysfunction does not appear to be a factor. Chronic severe anemia may increase neurohormonal activation and thereby contribute to the progression of heart failure. However, further studies are required to understand the basis of the remarkable association of anemia with CHF mortality and morbidity, to prospectively assess the potential benefit of correcting anemia, and to evaluate the ideal threshold at which therapy should be initiated and the extent of correction considered safe and desirable in the individual patient with CHF. Such studies are in progress. ■

References

1. Al-Ahmad A, Rand WM, Manjunath G, 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.
2. Gottlieb SS, Abraham W, Butler J, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail*. 2002;8:136-141.
3. McClellan WM, Flanders WD, Langston RD, et al. 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.
4. Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol*. 2001; 12:2465-2473.
5. Komajda M. Prevalence of anemia in patients with chronic heart failure and their clinical characteristics. *J Card Fail*. 2004;10:S1-S4.
6. McMurray JJ. What are the clinical consequences of anemia in patients with chronic heart failure? *J Card Fail*. 2004;10:S10-S12.
7. Dallman PR. *Iron Nutrition in Health and Disease*. London: John Libbey & Co; 1996.
8. Sarnak MJ, Tighiouart H, Manjunathg, et al. Anemia as a risk factor for cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol*. 2002; 40:27-33.
9. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin*. 2004;20: 1501-1510.
10. Ishani A, Weinhandl E, Zhao Z, et al. Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the

Main Points

- Anemia is common in patients with chronic kidney disease (CKD) and is frequently present in patients with chronic heart failure (CHF); its presence is associated with worse long-term CHF outcomes and contributes to increased morbidity and mortality from CKD.
- Causes of anemia in CHF patients include, but may not be limited to: impaired renal perfusion resulting in renal dysfunction and decreased erythropoietin (EPO) secretion; inflammation as indicated by elevated levels of tumor necrosis factor-α, circulating neutrophils, and C-reactive protein; the use of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapies, which can cause decreases in hemoglobin (Hb) levels; and hemodilution due to expansion of plasma volume.
- The increased cardiac workload characteristic of severe, chronic anemia, coupled with neurohormonal activation, may cause left ventricular hypertrophy, a risk factor for worse cardiovascular outcomes, as well as, in the long term, necrosis and apoptosis of the cardiac myocytes, leading to cardiac fibrosis and progressive left ventricular remodeling and dysfunction.
- Several studies, including the Valsartan in Heart Failure Trial and the Studies of Left Ventricular Dysfunction (SOLVD), have reported that anemia and low Hb are independent predictors of mortality in patients with CHF, and a few studies have shown that anemia and lower Hb concentrations are also independently associated with higher rates of hospitalizations for heart failure.
- The SOLVD trial also examined the effect of spontaneous changes in Hb over time, showing that prevalent anemia at baseline was associated with a 44% increase in mortality, whereas new onset anemia was associated with a much greater 108% increase in mortality.
- Several small clinical studies have shown that treatment of anemia with EPO in patients with CHF is clinically beneficial.

impact of incident anemia on mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2005;45:391-399.
11. Anand IS, Kuskowski MA, Rector TS, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: Results from Val-HeFT. *Circulation*. 2005 (in press).
12. Horwich TB, Fonarow GC, Hamilton MA, et al. 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;39:1780-1786.
13. Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. *Circulation*. 2004;110:149-154.
14. Maggioni AP, Opasich C, Anand I, et al. Anemia in patients with heart failure: Prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail*. 2005;11:91-98.
15. Brucks S, Little WC, Chao T, et al. Relation of anemia to diastolic heart failure and the effect on outcome. *Am J Cardiol*. 2004;93:1055-1057.
16. Nair D, Shlipak MG, Angeja B, et al. Association of anemia with diastolic dysfunction among patients with coronary artery disease in the Heart and Soul Study. *Am J Cardiol*. 2005;95: 332-336.
17. 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.
18. George J, Patal S, Wexler D, et al. Circulating erythropoietin levels and prognosis in patients with congestive heart failure: comparison with neurohormonal and inflammatory markers. *Arch Intern Med*. 2005;165:1304-1309.
19. Deswal A, Petersen NJ, Feldman AM, et al. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation*. 2001;103:2055-2059.
20. Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure: Prognostic value and the effect of valsartan. *Circulation*. 2005; (in press).
21. Albitar S, Genin R, Fen-Chong M, et al. High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients. *Nephrol Dial Transplant*. 1998;13: 1206-1210.
22. Cromie N, Lee C, Struthers AD. Anaemia in chronic heart failure: what is its frequency in the UK and its underlying causes? *Heart*. 2002;87:377-378.
23. Witte KK, Desilva R, Chattopadhyay S, et al. Are hematinic deficiencies the cause of anemia in chronic heart failure? *Am Heart J*. 2004;147: 924-930.
24. Anker SD, Chua TP, Ponikowski P, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation*. 1997;96:526-534.
25. Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. *Circulation*. 2003;107:226-229.
26. Adamson JW. Regulation of red blood cell production. *Am J Med*. 1996;101:4S-6S.
27. Anand IS, Chandrashekhar Y, Ferrari R, et al. Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. *Br Heart J*. 1993;70:357-362.
28. Anand IS, Florea VG. High output cardiac failure. *Current Treatment Options in Cardiovascular Medicine*. 2001;3:151-159.
29. Anand IS, Ferrari R, Kalra GS, et al. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. *Circulation*. 1989;80:299-305.
30. Anand IS, Chandrashekhar Y, Wander GS, Chawla LS. Endothelium-derived relaxing factor is important in mediating the high output state in chronic severe anemia. *J Am Coll Cardiol*. 1995;25:1402-1407.
31. Ni Z, Morcos S, Vaziri ND. Up-regulation of renal and vascular nitric oxide synthase in iron-deficiency anemia. *Kidney Int*. 1997;52:195-201.
32. Olivetti G, Quaini F, Lagrasta C, et al. Myocyte cellular hypertrophy and hyperplasia contribute to ventricular wall remodeling in anemia-induced cardiac hypertrophy in rats. *Am J Pathol*. 1992;141:227-239.
33. Elhendy A, Modesto KM, Mahoney DW, et al. Prediction of mortality in patients with left ventricular hypertrophy by clinical, exercise stress, and echocardiographic data. *J Am Coll Cardiol*. 2003;41:129-135.
34. Deray G, Heurtier A, Grimaldi A, et al. Anemia and diabetes. *Am J Nephrol*. 2004; 24: 522-526.
35. Bosman DR, Winkler AS, Marsden JT, et al. Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. *Diabetes Care*. 2001; 24:495-499.
36. Winkler AS, Marsden J, Chandhuri KR, et al. Erythropoietin depletion and anaemia in diabetes mellitus. *Diabet Med*. 2000;17:410.
37. Weiner DE, Tighiouart H, Vlagapoulos PT, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. *J Am Soc Nephrol*. 2005; 16:1803-1810.
38. Philipp S, Ollmann H, Schink T, et al. The impact of anemia and kidney function in congestive heart failure and preserved systolic function. *Nephrol Dial Transplant*. 2005; 20:915-919.
39. 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;41: 1933-1939.
40. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12, 065 patients with new-onset heart failure. *Circulation*. 2003;107:223-225.
41. Kosiborod M, Smith GL, Radford MJ, et al. The prognostic importance of anemia in patients with heart failure. *Am J Med*. 2003;114: 112-119.
42. 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 reduces hospitalizations. *J Am Coll Cardiol*. 2000;35:1737-1744.
43. 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.
44. Mancini DM, Katz SD, Lang CC, et al. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation*. 2003;107:294-299.
45. 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 epoetin. *N Engl J Med*. 1998;339:584-590.
46. Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol*. 2003;4:459-460.
47. FDA ODACMot. Safety of Erythropoietin Receptor Agonists in Patients with Cancer. www.fda.gov/ohrms/dockets/ac/04/agenda/ 4037a_final.htm_05-06-2004.
48. Dunlap SH, Pina IL, Cotts WG, et al. for the STAMINA-HFP Investigators. Lower hemoglobin is associated with persistently reduced quality of life in unselected patients with heart failure: Results from the Study of Anemia in a Heart Failure Population (STAMINA-HFP) Registry. Abastract 311, presented at the Heart Failure Society of America 8th Annual Scientific Meeting. Toronto, Canada, September 13, 2004.
49. Anker SD, Coats AJS, Roecker EB, et al for the COPERNICUS Study Group. Hemoglobin level is associated with mortality and hospitalization in patients with severe chronic heart failure: Results from the COPERNICUS study. *J Am Coll Cardiol*. 2004;43 (Suppl A):842-2.
50. Sharma R, Francis DP, Pitt B, et al. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. *Eur Heart J*. 2004;25:1021-1028.
51. Szachniewicz J, Petruk-Kowalczyk J, Majda J, et al. Anaemia is an independent predictor of poor outcome in patients with chronic heart failure. *Int J Cardiol*. 2003;90:303-308.
52. Tanner H, Moschovitis G, Kuster GM, et al. The prevalence of anemia in chronic heart failure. *Int J Cardiol*. 2002;86:115-121.
53. Wexler D, Silverberg D, Sheps D, et al. Prevalence of anemia in patients admitted to hospital with a primary diagnosis of congestive heart failure. *Int J Cardiol*. 2004;96:79-87.
54. Felker GM, Adams KF, Jr., Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. *J Am Coll Cardiol*. 2004; 44:959-966.
55. Herzog CA, et al. Impact of congestive heart failure, chronic kidney disease, and anemia on survival in the Medicare population. *Circulation*. 2002;106:2333A.
56. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J*. 2003;24:442-463.