

# The Interaction Between Heart Failure and Other Heart Diseases, Renal Failure, and Anemia

Donald S. Silverberg, Dov Wexler, Adrian Iaina, and Doron Schwartz

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Anemia, defined as a hemoglobin level of less than 12 g/dL, often is seen in congestive heart failure (CHF). It is associated with an increased mortality and morbidity and increased hospitalizations. Compared with nonanemic patients the presence of anemia also is associated with worse cardiac clinical status, more severe systolic and diastolic dysfunction, a higher beta natriuretic peptide level, increased extracellular and plasma volume, a more rapid deterioration of renal function, a lower quality of life, and increased medical costs. The only way to determine if anemia is merely a marker for more severe CHF or actually is contributing to the worsening of the CHF is to correct the anemia and see if this favorably influences the CHF. In several controlled and uncontrolled studies, correction of the anemia with subcutaneous erythropoietin (EPO) or darbepoetin in conjunction with oral and intravenous iron has been associated with an improvement in clinical status, number of hospitalizations, cardiac and renal function, and quality of life. However, larger, randomized, double-blind, controlled studies still are needed to verify these initial observations. The effect of EPO may be related partly to its nonhematologic functions including neovascularization; prevention of apoptosis of endothelial, myocardial, cerebral, and renal cells; increase in endothelial progenitor cells; and anti-inflammatory and antioxidant effects. Anemia also may play a role in increasing cardiovascular morbidity in chronic kidney insufficiency, diabetes, renal transplantation, asymptomatic left ventricular dysfunction, left ventricular hypertrophy, acute coronary syndromes including myocardial infarction and chronic coronary heart disease, and in cardiac surgery. Again, controlled studies of correction of anemia are needed to assess its importance in these conditions. The anemia in CHF mainly is caused by a combination of renal failure and CHF-induced increased cytokine production, and these can both lead to reduced production of EPO, resistance of the bone marrow to EPO stimulation, and to cytokine-induced iron-deficiency anemia caused by reduced intestinal absorption of iron and reduced release of iron from iron stores. The use of angiotensin-converting enzyme inhibitor and angiotensin receptor blockers also may inhibit the bone marrow response to EPO. Hemodilution caused by CHF also may cause a low hemoglobin level. Renal failure, cardiac failure, and anemia therefore all interact to cause or worsen each other—the so-called *cardio-renal-anemia syndrome*. Adequate treatment of all 3 conditions will slow down the progression of both the CHF and the chronic kidney insufficiency.

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In a recent population study 26% of patients with congestive heart failure (CHF) died within a year compared with 3% in a matched reference group without CHF.<sup>1</sup> The 2-year figures were 35% and 6%, respectively. Although a lack of

adequate and aggressive therapy by the doctor<sup>2</sup> and poor compliance with therapy by the patient partly may be responsible for these dismal figures is it possible that inadequate control of anemia also is contributing? We found that many patients resistant to maximal CHF therapy were anemic and correction of the anemia with subcutaneous erythropoietin (EPO) and intravenous (IV) iron improved their cardiac function and clinical status, stabilized their renal function, and markedly reduced the number of days and number of hospitalizations.<sup>3-7</sup> Studies of the effect of correction of anemia in

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Department of Nephrology, Department of Cardiology and Heart Failure Unit, Tel Aviv Medical Center, Tel Aviv, Israel.

Address reprint requests to Dr. Silverberg, Department of Nephrology, Tel Aviv Medical Center, Weizman 6, Tel Aviv 64239, Israel. E-mail: donald@netvision.net.il

chronic kidney insufficiency (CKI) and dialysis have been reviewed elsewhere in this symposium.

## How Common Are Renal Failure and Anemia in CHF?

The World Health Association considers anemia in adults to be present when the hemoglobin (Hb) level is less than 13 g/dL in men and less than 12 g/dL in women.<sup>8</sup> The average lower limit of normal Hb level for men and women together therefore is about 12.5 g/dL, and anything less than this could be considered to be anemia. In a study of 32,229 consecutive patients admitted to 263 US hospitals with a primary diagnosis of CHF [the Acute Decompensated Heart Failure National Registry (ADHERE) study], the mean Hb level was 12.4 g/dL and the mean serum creatinine level was 1.8 mg/dL (roughly equivalent to a calculated creatinine clearance of about 40 mL/min/1.73 m<sup>2</sup>).<sup>9</sup> Clearly then about half of the patients admitted to the hospital with a primary diagnosis of CHF in the United States have anemia and, because a creatinine clearance of less than 60 mL/min/1.73 sq m is considered to be CKI, the great majority also have CKI.

Is this anemia important? How does the anemia affect the CHF and the CKI? What are the causes of this anemia? Is it worth treating, and with what?

## Increasing Recognition of Anemia as a Contributing Factor in CHF

The past 5 years has seen an enormous upsurge in interest in the role of anemia in CHF. In the US guidelines committee report on diagnosis and treatment of CHF in 1999<sup>10</sup> and 2001<sup>11</sup> anemia was not even discussed, but since then the number of reports published on this subject has increased dramatically. This includes re-analysis of several key CHF medication trials and studies on anemia and CHF by several large medical centers of hospitalized and clinic CHF patients throughout the world, as recently summarized by us<sup>12-16</sup> and by others.<sup>17-19</sup> This has resulted in a recognition by the same US guideline committee on CHF in 2005<sup>20,21</sup> that anemia is indeed common in CHF and is associated with increased morbidity and mortality, although the investigators stated that they were awaiting further data to confirm the direct causative role of anemia in CHF. As summarized in the reviews on this subject,<sup>12-19</sup> studies of the CHF anemia relationship have shown the following.

### Anemia is Common in CHF

Anemia is common in CHF, with a prevalence of anywhere from 2% to 60%, with the average prevalence being around 40%.<sup>12-19</sup> Examination of these CHF studies<sup>12-19</sup> shows that the differences in prevalence were dependent on many factors. The anemia was generally more common in the elderly, in diabetics, in those with more severe renal damage, and in those more severe CHF. It was also more common in those

who were hospitalized than in those treated in the community, and more common in those in whom the anemia was defined as a Hb level of less than 12 to 13.5 g/dL as compared with less than 11 g/dL. In many of the larger controlled intervention studies of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, and  $\beta$ -blockers in CHF, patients with CKI or severe anemia were excluded specifically, which partially could explain the lower prevalence of anemia in these studies. In some studies anemia was not present when first seen but developed over the follow-up period. Some of the CHF studies defined anemia as merely a physician's recorded diagnosis of anemia in the medical discharge chart without actual values of Hb being given. The problem with this is that some doctors may recognize the presence of anemia only if it is very severe.

### Anemia in CHF Patients and Associated Cardiovascular Abnormalities

Compared with CHF patients without anemia, the presence of anemia in CHF patients has been associated with many more cardiovascular abnormalities.<sup>12-19</sup> These include higher mortality rates, more hospitalizations, longer hospitalizations, higher hospitalization costs, higher annual medical costs, a worse New York Heart Association (NYHA) functional class, lower left ventricular systolic function (as judged by a lower left ventricular ejection fraction (LVEF)), poorer ventricular diastolic function, lower exercise capacity, less walking distance on the 6-minute walk test, reduced oxygen use during peak exercise (MvO<sub>2</sub>) and at the anaerobic threshold, lower quality of life, higher serum  $\beta$  natriuretic peptide (BNP) levels (which suggests more severe CHF), higher plasma and extracellular volume total body water, lower red cell volume, hyponatremia, more severe peripheral edema, lower blood pressure, higher heart rate, poorer peripheral perfusion, higher ventricular filling pressures, higher pulmonary capillary wedge pressures, and a greater resistance to therapy as judged by the need for higher doses of diuretics and digoxin. Anemia in CHF also often was associated with lower renal function, more rapid deterioration of renal function, and with signs of malnutrition and inflammation such as a low body mass index, low serum albumin level, low serum total protein level, low serum cholesterol level, increased C-reactive protein level, and deranged adrenal steroid metabolism characteristic of catabolism, as quantified by the cortisol/dehydroepiandrosterone ratio. The anemia, malnutrition, and inflammation seen in CHF may be caused partly by increased inflammatory cytokines such as tumor necrosis factor  $\alpha$  and interleukin 6.<sup>12-19</sup>

On average, in these many studies, the mortality and hospitalization rates in CHF increased by about 15% to 20% for every decrease in the Hb level of 1 g/dL.<sup>12-19</sup> Thus, a decrease in Hb level from 15 to 10 g/dL would be associated with about double the mortality rate and double the rate of hospitalization. This is similar to the odds ratio of mortality and hospitalization seen with 4 other common cardiovascular risk factors: smoking, diabetes, hypertension, and hypercholesterolemia. It is for this reason that we have called the

anemia the fifth cardiovascular risk factor after smoking, diabetes, hypertension, and hyperlipidemia.<sup>22</sup>

### Decreases in Hb Level Over Time in CHF May Worsen the Clinical Course and Impair Cognitive Function

A decrease in Hb level over a period of time in CHF patients has been associated with an increase in mortality rate, an increase in hospitalization rate, and an increase in left ventricular mass index,<sup>23-26</sup> and a decrease in cognitive function.<sup>27</sup>

### Increased BNP in CHF Is Related Partly to the Associated Anemia

BNP now is used commonly for both the diagnosis of CHF and for assessing its prognosis.<sup>28,29</sup> Even in CKI, BNP is one of the strongest predictors of development of CHF (hazard ratio, 6.31)<sup>30</sup> and is a reliable marker of LV overload as judged by left ventricular volumes and pressures.<sup>30</sup> BNP reflects the volume, stretch, and pressure in the ventricles. Studies in CHF have found that the BNP levels in cardiac patients both with<sup>31-34</sup> and without CHF<sup>35,36</sup> were related inversely and independently to Hb levels—the lower the Hb level the higher the BNP level. Even in studies in the general population the level of BNP is related inversely to the level of Hb.<sup>37</sup> In 1 study anemia was found to be an even better predictor of long-term survival in CHF than the BNP level.<sup>32</sup> The effects of anemia, BNP, and cardiac troponin I all are independent and additive risk factors for 1-year mortality rates in CHF.<sup>34</sup> Preliminary studies have shown that correction of the anemia in CHF reduces the BNP levels.<sup>38,39</sup> All this suggests that part of the increased BNP levels seen in CHF simply may be owing to the associated anemia. The increased BNP level in anemia could be related to the increased plasma volume caused by anemia, the LVH caused by the anemia, and to the increase in the various neurohormones that also are caused by anemia and can trigger the increased BNP level.<sup>40</sup>

### Anemia May Be an Important Cause of Diastolic Dysfunction in CHF

In an echocardiographic study of diabetic patients it was found that more than a third of patients with evidence of abnormal cardiac function (diastolic or systolic dysfunction) had anemia whereas anemia was present in less than 5% of patients with normal echocardiographic findings.<sup>41</sup> Therefore, anemia is much more common in diabetic patients with cardiac abnormalities than in those without cardiac abnormalities. The converse also was true. Patients with anemia were almost certain to have cardiac abnormalities on echocardiogram—94% of anemic diabetics did. These abnormalities mainly were diastolic dysfunction associated with an increase in LV mass and impaired relaxation indices. The severity of the diastolic dysfunction was associated directly with the severity of the anemia and this was independent of renal function. The severity of the anemia correlated with the N-terminal pro brain natriuretic peptide (NT-proBNP) level

independent of renal impairment, hypertension, or the presence of microvascular disease. Anemia was as powerful a predictor of cardiac dysfunction as NT-proBNP level. However, the predictive value of NT-proBNP level for cardiac dysfunction was eliminated after adjusting for Hb levels. In patients with known cardiac disease, those with anemia also were twice as likely to have systolic dysfunction.

In a recent study of patients with coronary heart disease and anemia, 24% of those with a Hb level of less than 11 g/dL were found to have diastolic dysfunction compared with only 8% of those with a Hb level of more than 13 g/dL, independent of LVH.<sup>42</sup>

Brucks et al<sup>31</sup> studied the role of anemia on survival and risk of hospitalization in 137 patients with diastolic CHF. They found that anemia was common in these patients (42%) and at least as common as in published reports on systolic CHF. These anemic patients had worse diastolic function than the nonanemic patients, as evidenced by more severe abnormalities of LV filling and increased diastolic mitral inflow to diastolic mitral annular velocity ratio, consistent with higher left atrial pressures. Patients with anemia also had higher BNP values, suggesting more severe CHF, and they had a worse survival rate than nonanemic patients. The prognostic effect of anemia was independent of sex, diabetes, hypertension, renal failure, coronary heart disease (CHD), or medications.

Wu et al<sup>33</sup> also have confirmed that BNP level is a valuable test in the diagnosis and prognosis of diastolic heart failure and that there is an inverse correlation between Hb level and BNP level that is independent of other factors.

In 210 patients with diastolic CHF who were hospitalized,<sup>43</sup> anemia was common and was the strongest predictor of mortality, increasing the risk of death by a factor of 2.7. The anemic patients also were more likely to be older, have reduced renal function, spend a longer time in the hospital, have a greater prevalence of ischemic heart disease and left bundle branch block, and have a higher sedimentation rate, a lower serum cholesterol level, and a lower body mass index. These characteristics in anemic patients with diastolic CHF are similar to those found for anemic CHF patients with systolic failure.<sup>44</sup>

### CHF and Anemia May Act Together to Cause Progressive Renal Failure

We<sup>12-16</sup> and others<sup>45</sup> recently have summarized the evidence that CHF is an important cause of progressive CKI. CHF is found in about one quarter of patients with CKI.<sup>46</sup> The prevalence of CHF increases greatly in CKI as the patient's renal function deteriorates,<sup>47</sup> and at end stage renal disease the prevalence of CHF can reach 65% to 70%.<sup>47,48</sup> There also is evidence that uncontrolled CHF often is associated with a rapid decrease in renal function<sup>49,50</sup> and need for dialysis.<sup>51</sup> In the SOLVD study of ACEIs in asymptomatic or symptomatic systolic dysfunction,<sup>50</sup> the estimated glomerular filtration rate (eGFR) deteriorated rapidly (>15 mL/min/1.73 sq m/y) in 12% of participants and, compared with those with a slower decrease in GFR (<5 mL/min/1.73 sq m/y) this rapid

decrease was associated with a significant increase in mortality despite adjustments for baseline kidney function, baseline severity of CHF, or change in CHF severity. Of the CHF patients, 30% had no decrease in eGFR, 34% had a decline of less than 5 mL/min/1.73 sq m/y, 19% had a reduction of 5 to 10 mL/min/1.73 sq m/y, 5% had a reduction of 11 to 15 mL/min/1.73 sq m/y, and 12% had more than 15 mL/min/1.73 sq m/y. A total of 22% had a reduction of eGFR of at least 20% from baseline and this percentage reduction was seen at all levels of baseline eGFR. The degree of anemia and severity of CHF (as judged by LVEF and NYHA) were significant independent predictors of this rapid decrease in renal function whereas diabetes, hypertension, and use of enalapril and diuretics were not. Similarly, anemia was found in another study to be an independent predictor of progression of renal failure in CHF.<sup>52</sup> That adequate control of CHF can help prevent this deterioration of renal function is suggested by another SOLVD study<sup>53</sup> in which the addition of a  $\beta$ -blocker to the ACEI was associated with less deterioration of renal function than in those not receiving a  $\beta$ -blocker. Renal ischemia is probably the most important mechanism of this progressive renal failure in CHF.<sup>45,54</sup>

## **Anemia Increases Chance of CHF in Many Conditions**

Anemia increases the chances of eventually developing CHF in healthy people,<sup>55</sup> in CKI patients,<sup>56</sup> in dialysis patients,<sup>57</sup> in renal transplant patients,<sup>58,59</sup> in patients with asymptomatic systolic dysfunction,<sup>60</sup> and in patients with acute coronary syndrome.<sup>61</sup> In 2 uncontrolled studies, treatment of predialysis CKI patients with EPO was associated with a lower incidence of CHF than was found in those not treated.<sup>62,63</sup>

## **Experimentally Produced CHF in Animals Has Improved After Treatment With EPO**

In rats with established CHF and anemia, EPO therapy was associated with an improvement in the cardiac function.<sup>64</sup>

## **Treatment of Anemia With EPO and Iron in CHF in Human Beings Improves Cardiac Function**

Does anemia actually contribute to the worsening of CHF or is it just an innocent bystander, merely a marker of more severe CHF? One way of finding out is to actually treat the anemia and see if this improves the CHF. In both uncontrolled<sup>3,5-7</sup> and controlled<sup>4</sup> studies we showed that when anemia was corrected to a Hb level of 12.0 to 13.5 g/dL by subcutaneous EPO and IV iron (Ferric sucrose; Venofer, Vifor Int, St. Gallen, Switzerland), the CHF improved, as evidenced by improvement of the NYHA functional class, increased LVEF, reduced number and days of hospitalization, reduced doses of oral and IV furosemide required, and improved self-assessed shortness of breath and fatigue. In the uncontrolled studies<sup>3,5-7</sup> we also found that the creatinine clearance, that had been decreasing at a rate of about 1 mL/min/mo before anemia was corrected, stabilized after correc-

tion of the anemia. All these patients had been under a cardiologist's care before we intervened to treat the anemia, and had been on maximally tolerated doses of all the recommended CHF medications but still were resistant to therapy and were highly symptomatic. In the controlled study,<sup>4</sup> the group in which anemia was treated (16 patients) had an improvement in NYHA class, LVEF, days in hospital, dose of oral and IV furosemide, and no change in mean serum creatinine level whereas in the untreated group (also 16 patients) all the earlier-described parameters worsened and the mean serum creatinine levels increased significantly.<sup>4</sup> In addition one quarter of the patients in the controlled group died—all owing to severe progressive CHF, whereas none died in the treatment group in which the anemia had been corrected.

In a randomized, placebo-controlled, single blind study of 22 patients with anemia and severe CHF, Mancini et al<sup>65</sup> evaluated the use of subcutaneous EPO 15 to 30,000 IU weekly and oral iron over a 3-month period. Exercise duration, 6-minute walking distance, peak oxygen use during maximal exercise (MVO<sub>2</sub>), oxygen use at the anaerobic threshold, and the quality of life all improved in the treated group (whose mean Hb level increased from 11.0 to 14.3 g/dL) and did not change significantly in the placebo group. The degree of improvement in MVO<sub>2</sub> was proportional to the degree of change in the Hb level. This is important because MVO<sub>2</sub> is an important prognostic predictor of survival in CHF.<sup>65</sup> In another study by the same group the anemia was found to be associated with a reduced red cell mass in the majority of patients and with an increased plasma volume in the rest.<sup>66</sup> Correction of the anemia reduced the plasma volume to normal and increased the red cell mass.<sup>65</sup>

In a preliminary US study,<sup>67</sup> 84 CHF patients with anemia (Hb level, <12 g/dL) and CKI (serum creatinine level,  $\geq$ 1.5 mg/dL) were treated with IV iron (ferric gluconate, Ferrlecit, Watson Pharm, Corona, California) and epoetin  $\alpha$  over a period of up to 15 months. By the end of the treatment period, compared with a similar period of time before the treatment, 37% had a decrease in serum creatinine level and 30% had a decreased oral diuretic dose. The number of admissions to the hospital had decreased by 43% and the number of hospital days had decreased by 33%.

In another preliminary US study,<sup>68</sup> 81 patients with predominantly NYHA III and IV CHF and anemia (Hb level, <11 g/dL) were treated with EPO and oral iron. The mean follow-up period was  $438 \pm 336$  days. The mean initial blood urea nitrogen level was  $51 \pm 31$  mg/dL and the mean initial serum creatinine level was  $2.1 \pm 1.8$  mg/dL. The Hb level increased from a mean of  $9.9 \pm 1.1$  initially to  $11.7 \pm 1.7$  g/dL after treatment. The mean blood urea nitrogen level decreased to  $38 \pm 23$  mg/dL. The number of hospital days compared with an equal period of time before treatment decreased by 50%.

In another preliminary study from Spain,<sup>38</sup> 10 patients with severe CHF and a Hb level of less than 12 g/dL were treated for a mean of  $5.0 \pm 2.7$  months with EPO and IV iron. All were receiving maximal medication for CHF. The results were compared with 18 matched patients in whom the ane-

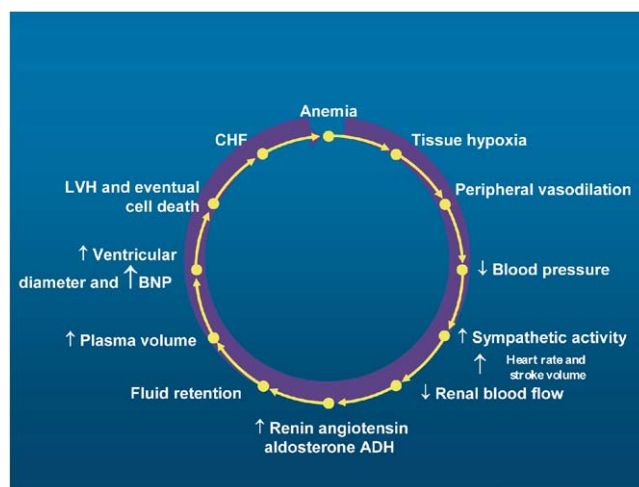
mia was not treated. The Hb in the treated group increased from  $10.2 \pm$  to  $13.7 \pm 1.2$  g/dL, but remained unchanged at  $10.6 \pm 0.9$  in the untreated group. Compared with the untreated group, correction of the anemia was associated with a marked improvement in NYHA (1.7 in the treated versus 3.2 in the untreated), 90.3% less episodes of severe CHF, 88.7% less hospitalizations, and 61% less IV diuretics. In addition the NT-proBNP, which had been increased markedly initially had decreased by 51% in the treated group and had increased by 135% in the nontreated group.

In a preliminary study from Greece,<sup>69</sup> 31 patients with CKI and normal systolic function but impaired diastolic function and increased left ventricular mass (LVM) were randomized into 2 groups; 15 received EPO (group 1) and 16 did not (group 2). After 1 year the Hb levels had increased from 9.2 to 11.3 g/dL in group I and had increased from 9.1 to 9.3 g/dL, respectively, in group II. In group I the LVM, LVEF, and all 3 diastolic functional parameters that were measured were significantly better than in group II.

In a preliminary study from Belgium,<sup>70</sup> in 18 patients with severe CHF and anemia (Hb level, <12 g/dL) who were treated with EPO for a mean of 10.2 months the Hb level increased from 10.1 to 13.3 g/dL. The mean NYHA decreased from 3.5 to 2.2, the mean serum creatinine level decreased by 15.6%, the need for oral loop diuretics decreased by 35%, the hospitalization rate decreased by 82% compared with the time before the study, and the E/Em ratio, a sign of diastolic dysfunction and left ventricular filling pressure, decreased significantly from a mean of 16 to a mean of 8 (50%), suggesting an improvement in diastolic function. The latter 2 studies suggest that treatment of anemia in CHF improves not only systolic dysfunction but diastolic dysfunction as well.

In another preliminary study, a double-blind, randomized, controlled study from Italy,<sup>39</sup> 38 CHF patients with NYHA III or IV and a Hb level of less than 11 g/dL received either  $\beta$  EPO (Recormon-Roche) or placebo for 3 months. In the group in which the anemia was corrected with EPO there was an increase in exercise capacity on exercise testing, a significant increase in peak oxygen utilization ( $V_{O_2}$ ) and  $V_{O_2}$  at the anaerobic threshold, a significant reduction in serum creatinine level and an increase in creatinine clearance, a significant increase in ejection fraction and a decrease in BNP level, whereas in the control group without EPO there were no significant changes in any of these parameters.

In a randomized double-blind multicenter study, the STAMINA study, the effect on exercise tolerance with the use of darbepoetin  $\alpha$ , a long-lasting EPO preparation, was compared with placebo in 319 patients with CHF. Only preliminary results have been presented.<sup>71,72</sup> A total of 162 patients were randomized to darbepoetin given subcutaneously every 2 weeks for 1 year. The other 157 received placebo. The mean Hb level initially was  $11.4 \pm 0.8$  and increased by  $0.45 \pm 1.11$  in the control group and by  $1.80 \pm 1.2$  in the treated group. Exercise duration was increased significantly only in the treated group. There were trends toward greater improvement in the treated group in the quality-of-life scale and NYHA and in mortality and CHF-related hospitalization, but



**Figure 1** The mechanism for fluid retention and heart failure in anemia. (Color version of figure is available online.)

none of these reached statistical significance. There were no differences in incidence of hypertension, deep vein thrombosis, or myocardial infarction between the groups. The results were positive enough that a much larger study now is being planned.

A recent uncontrolled study in hemodialysis patients in whom 90.6% had CHF (NYHA II-IV) found that complete correction of anemia to 13.5 to 14.5 g/dL, along with aggressive therapy with all standard CHF cardioprotective agents and excellent blood pressure control, was associated with an extremely low mortality rate over a mean of 3.4 years.<sup>73</sup> This study also showed that such treatment was associated in many patients with total correction of their LVH and an improvement in their cardiac function as measured by both LVEF and by NYHA.

## How Does Anemia Cause or Worsen CHF?

It has been known for years that anemia, if severe enough, can cause heart failure even in normal individuals<sup>40</sup> (Fig 1). Indeed 1 recent study of more than 1 million elderly US Medicare patients showed that anemia was an independent predictor of the development of CHF over a 1-year period, with CHF developing more than twice as often in those who were anemic.<sup>55</sup> The tissue hypoxia and peripheral vasodilation present in anemia causes a decrease of blood pressure, leading to an increased sympathetic response, which leads to tachycardia, increased stroke volume, renal vasoconstriction, reduced renal blood flow, and salt and water retention (Fig 1). This will lead to an increase in extracellular fluid including an increase in plasma volume.<sup>40</sup> The reduced renal blood flow also will cause an increased secretion of renin, angiotensin, aldosterone (RAAS), and antidiuretic hormone, further augmenting the renal vasoconstriction and salt and water retention, and further increasing the extracellular fluid and plasma volume.<sup>40</sup> In addition, norepinephrine, renin, angiotensin, and aldosterone all are toxic to renal, cardiac, endo-

thelial, and other cells.<sup>74,75</sup> The tachycardia and increased stroke volume eventually can lead to ventricular dilation and hypertrophy and to myocardial cell death, cardiac fibrosis, and CHF.<sup>74,75</sup>

The physiologic responses of anemia and CHF are similar and may explain why they are such a dangerous combination. Unlike anemia, in which the cardiac output is increased and peripheral resistance is decreased,<sup>40</sup> in CHF the primary defect is a reduction in cardiac output and this causes a reduced blood pressure, which leads to an increase in sympathetic activity, which causes tachycardia (as does anemia) and increased peripheral resistance.<sup>76,77</sup> However, from then on the physiologic responses are similar to anemia, each causing renal vasoconstriction with reduced renal blood flow and GFR, an increase in the RAAS system activity and anti-diuretic hormone, an increase in plasma volume and extracellular volume and BNP level and the development of left ventricular hypertrophy (LVH) and LV dilation, and increased prevalence or severity of the CHF.<sup>76,77</sup>

## The Additive Effects of CHF, CKI, and Anemia

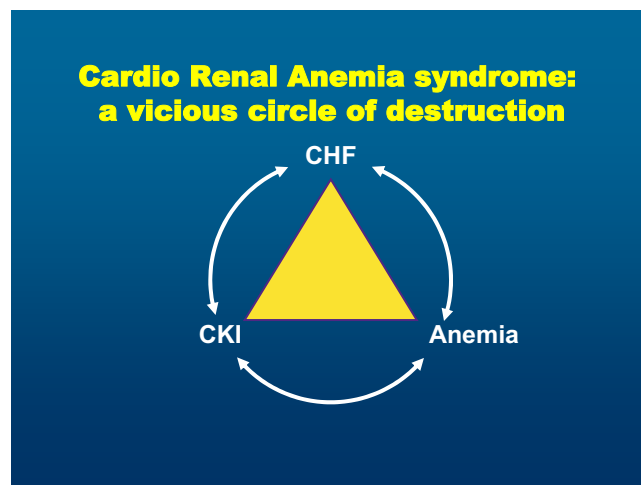
In a study of more than 1 million US Medicare elderly patients<sup>78</sup> it was found that CHF, CKI, and anemia are additive in increasing the risk of mortality, and in the risk of developing end-stage renal disease. On the other hand, correction of the anemia in CKI in some studies with EPO has slowed the progression of CKI.<sup>79,80</sup>

## The Economic Burden of Patients With Anemia in CHF in the Community

The direct cost of CHF in the community (which includes the cost of inpatient hospital care, emergency room care, outpatient hospital care, physician office visits, and pharmacy) and the indirect costs per year (short-term disability and absenteeism) for CHF per patient in unadjusted costs was estimated in 1 study to be \$72,078 in anemic CHF patients and \$30,938 in nonanemic patients, a difference of \$41,140.<sup>81</sup> In another study annual costs per patient were \$14,535 dollars for anemic patients and \$9451 for nonanemic patients.<sup>82</sup> In an analysis of 8,569 hospitalized CHF patients a 1 g/dL increase in Hb level was associated with a 4.3% decrease in costs.<sup>83</sup> Similarly, hospital expenses in the SOLVD study were 19.9% less in those CHF patients with a Hct level of 36 or more compared with a Hct level of less than 33.<sup>84</sup>

## The Vicious Circle of CHF, CKI, and Anemia

Anemia can cause or worsen CHF and CKI, CKI can cause or worsen anemia and CHF, and CHF can cause or worsen anemia and CKI. So what we frequently see in our hospital wards and clinics is this unholy trio, each causing and wors-



**Figure 2** The cardio-renal-anemia syndrome. (Color version of figure is available online.)

ening each other. We have called this vicious circle the *cardio-renal-anemia syndrome*<sup>12-16</sup> (Fig 2).

## Anemia May Increase Cardiovascular Morbidity in Many Conditions Other Than CHF

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.<sup>85,86</sup> This is consistent with our findings in CHF and those of others<sup>12-19</sup> as mentioned previously. But even patients with heart disease or renal disease but without CHF may be very sensitive to the damaging effects of anemia. Anemia may play a role in increasing cardiovascular morbidity in CKI,<sup>87-90</sup> diabetes,<sup>91,92</sup> renal transplantation,<sup>58,59</sup> asymptomatic left ventricular dysfunction,<sup>60</sup> CKI and left ventricular hypertrophy,<sup>93</sup> acute coronary syndromes including myocardial infarction,<sup>61,94-97</sup> and chronic coronary heart disease.<sup>98-100</sup> Anemia also may make the kidney more susceptible to contrast media, increasing the chances of developing contrast-media-induced acute renal failure.<sup>101</sup> Again, controlled studies of correction of anemia in all these conditions are needed to assess its importance.

## The Cause of the Anemia in CHF

The main cause of the anemia most likely is renal damage produced by the poor cardiac function. Certainly the mean serum creatinine level in patients with CHF and anemia is increased in most studies, whether these are in-hospital or outpatient studies.<sup>12-19</sup> Indeed, in a recent study of CHF patients referred to our department for treatment of the anemia the mean serum creatinine level was  $2.2 \pm 0.9$  mg/dL and the mean calculated creatinine clearance was  $32.5 \pm 26.5$  mL/min/1.73 meters squared.<sup>7</sup> The most likely mechanism for

this reduced renal function is that the reduced cardiac output causes renal vasoconstriction and leads to prolonged renal ischemia, causing renal damage and reduced production of EPO in the kidneys. However, CHF alone, even without renal failure, may be able to cause anemia. Although EPO levels increase greatly in control patients with anemia but without renal failure or CHF, the EPO response to anemia in CHF is blunted markedly, suggesting reduced EPO production.<sup>32</sup> Studies in animals have shown that CHF itself may cause anemia.<sup>102</sup> The damaged heart may secrete cytokines such as tumor necrosis factor  $\alpha$ ,<sup>32,103</sup> which can cause anemia in 4 ways<sup>104-106</sup>: by reducing EPO production in the kidneys, by interfering with EPO activity at the level of the bone marrow, by inhibiting the release of Fe from the reticuloendothelial system (where it is stored) so that it cannot get to the bone marrow to be used in Hb production, and by reducing iron absorption from the gut. The reduced iron absorption from the gut probably is caused by the release of hepcidin from the liver. This peptide is released by interleukin 6 and goes to the gut where it prevents the absorption of iron.<sup>105,106</sup> Hepcidin also may prevent the release of iron from macrophages and hepatocytes where it is stored,<sup>105,106</sup> resulting in an accumulation of iron in these sites. The defective iron supply is manifested in CHF as low levels of serum iron, a low percentage transferrin saturation and increased soluble transferrin receptor protein.<sup>107</sup> It therefore is possible that some of these anemic CHF patients may respond to IV iron alone, although this needs to be proven.

There are many other possible causes of anemia in CHF. Many CHF patients take aspirin, which may cause blood loss. CHF patients often have proteinuria, and EPO, iron, and transferrin can be lost in significant amounts in the urine,<sup>108</sup> also contributing to the anemia. EPO production can be inhibited by ACEIs and angiotensin receptor blockers and thus cause anemia.<sup>24,26,109</sup> Indeed, in a recent analysis of a randomized controlled study of ACEIs in CHF, the SOLVD study, the use of ACEIs increased the risk of developing anemia by 56% and this was associated with a significant increase in mortality rate.<sup>26</sup> The Hct level decreased by at least 4% in 14% of those taking enalapril but in only 9.5% of those on placebo. The anemia of ACEI probably mainly is caused by (1) inhibition of angiotensin II production and by decreasing of insulin growth factor levels, both of which can cause inhibition of erythroid precursors, and also by (2) an ACEI-induced increase in N acetyl-seryl-aspartyl-lysyl proline, a natural peptide that also decreases red cell precursors.<sup>26,109</sup> The angiotensin receptor blockers in CHF have been associated with a reduction of Hb level of about 0.5 g/dL.<sup>24</sup> As previously mentioned, many patients with CHF have CKI, which itself is known to cause reduced iron absorption from the gut.<sup>110</sup> CHF causes both hypoperfusion of the bowel and bowel edema, both of which may cause malabsorption,<sup>111</sup> which can lead to malnutrition and anemia. Diabetics are about 2 to 4 times as likely to develop anemia as nondiabetic patients.<sup>91</sup> This probably mainly is owing to the fact that the increased blood sugar damages the EPO-producing cells in the kidney, decreasing the secretion of EPO.<sup>91</sup> Finally, part of the anemia in CHF may be caused by hemodilution, but

recent studies showed that the majority of anemic CHF patients actually have a reduced red cell volume.<sup>66</sup>

## Nonhematopoietic Actions of EPO

EPO modulates a broad array of cellular processes outside of the hematopoietic system including increasing the number of endothelial progenitor stem cells and their activity, and improving neoangiogenesis.<sup>112,113</sup> EPO also inhibits the apoptotic mechanisms of injury of the endothelial and myocardial cells and also inhibits inflammatory damage. It may offer similar protection in other areas as well such as the central and peripheral nervous system, the eyes, the kidney, and the blood vessels.<sup>112,113</sup> Not only does EPO administration at the time of an induced myocardial infarction in animals reduce the size of the infarct but it also maintains its cardiac function.<sup>112,113</sup> In a recent study in rats who had a myocardial infarction caused by coronary vessel ligation and went into CHF within 3 weeks, the addition of EPO at 3 weeks was associated with improved cardiac performance, reflected by a 34% reduction in left ventricular end-diastolic pressure, improved contractility and relaxation of the heart, and a 46% reduction in atrial natriuretic peptide level.<sup>64</sup> There also was an increase in the number of capillaries relative to the number of myocytes. How much of the improvement in CHF with EPO administration was owing to an increase in Hb level and how much was owing to the direct effects of EPO on tissues was not determined.

## Attitude of Cardiologists and Internists to Anemia in CHF

In a preliminary report from the Cleveland Clinic,<sup>114</sup> 2,011 consecutive ambulatory patients with chronic CHF seen in tertiary care cardiology or internal medicine clinics were studied. Anemia was defined as a Hb level of 12 g/dL or less in men and 11 g/dL or less in women. Twenty-nine percent of these CHF patients had or developed anemia. Yet anemia was recognized as a diagnosis in only 11.1% of those cases by the internists and in only 4.4% of those cases seen by cardiologists. Diagnostic evaluation was performed in only 6% of these anemic patients and only 10% received medical therapy for the anemia. The conclusion of the investigators was that anemia in ambulatory patients with CHF was underrecognized, underdiagnosed, and undertreated by cardiologists and internists. In another study anemia was found as a physician-recorded diagnosis in 17% of the records of CHF patients,<sup>115</sup> but when actual Hb values were examined in the charts of such patients by the same group in another study the prevalence of anemia actually was 38%.<sup>116</sup> In a recent study of 14,985 patients with anemia and CHF<sup>82</sup> over a 1-year period, 10.2% had received a blood transfusion, only 3.5% were given EPO, and only 0.2% were given IV iron. The other 86% had no anemia treatment whatsoever. Again this stresses the lack

of awareness of physicians about the importance of anemia in cardiovascular conditions.

## Attitude of Nephrologists to CHF

In a recent assessment of general medical care among patients with CKI only 51% had an echocardiogram, 61% of diabetics and 41% of nondiabetic patients.<sup>117</sup> In this report no comment was made if the BNP level was measured. Because early treatment of CHF in patients with associated CKI with the  $\beta$ -blocker bisoprolol has been shown in a randomized, double-blind, controlled study to cause a marked reduction in cardiovascular events and hospitalization,<sup>118</sup> early diagnosis and treatment of CHF would seem to be indicated in CHF associated with CKI, yet the echocardiogram and BNP level, 2 of the most useful tests for helping to diagnose CHF, as suggested by recent US guidelines on CHF,<sup>20,21</sup> seem to be performed infrequently by nephrologists. This would seem to be a good direction for prevention studies in CKI because early detection and adequate care of CHF, as summarized earlier, would prevent the progression of both the CHF and CKI.

## Conclusions

The final evidence about the value of correction of the anemia of CHF with EPO and iron is not yet in. However, the epidemiologic studies in CHF overwhelmingly attest to the strong association between anemia and increased mortality rate, increased hospitalizations, increased severity of CHF, and reduced quality of life in those who are anemic. The present clinical evidence on the correction of the anemia on CHF with EPO and oral or IV iron also suggests that this treatment may improve many aspects of CHF including cardiac function, renal function, hospitalizations, exercise capacity, and quality of life. However, a large, randomized, double-blind, controlled study really is needed to answer this question, but only now is being completed and even larger studies are being planned. In CHF patients who are being treated maximally with all the recommended CHF medications in the recommended doses but who still are not doing well and who have Hb levels of less than 12 g/dL, physicians should at least be aware that this form of therapy is available, appears to be safe, and in the interventional studies currently available appears highly effective in improving CHF.

Clearly cooperation must exist between cardiologists, diabetologists, and nephrologists in treating these anemic CHF patients because the vast majority of these patients also will have moderate to severe renal insufficiency.

The value of anemia correction using these agents in other types of diseases with anemia—from acute coronary syndromes to chronic coronary heart disease, to asymptomatic ventricular dysfunction to LVH and renal transplantation—remains an unanswered question for future investigation as well. EPO may be useful in these conditions not only because of its ability to correct anemia but also because of the many

positive nonhematologic effects it has in on endothelial, myocardial, renal, brain, and other cells.

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