Iron Deficiency and Heart Disease: Ironclad Evidence?

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Patients with heart failure have elevated levels of circulating inflammatory cytokines and commonly have iron deficiency anemia or anemia of chronic inflammation. Clinical trials in patients with congestive heart failure and iron deficiency have demonstrated that intravenous iron treatment appears to improve subjective and objective outcomes. Most patients in these trials were not anemic or only had mild anemia, and hemoglobin concentration rose only slightly after treatment with iron. Experimental evidence demonstrates that iron is a cofactor for muscle function, which could explain the improvement in clinical outcomes. Many questions remain to be answered to understand the role of iron therapy in patients with congestive heart failure.

In a landmark randomized clinical trial, Anker and colleagues[1] found that intravenous iron improved symptoms and physical function in patients with chronic heart failure and anemia. This trial potentially has broad implications for the hematologist, cardiologist, and internist. In this paper, we review the essential background information on anemia and heart failure, including the frequency, causes, and consequences of anemia in heart failure. We summarize the results of this trial in detail and describe the strengths and weaknesses. We then describe potential pathophysiological explanation(s) for the results. We finish with a description of the many uncertainties and questions that this trial raises.

Prevalence and Consequences of Anemia in Heart Failure

The prevalence of anemia varies by age and gender. In an analysis of a representative population of community-dwelling persons from the US (NHANES-III [Third National Health and Nutrition Examination Survey]), the prevalence of anemia in patients 65 years and older was 10.6% and rises to over 20% in 85-year-old individuals.[2] However, in patients with congestive heart failure, the prevalence may be much higher. In a large cohort of patients with congestive heart failure, 37.2% were anemic.[3] In contrast, the prevalence of anemia was 17% in a population-based cohort of patients with new-onset congestive heart failure (mean age 78) from Canada.[4]

The patient with heart failure who has anemia has an increased risk of death. In a systematic review of 153,180 patients with heart failure, 48% of anemic patients died within 6 months, compared with 29.5% of nonanemic patients (adjusted hazard ratio 1.46; 95% CI 1.26–1.69).[3] This experience is similar to the Canadian cohort in which the risk of death was 1.34 times higher in anemic than in nonanemic patients with heart failure.[4] It is unknown if the increased risk of death is from anemia or is just a marker for underlying severity of disease.

Cause of Anemia in Heart Failure

The cause of anemia in patients with heart failure varies. Iron deficiency (based on physician hospital discharge diagnosis) is reported in up to 21% of heart failure patients with anemia.[4] This most likely results from the common use of aspirin, other platelet function inhibitors (ie, clopidogrel), and anticoagulants.

Anemia of chronic inflammation is the most common cause of anemia and occurs in 58% of heart failure patients with anemia.[4] Patients with congestive heart failure have inflammatory activation, leading to higher levels of circulating inflammatory cytokines, including tumor necrosis factor[5] and interleukin-6,[6] and nonspecific markers of inflammation, such as C-reactive protein.[7] Heart failure is associated with renal insufficiency, which also stimulates cytokine production.[8] Many patients with heart failure have concomitant renal insufficiency from medications, such as diuretics and angiotensin-converting enzyme inhibitors and primary renal disorders resulting from hypertension and renal artery stenosis. Renal insufficiency is associated with anemia that results, at least in part, from low erythropoietin levels.

Iron Therapy in Heart Failure

Three randomized clinical trials have been performed evaluating intravenous iron therapy in patients with anemia and heart failure. The first trial randomly allocated 40 patients to placebo or intravenous iron.[9] Patients were eligible with (a) ejection fraction less than 35%, (b) New York Heart Association functional class 2 to 4; (c) iron deficiency anemia defined as hemoglobin concentration $<$ 12.5 g/dL for men and 11.5 g/dL for women, and either ferritin $<$ 100 ng/mL and/or with transferrin saturation less than 20%; and (d) normal renal function. After a follow-up of 6 months, the hemoglobin concentration increased in the iron-treated group from 10.3 to 11.8 g/dL and was stable in the placebo group. All the outcomes significantly improved with iron therapy, including NT-probrain natriuretic peptide, C-reactive protein, ejection fraction (31.3%–35.7%), and a 6-minute walk (192.3–240.1 meters). It is unclear how iron therapy reduces inflammatory markers, such as C-reactive protein.

The second trial enrolled 35 patients with congestive heart failure and administered 16 weeks of intravenous iron or placebo.[10] Patients either had a serum ferritin $<$ 100 ng/mL or transferrin saturation less than 20%, if the ferritin was between 100 to 300 ng/mL. About half of the patients had hemoglobin concentration less than $<$ 12.5 g/dL, and the remaining patients were not anemic. The primary outcome, change in absolute peak oxygen consumption, did not reach statistical significance (placebo, -21 $\pm$ 120; iron 75 $\pm$ 156; P = .08) nor did treadmill exercise duration (placebo

–15 ± 109, iron 45 ± 84; $P = .08$). However, change in New York Heart Association function class improved (placebo 0.2 ± 0.4, iron -0.4 ± 0.6; $P = .007$), and patient global assessment (placebo -0.2 ± 1.6, iron 1.5 ± 1.2; $P = .002$) was improved in patients administered intravenous iron.

In the third, and largest trial, Anker and colleagues[1] enrolled 459 patients with (a) hemoglobin concentration between 9.5 to 13.5 g/dL; (b) New York Heart Association functional class 2; (c) ejection fraction ≤ 40%; or (d) New York Heart Association functional class 3, with ejection fraction < 45% fraction; and (e) a diagnosis of iron deficiency, which was defined as a ferritin of < 100 μg/L or between 100 to 200 μg/L if the transferrin saturation was < 20%. Patients were randomly allocated to placebo or iron repletion based on Ganzoni's formula[11] and the hemoglobin concentration at the start of the trial. Ferric carboxymaltose was given in doses of 200 mg on a weekly basis until iron repletion and every 4 weeks for maintenance. Blinding of treatment assignment was maintained by administering iron with a black syringe using a curtain or equivalent to shield the patient. Study personnel involved with implementing the iron therapy reviewed laboratory results. Iron was administered weekly until ferritin exceeded 800 μg/L or was between 500 to 800, with iron saturation > 50%, or if hemoglobin was > 16 g/dL. Iron was reinitiated when the following three criteria were met: (1) the serum ferritin fell to < 400 μg/L, (2) the transferrin saturation was < 45%, and (3) the hemoglobin was < 16 g/dL. At baseline, the hemoglobin concentration was 11.9 ± 1.3, mean ferritin in the two groups was 52.5 and 60.1, and transferrin saturation was between 6.7 to 17.7.

Efficacy was assessed up to 24 weeks. The primary outcomes were self-reported Patient Global Assessment, which was moderately or much improved in 50% of the iron group and in 28% of the control group, and the New York Heart Association class improved to class 1 or class 2 in 47% of the iron group, compared with 30% in those receiving placebo. These outcomes were also significantly improved in the iron group at 4 and 12 weeks. The secondary outcomes of 6-minute walking distance (an increase of 35 ± 8 meters for the iron group, compared with placebo), quality of life as measured by EQ-5D score, and Kansas City Cardiomyopathy Score were significantly improved in the iron-treated group. Overall, the mean difference between the iron group and placebo group at 24 weeks for serum ferritin was 246 μg/L and in hemoglobin concentration was 0.5 g/dL. The mean difference between iron group and placebo group for hemoglobin concentration in patients with anemia (defined as hemoglobin concentration < 12 g/dL) was 0.9 g/dL but only 0.1 g/dL in patients without anemia. There was a trend toward fewer hospitalizations in patients receiving iron therapy.

This clinical trial has many strengths and some weaknesses. The investigators enrolled a large number of subjects with documented heart failure and demonstrate improvement in multiple outcomes. The trial was double-blind, which is important given that most of the outcomes were subjective and based on symptoms. Multiple outcomes were assessed and were consistent in showing a positive effect of iron therapy. The hemoglobin was normal or near normal in most patients, suggesting that correction of anemia may not be mediating the treatment effect.

However, there are several weaknesses. First, nearly all the outcomes were subjective. If blinding was not maintained, it is possible that the outcomes were biased by knowledge that the patient was receiving iron therapy rather than a placebo. Second, the cause of the anemia cannot be determined by the report. It is likely that some patients had anemia of chronic inflammation, and it is not possible to determine if only patients with iron deficiency responded to iron therapy. Third, no objective measures of cardiac function (ie, ejection fraction) were made on follow-up to determine if symptomatic improvement was from better cardiac function or for another cause, such as skeletal muscle function. Finally, most patients had normal or near-normal hemoglobin concentrations; so, it is unclear if this effect differs, depending on the hemoglobin concentration.

Experimental Evidence With Iron and Muscle Function

It is important to understand the reason why symptoms in heart failure patients improve with treatment of iron. It does not appear that treating anemia is the explanation or the only explanation. Most patients in these trials were either not anemic or had mild anemia, and there were small increases in the hemoglobin concentration after treatment. Most of the experimental evidence suggests that iron improves muscle function.

Finch and colleagues[12] compared work performance of rats with and without iron deficiency while controlling for hemoglobin concentration. Work performance increased to normal when the hemoglobin was corrected, but only after iron therapy. In iron-deficient rats, marked impairment in running ability persisted even after hemoglobin was corrected. In mitochondrial preparations of skeletal muscle, the rate of phosphorylation with α-glycerophosphate as substrate was associated with increase in work performance with treatment of the iron-deficient rats.

These results were confirmed in two other experimental studies. In severely iron-deficient rats with a hemoglobin concentration of 4.1 to 5.2 g/dL, walking duration increased 6- to 10-fold for 15 to 18 hours after iron dextran therapy. This rapid improvement in exercise capacity without change in hemoglobin concentration suggests that iron is a cofactor needed for exercise.[13] In a second study in rats, exercise training did not increase Vo_{2max} or change hemoglobin concentration in iron-deficient rats.[14]

There is limited data that iron deficiency may alter cardiac muscle function. Two studies fed iron-deficient diets to rats and examined cardiac muscle.[15,16] Rats receiving iron-deficient diet were anemic. Cardiac muscle examined by transmission electron microscopy showed mitochondrial swelling and abnormal sarcomere structure.[15] In another study, iron deficiency was associated with impairment of myocardial mitochondrial electron transport in rat heart.[16]

Conclusions

Intravenous iron treatment appears to improve subjective and objective outcomes in patients with heart failure. The reported trials enrolled patients who had iron deficiency or anemia of chronic inflammation. Most patients were not anemic or only had mild anemia. After treatment, hemoglobin concentration rose slightly. This suggests that the effect of iron was mediated by mechanisms other than correction of anemia. Experimental evidence points to iron serving as a cofactor for muscle function.

However, many questions remain and require further research. Does iron need to be administered intravenously or would oral iron have the same effect? Is there a difference in the response of patients with iron deficiency versus anemia of chronic inflammation? Is left ventricular function improved by iron therapy? Is there a multiplicative effect of iron therapy in patients with clinically significant

anemia and heart failure? In patients with anemia of chronic inflammation, should intravenous iron be used more widely? In patients with anemia of chronic inflammation, how long can intravenous iron be used and will iron accumulate in the liver or heart if used for long periods of time? We look forward to future research to answer these and many other important questions about the use of intravenous iron.

Disclosure

Conflict-of-interest disclosure: J.L.C. declares no competing financial interests. J.W.A. has received honoraria and has membership on the Board of Directors/Advisory Committees of AMAG Pharmaceuticals and Watson Pharma.

Off-label drug use: Iron therapy in patients with heart failure.

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