

Review Article

Correction of Iron Deficiency in the Cardiorenal Syndrome

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Impaired energy metabolism is a feature of Congestive Heart Failure (CHF). Iron deficiency has been shown to reduce energy production in the cell in animals and humans. Iron deficiency is common in both Chronic Kidney Disease (CKD) and in CHF. Recent studies suggest that iron deficiency is an independent risk factor for mortality in CHF. Studies of correction of the anemia with intravenous (IV) iron in both CKD and CHF have shown an improvement in the anemia and, in some cases, in the renal function as well. Some CHF studies of correction of the iron deficiency have shown an improvement in cardiac function and structure as well as in exercise capacity and quality of life. This occurred independent of whether or not they had anemia, suggesting that the iron deficiency itself may be independently contributing to the worsening of the CHF and CKD. If future long-term studies confirm the safety and efficacy of IV iron in the treatment of iron deficiency in CKD and CHF, this will become a new addition to the therapeutic armamentarium of the cardiorenal syndrome, and parameters of iron deficiency will become part of the routine measurements performed in both CKD and CHF whether or not the patient is anemic.

1. Introduction

Impaired energy metabolism is a feature of the Congestive Heart Failure (CHF) syndrome [1]. The failing heart is an energy-starved heart, and energy-sparing treatments such as beta blockers, ACE inhibitors, or Angiotensin II blockers improve the prognosis [1]. Iron metabolism is crucial in all aspects of energy production in the body [2–4] and is particularly important for cells that are characterized by high energy demands such as skeletal myocytes and cardiomyocytes [2–4]. Iron has the ability to shuttle between two oxidative states, (ferric and ferrous iron) which makes it an efficient cofactor for several enzymes and the catalyst of numerous biochemical reactions [2–4]. The ferrous form Fe II can donate electrons while the Fe III form can accept electrons. Iron plays a crucial role in oxygen transport (as a component of hemoglobin (Hb)), oxygen storage (as a component of myoglobin), and oxidative metabolism (as a component of oxidative enzymes and respiratory chain processes).

It is also involved in the synthesis and degradation of lipids, carbohydrates, DNA, and RNA and in the metabolism of collagen, tyrosine, and catecholamines [2–4].

Therefore, iron deficiency can impair oxidative metabolism, cellular energetics, and cellular immune mechanisms. Iron deficiency in experimental models causes a major disruption in energy production and can lead to cardiac damage and dysfunction [5, 6]. Even in otherwise normal people, iron deficiency can reduce endurance and optimal energetics of skeletal muscle even if no anemia is present initially [7–10].

There is growing evidence that iron deficiency is common in CHF and may contribute to the increased mortality in this condition and that correction of the iron deficiency with IV iron can improve both cardiac and renal function, symptoms of CHF, exercise endurance, inflammation, and quality of life and may reduce hospitalization. However, more studies are needed to confirm this. Thus, correction of iron deficiency could become an important new addition to the treatment of the cardiorenal syndrome.

2. Prevalence of Iron Deficiency in CHF with and without Anemia and Its Prognostic Significance

The prevalence of iron deficiency in CHF depends on how iron deficiency is defined. If merely defined as a % Transferrin Saturation (%TSat) of <16, it was found in one preliminary study in 78% of anemic and 61% of nonanemic CHF patients, whereas if it was defined as a %TSat of <16 and a serum ferritin of 30–100 ug/L, it was found in only 15% of anemic and 20% of nonanemic CHF patients [11]. In one study of CHF patients, a low serum iron was found in 31% of anemics and 7% of nonanemics, a low serum ferritin in 21% of anemics and 7% of nonanemics, and at least one of the two in 43% of anemics and 15% of nonanemics [12]. In a study of CHF patients undergoing coronary stenting, 31% had iron deficiency as judged by a low serum iron and increased Total Iron Binding Capacity. Iron deficiency anemia strongly predicted cardiac mortality [13]. In another study of anemia in CHF, about half the patients had serum iron levels below normal, and the great majority of anemic patients also had an elevated soluble transferrin receptor (a quite dependable measure of iron deficiency) [14]. In a study of anemia in severe CHF, markedly reduced iron stores in the bone marrow were found in 73% of the cases [15] even though the great majority had a normal serum ferritin level.

In the largest observational study done to date [16], a prospective observational study, 546 patients with stable systolic mild to severe CHF were followed for a mean of 731 ± 350 days. Patients with severe renal disease were excluded and indeed the mean calculated glomerular filtration rate (GFR) was 80.5 mL/min/1.73 sq m. Iron deficiency was defined as a serum ferritin <100 ug/L or 100–300 ug/L with %TSat <20%. The prevalence of iron deficiency was $37 \pm 4\%$ for the entire population and was $32 \pm 4\%$ in the nonanemics and $57 \pm 10\%$ in the anemics (anemia was defined as a Hb < 12 g/dL in women and <13 g/dL in men). Even in those with mild heart failure as judged by NYHA I and II, the frequency of iron deficiency did not drop below 30%. The prevalence of iron deficiency was related to the female sex, the severity of the CHF as judged by the New York Heart Association class (NYHA) and by the Beta Natriuretic Peptide (BNP), and the severity of the inflammatory process as judged by C Reactive Protein (CRP). In univariate models, the 3-year survival rate was 59% in the iron deficiency group and 71% in the noniron deficiency group ($P = .0006$). In multivariable analysis, iron deficiency was considered an independent predictor of all-cause mortality after adjustment for confounders including anemia and severity of the CHF. The effect was seen as early as 6 months. The inclusion of anemia in the multivariable models did not change significantly the significance suggesting that iron deficiency may be a stronger prognostic indicator of survival than anemia. Thus, iron deficiency, independent of anemia and cardiac function, is related to a poor outcome in CHF.

Therefore absolute iron deficiency (defined as a serum ferritin < 100 ug/L and %TSat < 20%) or functional iron deficiency (defined as a serum ferritin > 100 ug/L and %TSAT < 20%) are commonly seen in CHF patients with anemia or even without anemia and are associated with an increased mortality.

3. Does Correction of the Anemia with Erythropoiesis Stimulating Agents (ESA) in Patients with CHF Improve the CHF?

Several metaanalyses which included nonplacebo controlled studies, and placebo-controlled studies of ESA along with oral or IV iron have shown improvement in many aspects of CHF without causing undesirable side effects [17–21]. But all of these studies have been small and/or short term and a total of about only 700 patients in all have been studied. On the other hand, in a larger metaanalysis of ESA treatment in CHF that included the CHF patients in the TREAT study, the Reduce Cardiovascular Events with Aranesp (TREAT) study in diabetics with renal insufficiency, pooled data from 9 placebo-controlled studies enrolling a total of 2,039 anemic CHF patients treated with ESA was associated with a neutral effect on both mortality and nonfatal heart failure events [22]. Therefore, the value of ESA in the anemia of CHF is still uncertain.

4. Growing Concern about the Safety of ESA

There is growing concern about the safety of ESA because of the hypertension, increased thrombotic events, and other cardiovascular complications and possible increased cancer risk seen with its use in CKD [23–25] so that there is growing interest in the use of IV iron alone or at least as the first step in the treatment of the anemia of CKD and CHF before an ESA is started.

5. Does Correction of Iron Deficiency in Patients with CHF Improve the CHF?

Six studies where intravenous (IV) iron has been used in iron-deficient CHF patients have been performed, but only two were placebo-controlled double blind studies [26, 27].

In one of these two studies [26], a single center study, 40 patients received either IV iron as iron sucrose (Venofer, Vifor Int Zurich) 200 mg a week for 5 weeks or a placebo infusion. Their Hb was <12.5 d/gL for men and <11.5 g/dL for women. Their initial serum ferritin was <100 ng/mL and/or %TSat $\leq 20\%$. At 6-month followup there was a significant improvement in the Hb levels, NYHA, Left Ventricular Ejection Fraction (LVEF), 6 minute walk test (6MWT), hospitalization rate, Minnesota Living with Heart Failure Questionnaire Quality of Life (MLHFQ) scale, creatinine clearance, C-Reactive protein, and NT pro BNP, a slowing of the heart rate, and lower diuretic requirements in the treated compared to the control group.

In the other double blind placebo-controlled study, this one a multicenter study (The FAIR-HF study [27]), the patients were randomly assigned to IV ferric carboxylase 200 mg (Vifor Int Zurich) versus matching control in a 2:1 ratio. A total of 459 subjects with chronic left ventricular systolic dysfunction were studied. Their initial serum ferritin was <100 ug/L or 100–299 ug/L if %TSat was <20%. The mean initial Hb was between 9.5 and 13.0 g/dL. The exclusion criteria were uncontrolled hypertension, other significant heart disease, or impaired liver or renal function. They were given enough iron to maintain the %TSat at 25–45% and serum ferritin at 400–800 ng/mL. The primary end points were patient self assessment and investigator-assessed NYHA at 6 months. Secondary end points were 6-minute walk and quality of life (QOL) as assessed by the Kansas City Cardiomyopathy questionnaire and the European EQ 5D QOL visual analogue scale. Safety outcomes included hospitalizations and death. The initial Hb level was 11.9 g/dL, mean serum ferritin 50–60 ug/mL, and mean transferrin saturation 17%. At week 24 in the IV iron group the serum ferritin had increased to 313 ± 13 versus 74 ± 8 ng/mL. %TSat to 29 ± 1 versus $19 \pm 1\%$ and Hb to 13.0 ± 0.1 versus 12.5 ± 0.1 g/dL. All these were significant differences from placebo. The use of IV iron was associated with significant improvements in NYHA functional class, 6-minute walk distance (mean study effect 35.8 m) EQ5 patient global assessment scale, and Kansas City QOL scale. Renal function improved significantly only in the treated group. At 4 weeks the difference in GFR between the active treatment and placebo was 2.5 ± 1.5 mL/min/1.73 sqm, at 12 weeks it was 3.0 ± 1.3 , and at 24 weeks it was 4.0 ± 1.7 mL/min/1.73 sqm. The magnitude of all the treatment effects did not differ in subjects with or without anemia (defined as a Hb ≤ 12 g/dL). The treatment effects were also not related to the initial age, presence of diabetes, initial severity of the CHF, renal function, or ferritin levels. Although there was no difference in first hospitalization for cardiovascular causes or death in the treated and nontreated, there was a trend to improvement in the two. There was no evidence of any adverse effects of the IV treatment compared to placebo. The improvements compared to controls were seen quite rapidly, even within the first month. The fact that the improvement was similar in the treated group unrelated to the initial Hb suggests that part of the effect of the IV iron might have been due to its direct effect on body tissues.

In the Ferric Iron Sucrose in Heart Failure study (FERRIC-HF) [28], a randomized open label observer blind study lasting 4 months in 35 patients with CHF who were either anemic (Hb < 12.5 g/dL) or non-anemic (Hb 12.5–14.5 g/dL) but all of whom were iron deficient, patients were assigned in a 2:1 ratio to receive 16 weeks of IV iron sucrose (Venofer) or to a control group. Unlike the previous 2 studies, treatment did not result in a significant improvement in Hb levels. Nevertheless there was a trend toward an improvement in exercise tolerance as judged by peak VO₂ and a significant increase in peak VO₂/kg in the treated group but not in the control group. There was also a trend toward an increase in absolute exercise duration

and percentage change in exercise duration in the iron group but not in the control group. There were significant improvements in NYHA, patient global assessment, MLHFQ quality of life scale, and fatigue score in the iron group. All the changes were more pronounced in the anemic group than the nonanemic group. The heart rate fell in the anemic group only. The changes in peak VO₂ were related to changes in %TSat but not to Hb in anemic patients suggesting therefore, as did the previous paper, that the improvement in CHF was due at least partially to the correction of the iron deficiency and not to an increase in Hb.

Bolger et al. [29] treated 16 CHF patients with intravenous iron sucrose (Venofer-Zurich) in an uncontrolled open label study. The Hb was <12 g/dL and the serum ferritin <400 ug/L. Patients were treated for 12–17 days and followed for 92 ± 6 days. Treatment was associated with an increase in the Hb level (11.2 ± 0.7 to 12.6 ± 1.2 g/dL) and a significant improvement in the NYHA class, MLHFQ score, and 6-min walk distance (6MWD). There was a trend toward improved renal function.

Usmanov et al. [30] treated 32 moderate to severe (NYHA III and IV) CHF patients and moderate renal failure (mean serum creatinine 2.3 mg/dL) with IV iron (Venofer) in an uncontrolled study for 26 weeks. The inclusion Hb was <11 g/dL. Iron sucrose was given in a dose of 100 mg 3 times a week for 3 weeks and then once weekly for 23 weeks (total dose 3200 mg of iron). The mean Hb increased from 10.7 ± 0.4 to 13.7 ± 0.4 in NYHA III and from 9.4 ± 0.6 to 12.7 ± 0.08 in NYHA IV. The mean serum iron, %TSat, ferritin were all lower than normal before treatment and increased to normal after treatment. There was a significant improvement in NYHA in the NYHA III group but not in the NYHA IV group. Initially there was evidence of severe cardiac hypertrophy and dilation and reduced LVEF, and these improved after 6 months of IV treatment, but more so in NYHA III than in NYHA IV. There was no change in renal function.

In a sixth study [31] which examined the effect of IV iron in bone marrow-confirmed iron deficiency anemia in severe CHF with anemia, 8 patients were randomly assigned to treatment with IV iron 300 mg once weekly for 6 weeks (total 1800 mg) and 8 others to the same treatment along with 50 ug darbepoetin once weekly for six weeks. Over the entire 3 months of treatment and followup, the Hb increased by 2.4 g/dL in the IV iron alone group and by 2.8 g/dL in the group with both agents. This small study suggests that the IV iron is a major contributor to the anemia. This study and that of Usmanov et al. [30] mentioned above also point out that higher doses of IV iron lead to greater Hb responses than lower doses, that is, there is a dose response relationship. This has been seen in CKD as well [32].

These studies suggest that the anemia of many CHF patients can be improved by IV iron alone. On the other hand, in several studies of anemia treatment in CHF [33, 34], the use of oral iron in anemic CHF patients for one year was not associated with any increase in Hb or improvement in any CHF parameters.

6. What Are the Causes of Iron Deficiency in CHF?

6.1. Chronic Kidney Disease (CKD). CKD is associated with reduced production of Erythropoietin (EPO) in the kidney. The renal damage seen in CHF is probably mainly due to reduced renal blood flow caused by the reduced cardiac output causing hypoxic renal damage [21, 35].

Iron deficiency is also common in CKD [36–39]. About half the cases of iron deficiency are absolute iron deficiency with low %TSat and low serum ferritin (usually associated with decreased iron stores), and about half are relative iron deficiency with low %TSat and normal or elevated serum ferritin (often associated with normal or increased iron stores). The iron deficiency is frequently associated with reduced iron deposits in the bone marrow [39, 40]. Because CKD is an inflammatory condition, increased cytokines may also contribute to the anemia and to the iron deficiency (see below). The use of Erythropoiesis Stimulating Agents (ESAs) in CKD will also rapidly reduce iron stores. The gastrointestinal causes of anemia in CKD are discussed below.

6.2. Elevated Cytokines Causing Abnormalities in EPO and Iron Metabolism. These cytokines are elaborated in CHF and CKD, especially Tumour Necrosis Factor alpha (TNF α) and interleukin-6 (IL-6). They can cause four haematological abnormalities [41, 42]:

- (a) reduced EPO production in the kidney leading to inappropriately low levels in the blood for the degree of anemia present,
- (b) reduced erythropoietic response of the bone marrow to ESA,
- (c) hepcidin-induced failure of iron absorption from the gut, and
- (d) hepcidin-induced trapping of iron in iron stores in the macrophages and hepatocytes.

Hepcidin [29, 30] is a protein released from the liver by IL-6. It inhibits the protein ferroportin which is found in the gastrointestinal tract and in macrophages and hepatocytes and is responsible for the release of iron from these three types of cells into the blood. Therefore if ferroportin is inhibited, gastrointestinal iron absorption is diminished, and iron is also not released from its storage in macrophages and hepatocytes. This results in a low serum iron leading to decreased delivery of iron to the bone marrow and therefore iron deficiency anemia, even in the presence of adequate total iron stores, the so-called functional iron deficiency. Since hepcidin is filtered and removed in the kidney, its levels increase in CKD, which can also partly explain the iron deficiency in CKD [43] and in CHF in whom about half the patients have renal insufficiency as judged by a creatinine clearance of <60 mL/min/1.73 sqm [44].

6.3. Gastrointestinal Problems. There are many other causes of iron deficiency in CKD including reduced iron intake

due to low protein diets and anorexia, gastrointestinal blood loss due to uremia causing platelet dysfunction, as well as esophagitis, gastritis, tumors, platelet inhibitors and anticoagulants [45], and phosphate binders which can also bind iron. It has also been found that proton pump inhibitors such as omeprazole, which are extremely widely used, reduce iron absorption [46]. In addition, CHF itself can cause intestinal cell dysfunction due to bowel edema and other causes [47]. Frequent removal of blood for blood tests may also contribute to the anemia.

Also, as mentioned earlier, both CKD and CHF are inflammatory conditions with increased cytokines which can cause hepcidin-induced iron deficiency.

7. The Cellular Effects of Iron Deficiency

Iron is indispensable for life, serving as a metal cofactor for many enzymes, either nonheme iron-containing proteins or hemoproteins. Hemoproteins are involved in many crucial biologic functions including oxygen binding (hemoglobins), oxygen metabolism (oxidases, peroxidase, catalases, etc.), and electron transfer (cytochromes). Many nonheme iron-containing proteins catalyze key reactions involved in energy metabolism and DNA and RNA synthesis. In addition, iron-containing proteins are required for the metabolism of collagen, tyrosine, and catecholamines [2–4].

Experimental studies in animals have shown that severe iron deficiency can cause diastolic dysfunction and heart failure with pulmonary congestion, left ventricular hypertrophy and dilation, cardiac fibrosis, a reduction in the erythropoietin levels and a worsening of the molecular signaling pathways (as measured by cardiac STAT 3 phosphorylation), an increase in the inflammatory cytokine TNF α , and proteinuria [5]. This defect in the molecular signaling pathway in iron deficiency may be critical for the transition from adaptive cardiac hypertrophy to cardiac dysfunction in long-term iron deficiency. In addition, iron deficiency in rat hearts causes mitochondrial ultrastructural aberrations, irregular sarcomere organisation, and release of cytochrome C [6].

Iron may have anti-inflammatory effects. Compared to haemodialysis patients taking EPO alone, those taking EPO and IV iron had lower proinflammatory TNF α levels and higher anti-inflammatory cytokine IL-4 levels as well as lower levels of total peroxide (a marker of free radical concentration) [48].

8. Oral versus IV Iron in CKD

As mentioned earlier, in patients with CKD who are anemic, iron deficiency has been found in at least half the patients using either blood tests [36–39] or bone marrow biopsies [39, 40], and IV iron alone may increase the Hb significantly [39, 40, 49–51]. In most studies comparing oral to IV iron in CKD, IV iron has been found to produce a greater Hb response than oral iron with less side effects [32, 50, 51], and many patients can reach a target Hb of 11.0 to 12 g/dL with this therapy alone and therefore avoid the use of ESA altogether [32, 40, 49–51]. Although there has been concern

about IV iron causing renal disease [52], this has not been confirmed by other studies [32, 39, 40, 49–51]. Indeed, in one study renal function in CKD improved in the IV iron group but not in the oral iron group [50]. In most studies comparing oral to IV iron in CKD, IV iron has been found to produce a greater Hb response with less side effects [51]. As mentioned above, in several studies of anemia treatment in CHF [33, 34], the use of oral iron in anemic CHF patients for one year was not associated with any increase in Hb or improvement in any CHF parameters.

9. Iron Deficiency and Thrombocytosis

The incidence of venous thromboembolism is greatly increased in CHF [53], and indeed CHF is considered to be a hypercoagulable state [54]. Could iron deficiency in these CHF patients be one cause of this? Iron deficiency can cause thrombocytosis [55] which can lead to increased thrombosis, atherosclerosis, and increased mortality [56, 57]. Correction of the iron deficiency with IV iron in EPO-treated dialysis patients reduced the platelet count significantly [58]. This may be important, since thrombocytosis may be one of the missing links in causing the increased incidence of cardiovascular effects of EPO in CKD [56, 57] and in cancer [59, 60]. High doses of EPO in CKD are associated with more iron deficiency, more severe thrombocytosis, and increased mortality [56, 57]. Iron deficiency also increases oxidative stress [61].

10. The Administration of Iron in Anemic and Nonanemic People

Beutler showed over fifty years ago that iron deficiency can negatively affect enzymes throughout the body with or even without actual anemia being present [7]. He also showed in a randomised double-blind placebo-controlled crossover study that oral iron can improve fatigue in anemic and also in nonanemic iron deficient women [7], and this has been subsequently confirmed by others [8–10]. All these studies suggest that iron has a specific effect on the cells in addition to its ability to make hemoglobin.

11. What Assays Predict the Response to IV Iron?

The two commonly used tests to detect iron deficiency are a low % Transferrin Saturation (%TSat) and a low serum ferritin. But though they are low in absolute iron deficiency where iron stores are low, the %TSat may become low but the serum ferritin high in the presence of inflammation and therefore may not reflect iron status accurately. This is the so-called anemia of chronic disease. In fact, iron stores may be elevated in inflammation in the face of a low %TSat, and the serum ferritin may be elevated in the presence of depleted iron stores. There is no test that can predict with great accuracy the degree of response to IV iron in patients taking ESA in CKD [39, 62, 63]. However, generally in CKD the %TSat is a better predictor than ferritin, and the reticulocyte

Hb is better than %TSat [62, 63], but the differences are probably not large enough to be clinically useful.

12. Concerns about the Safety of Iron

There is some evidence in hemodialysis patients that IV iron treatment is associated with a lower mortality [64–66]. Recently, in CKD patients not on dialysis, it was found that the lower the %TSat the higher the mortality, again raising the possibility that iron deficiency may be a common and reversible cause of severe cardiovascular disease [67]. However, IV iron can cause oxidative stress [68], and therefore long-term controlled studies of IV iron are needed to evaluate the effects of IV iron in CKD, as in CHF. Although there has been concern about increased iron stores being associated with increased risk of coronary heart disease [69] this has not been confirmed by others [70, 71], and the issue is still controversial. But the implications of the presence of iron deficiency in CHF are enormous since, as mentioned above, a high percentage of patients with CHF, whether anemic or not anemic, have true or functional iron deficiency. If correction of this iron deficiency proves both safe and effective, this could be a new and useful addition to the treatment of CHF.

13. How Does Anemia Cause or Worsen CHF?

It appears that anemia can exacerbate heart failure through a vicious circle in which tissue hypoxia and release of nitric oxide causes peripheral vasodilation which leads to decreased blood pressure which then causes increased sympathetic activation, renal vasoconstriction, reduced renal function, and activation of the renin-angiotensin aldosterone system [21, 35]. This in turn leads to fluid retention, left ventricular hypertrophy and dilatation, worsening heart failure, release of BNP arising from stress on the myocardium, and, to complete the vicious circle, further anemia.

14. The Cardiorenal Anemia Syndrome

About 10 years ago, we described the Cardio Renal Anemia syndrome (CRA syndrome) [72]. Our hypothesis was that there is a vicious circle operating between Congestive Heart Failure (CHF), Chronic Renal Failure, and anemia where each might cause or worsen the other. The correction of anemia was a major part of this vicious circle in the reduction of the severity of the CHF. In view of the possible independent association of iron deficiency and cardiac failure, renal failure, and anemia we now suggest renaming the syndrome the CRAID syndrome, the Cardio Renal Anemia Iron Deficiency Syndrome.

15. Conclusion

It is daunting to consider that the use of something as simple as IV iron in CHF patients with absolute or functional iron deficiency may have an important role to play in the treatment of a large percentage of CHF patients, both anemic

and nonanemic and with or without CKD. Clearly, long-term adequately-powered placebo-controlled studies of IV iron in CHF with hard endpoints are needed. In the meantime, in the assessment of patients with CKD and/or CHF, the laboratory markers of iron deficiency should be routinely measured. Faced with a patient with absolute or functional iron deficiency with or without anemia who has CHF with or without CKD, it is the authors' opinion that a trial of IV iron might reduce significantly the severity of these conditions and should be administered before an ESA is started.

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