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ORIGINAL ARTICLE

Iron deficiency in heart failure, an underdiagnosed and undertreated condition during hospitalization

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Abstract

Heart failure (HF) is a chronic medical condition affecting an estimated 1–2% of the world's population, and as many as 10% of patients age 65 and above. Among patients with HF, iron deficiency (ID) has an estimated prevalence of 30–83%, often without concomitant anemia. Thus, ID in HF is often underdiagnosed unless actively sought after. ID in HF has been shown to be an independent contributor of increased mortality, hospitalization, and early readmission compared with HF patients without ID or HF patients with anemia without ID. Previous trials suggest that intravenous iron supplementation for patients with chronic HF and ID with or without anemia has resulted in improved functional outcomes and quality of life; however, the role of iron supplementation in patients hospitalized with HF has not been well characterized. In this retrospective analysis conducted in a large urban health system, we show that of the greater than 10,000 patients admitted for HF in 1 year, only 158 patients underwent screening for ID. Of these, 109 met criteria for ID. Despite intravenous iron being the standard of care for treatment of ID in HF patients, only 23 patients received this therapy. These data suggest that iron deficiency, despite having major implications in HF, is not being adequately evaluated during hospitalizations for HF. Further, if ID is identified, it is not being appropriately addressed, as per current treatment guidelines.

Keywords Iron deficiency · Heart failure · Anemia · Intravenous iron

Background

Heart failure (HF) is a chronic medical condition affecting an estimated 1–2% of the world's population, and as many as 10% of patients age 65 and above [1, 2]. In the USA, HF is prevalent in approximately 6.5 million adults [3]. Management of HF results in approximately 12–15 million office visits and 6.5 million hospital days each year [4]. The American Heart Association estimates that an astounding $31.1 billion is spent annually for healthcare related to HF alone [5]. Future projections expect that these numbers will continue to rise [6]. Thus, HF presents a major public health risk.

Another global epidemic is iron deficiency (ID) and it is being increasingly recognized as a widespread medical problem in HF patients. Studies report that as many as 30–83% of patients with HF may have concurrent ID, oftentimes without overt anemia [2, 7–9]. ID has been shown to be an independent risk factor for mortality in patients with HF [7, 9]. ID in HF is defined by the American Heart Association/American College of Cardiology (AHA/ACC) guidelines as ferritin < 100 ng/mL or both transferrin saturation < 20% with ferritin 100–300 ng/mL [10].

The exact mechanism by which ID in HF portends worse patient outcomes is unknown, but it is believed to be secondary to the essential role iron plays in the body, namely in oxygen uptake, transport, storage, and erythropoiesis [11]. The etiology of ID in HF likely stems from either, or both, absolute and functional causes. Absolute ID in HF patients is attributed to gastrointestinal losses, poor nutrition, and malabsorption [12]. Functional ID in HF is due to chronic systemic

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inflammation resulting in increases in inflammatory markers, impairing iron utilization [13]. Studies have suggested myocardial iron content was decreased in HF patients resulting in reduced myocardial function [14, 15]. Furthermore, studies have suggested decreased myocardial function is due to reduced myocyte mitochondrial iron stores in HF patients with ID, resulting in worsening muscle function [14, 15]. In a study performed by Melenovsky et al. [14], myocardial tissue samples from patients with HF and those without HF were directly analyzed and myocardial iron content was noted to be lower in HF patients. This was associated with reduced mitochondrial enzyme activity in HF patients, suggesting the critical role that iron plays in myocardial function. On a macroscopic level, the presence of ID in HF results in overall poorer quality of life due to worsened dyspnea and fatigue [16].

The implications of ID in HF have prompted recent studies to find effective ways to address this problem. The Ferric Carboxymaltose in Heart Failure and Iron Deficiency (FAIR-HF) trial showed that intravenous iron (IVFe) supplementation for patients with chronic HF and ID with or without anemia resulted in improved functional outcomes and quality of life [17]. The Ferric Carboxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure (CONFIRM-HF) trial found that benefits were conferred to ID in HF patients even 1 year after treatment with IVFe [18]. Despite these findings, however, the investigation and treatment of ID in HF are not commonly performed in inpatient settings.

Purpose

In this study, we sought out to determine the degree of awareness regarding ID in HF and to determine if ID is being investigated in patients hospitalized for HF. Further, the use of IVFe during the hospitalization was determined.

Methods

Study sample

This was a retrospective study of patients admitted to a large urban academic health center between April 1, 2016, and April 1, 2017, with a primary or secondary diagnosis of HF. Patients included in our analysis were those admitted with acute exacerbation of HF, either HF with reduced ejection fraction or preserved ejection fraction, who had sufficient iron studies during hospitalization. Values analyzed in our study include hemoglobin, iron, ferritin, transferrin saturation (TSat). To be classified as iron deficient, AHA/ACC guidelines were employed, namely ferritin < 100 ng/mL or both a transferrin saturation < 20% with a ferritin 100–300 ng/mL [10]. Each patient was then also stratified into those who received intravenous iron sucrose (+IVFe) versus those that did not (−IVFe). Of note, while several formulations of intravenous iron are available on the market, only iron sucrose is used in our health system in the inpatient setting.

Primary outcomes

We characterized how many patients had adequate iron studies performed to appropriately evaluate iron stores while hospitalized for acute HF exacerbation. Furthermore, of those who were iron deficient, we identified how many received IVFe. We also compared iron panels between those who received IVFe versus those that did not.

Secondary outcomes

We also evaluated the number of patients discharged with oral iron.

Statistical analysis

In order to compare the number of patients with ID hospitalized with HF who received IVFe to those who did not, a two-tailed sign test was performed. In regard to iron study data, values are expressed as means ± standard deviation and χ^2 test was performed.

Results

Characteristics of the study population

A total of 10,381 patients were admitted with a diagnosis of HF to our hospital system during our study period. Of those, only 158 individual patients had adequate iron studies performed during at least one of their hospital admissions. Among 158 patients, 109 patients met the criteria for ID (69%; Fig. 1). Patient characteristics are detailed in Table 1. Twenty-three of the 109 patients received IVFe during their hospitalization (21%; $P < 0.0001$, $\alpha = 0.05$).

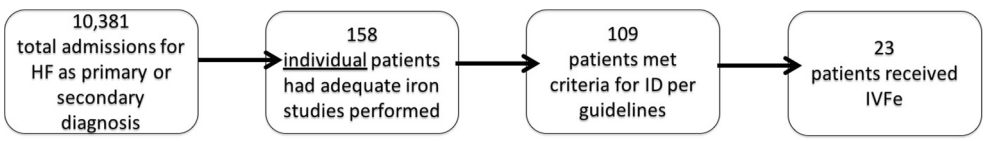

Fig. 1 Schematic representation of inclusion criteria for the study

Table 1 Baseline demographic and clinical characteristics of the study patients grouped according to intervention*

Variable	+IVFe ($n = 23$)	−IVFe ($n = 86$)
Age, years	59.2 ± 15.8	69.8 ± 16.3
Female sex, no. (%)	8 (34.8)	38 (44.2)
Male sex, no. (%)	15 (65.2)	48 (55.8)
Race, no. (%)‡		
Black	12 (52.2)	28 (32.6)
White	9 (39.1)	52 (60.5)
Hispanic	1 (4.3)	1 (1.2)
Asian	0 (0.0)	1 (1.2)
Not recorded	1 (4.3)	4 (4.7)
Heart failure type, no. (%)†		
Preserved ejection fraction	10 (43.5)	45 (52.3)
Reduced ejection fraction	13 (56.5)	41 (47.7)
Cardiovascular risk factors, no. (%)¤		
Hypertension	16 (69.6)	55 (64.0)
Diabetes mellitus	8 (34.8)	43 (50.0)
Chronic kidney disease	8 (34.8)	33 (38.4)
Hyperlipidemia	7 (30.4)	39 (45.3)
Creatinine, mg/dl	2.5 ± 2.8	1.6 ± 0.9
GFR, mL/min/1.73 m^{2}•	57.5 ± 44.4	56.1 ± 30.2

*Plus-minus values are means ± standard deviations

‡ Race was self-reported

† Heart failure type based on most recent echocardiogram report

¤ Cardiovascular risk factors based on reported co-morbidities in patient chart

¶ Creatinine values used were those obtained on the same day that iron panels were obtained

•Calculated using the following formula: GFR (ml/min/1.73m^2) = 175 × $SerumCr^{-1.154}$ × $age^{-0.203}$ × 1.212 (if patient is Black) × 0.742 (if female)

Characteristics of patients receiving or not receiving intravenous iron therapy

We further investigated the iron studies of those patients that ultimately received IVFe and those that did not (Table 2). Mean TSat for patients with ID who did and did not receive IVFe was 9.4 ± 6.1% and 10.1 ± 5.2%, respectively ($P = 0.58$, $\alpha = 0.05$). Mean ferritin for patients who did and did not receive IVFe was 79.1 ± 72.3 ng/dL and 77.9 ± 69.5 ng/dL, respectively ($P = 0.94$, $\alpha = 0.05$).

We also assessed if oral iron repletion was prescribed to HF patients with ID at the time of discharge (Table 3). In those patients who had received IVFe, only 1 patient was discharged on oral iron therapy (4.3%). Among those that did not receive IVFe, 17 patients were discharged on oral iron therapy (19.8%).

Table 3 Patients discharged on oral iron

Discharged on oral iron	+IVFe ($n = 23$)	−IVFe ($n = 86$)
Yes, no. (%)	1 (4.3)	17 (19.8)
No, no. (%)	22 (95.6)	69 (80.2)

Discussion

Increasing evidence highlights the prevalence of ID in HF. Studies suggest that the presence of ID in HF patients results in worsening of HF symptoms, thereby increasing office visits and hospital readmissions [2, 7, 9]. The role of iron administration in hospitalized patients has not been well characterized; however, several studies have suggested that there may be a benefit and failure to address this issue may be a missed opportunity to improve quality of life of HF patients [8, 11]. Despite this, iron studies in HF patients are often overlooked in the inpatient setting [11]. Our data supports this notion, as only 158 individual patients had adequate iron studies performed in the inpatient setting to evaluate ID, despite over 10,000 admissions for HF during our period of interest.

In instances where ID is diagnosed per the AHA/ACC guidelines, treatment is indicated and IVFe has been shown to be superior to oral iron repletion [17, 18]. Our data suggest that when ID was recognized in our patients, only 21% received IVFe during their hospital stay. What is most interesting was the lack of statistical significance between the TSat and ferritin values between the patients receiving IVFe and those who did not. Given that there was no statistical significance between the two values, the decision to administer IVFe is largely clinician-dependent, rather than based on the severity of ID itself. Furthermore, despite data suggesting that oral

Table 2 Characteristics of heart failure patients with iron deficiency who were treated and not treated with intravenous iron*

Variable	+IVFe ($n = 23$)	−IVFe ($n = 86$)	
Transferrin saturation, %	9.4 ± 6.1	10.1 ± 5.6	$P = 0.58$, $a = 0.05$
Ferritin, ng/dL	79.1 ± 72.3	77.9 ± 69.5	$P = 0.94$, $a = 0.05$
Hemoglobin, g/dL	10.5 ± 2.4	10.3 ± 2.2	$P = 0.78$, $a = 0.05$

*Plus-minus values are means ± standard deviations

iron is not an effective therapy for ID in HF, 18 patients were discharged on oral iron therapy.

There are several limitations to our study. For one, our sample size was relatively small due to the fact that not many full iron workups were performed on our patients during their hospital stays. While we characterize whether or not oral iron was prescribed at the time of discharge, we did not evaluate what therapies were administered to these patients in the non-hospital setting, specifically if IVFe was administered after hospitalization, such as in an office visit or infusion center.

Overall, our data suggest that ID in patients hospitalized for HF is prevalent, but underdiagnosed, and when it is diagnosed, it is undertreated. This finding comes despite increasing literature about the interplay between ID in HF and symptoms associated with the disease. We argue that it is imperative that iron stores be evaluated in patients who are hospitalized with HF given the significant role iron plays in the body, the increase in HF symptoms with ID, and the overall poor prognosis associated with ID in HF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Pennsylvania (confirmation number: cgdeedbi) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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