Fluctuating iron levels in heart failure: when and where to look at?

Ridha Ibrahim S. Alnuwaysir, Niels Grote Beverborg, and Peter van der Meer*

Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

This article refers to ‘Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure’ by F.J. Graham et al., published in this issue on pages 807–817.

Although our understanding of iron deficiency (ID) in heart failure (HF) has been evolving from merely a prevalent comorbidity that is associated with worse clinical course to an important player in disease progression that can be modified, many questions remain to be answered.1 In the most recent HF guidelines of the European Society of Cardiology (ESC) of 2021, it is suggested that haemoglobin and iron status should be checked periodically in all HF patients.2 How frequent this should be performed is not specified, as data on the longitudinal changes of iron status and anaemia in patients with HF are mostly lacking. In addition, the adopted definition of ID by the ESC (ferritin <100 μg/L or ferritin 100–299 μg/L with a transferrin saturation [TSAT] <20%) successfully identifies a group of patients who might benefit from treatment with intravenous (IV) iron, but its predictive value on true ID and prognosis is a topic of debate.3–5

In this issue of the Journal, the study by Graham et al.6 addresses some of these knowledge gaps by studying the dynamic changes of ID and anaemia in HF. In 906 outpatients with chronic HF (51% with reduced ejection fraction, HFrEF) from the Hull LifeLab cohort, Graham et al. investigated the longitudinal changes of haemoglobin and iron status over a year using various definitions for ID, including the ESC definition, serum iron (≤13 μmol/L) and TSAT <20%. One of the key findings of this work is the demonstration that iron status and haemoglobin levels are dynamic in these patients (Figure 1), with high incidence and resolution rates despite the exclusion of HF patients treated with erythropoietin analogues or IV iron.6 After 1 year, 30% of patients developed ID while 16% developed anaemia. On the other hand, natural resolution was high with a 44% resolution rate of ID and 23% of anaemia. Compared to those with repleted iron stores, patients with persistent ID, defined by a serum iron ≤13 μmol/L, were found to have a higher risk of both cardiovascular as well as all-cause mortality at 5 years (hazard ratio [HR] 1.90, 95% confidence interval [CI] 1.14–3.16, and HR 1.81, 95% CI 1.23–2.67, respectively). Similar associations with only all-cause mortality were also observed when defining ID as TSAT <20%, but not when the ESC criteria were used. On the other hand, HF patients in whom serum iron was normalized (>13 μmol/L) over time, had lower mortality rates when compared to HF with persistent ID (HR 0.61, 95% CI 0.44–0.86; p = 0.004). Albeit non-significant, there was a similar trend of reduced all-cause mortality when defining ID as TSAT <20% (HR 0.77, 95% CI 0.54–1.09; p = 0.14), but not when using the ESC criteria (HR 1.22, 95% CI 0.87–1.73; p = 0.25).

These observations are relevant as the natural history of these comorbidities is not well characterized. Recently, Fitzsimons et al.7 showed that persistent ID defined as TSAT <20% (and not the ESC criteria) at 6 months was associated with poor outcomes when compared to those who never had ID or in whom ID was naturally resolved. Graham et al. corroborate these findings; persistence of ID defined as per the serum iron or TSAT criteria was associated with higher all-cause mortality rates. As a significant number of patients developed ID in the course of a year, and these dynamic changes associate with prognosis, these data indicate that it might be useful to measure iron parameters at least once yearly.

Another interesting insight of the study by Graham et al. is the high spontaneous resolution rate of ID in HF (44%), with a median absolute change of +9% in TSAT. In the placebo arm of the EFFECT-HF trial, mean TSAT, albeit slightly, increased significantly from 18.1% to 20.2% after 24 weeks of follow-up.8 Similar improvements of TSAT in the placebo group were also observed in patients who were stabilized after an episode of acute HF (mean absolute change +5.4% after 6 weeks).9 In the present study, resolution of ID was more likely in those with isolated ID (Figure 1) compared to those with ID anaemia, suggesting either a different ID severity or aetiology. Although oral iron was allowed, and used in ~5% of the patients, it is unlikely that this is the main reason behind this substantial resolution rate as it been shown...
Recent perspectives on the mechanisms leading to ID in HF suggest that both systemic and myocardial ID in HF might be associated with over-activation of the neurohormonal system. Reducing sympathetic activation is one of the main therapeutic targets in HF. Accordingly, one may speculate that optimal HF treatment may improve iron status by mitigating the neurohormonal activation and/or inflammation, thereby improving dietary iron absorption and mobilization. However, it is probably unrealistic to think that only improvement of dietary iron absorption might be the main driving force behind the fluctuations seen in iron status of HF patients. This is because the magnitude of depleted iron stores in these patients is so severe that up to a year would be needed to restore the depleted stores based solely on dietary iron absorption. Evidence about dietary iron absorption in HF and whether it might be improved as a result of optimal treatment is lacking. These explanations remain to be assumptions and therefore, further mechanistic studies should be conducted to reveal the exact pathophysiology underlying ID in HF.

The work by Graham et al. also illustrates the limitations of the ESC definition. The ESC definition is useful in selecting a patient cohort that might benefit from treatment with IV iron, but it also appears to include patients without true ID, and with a prognosis that is not worse than patients who do not fulfil these criteria. According to the ESC definition, outcomes in this study were similar amongst those in whom ID persisted, resolved or did not develop compared to those who never developed ID. These observations are likely attributed to the dependence on ferritin. Although ferritin provides a useful indirect estimate of iron stores correlating poorly with iron indices in HF, it is probably unrealistic to think that only improvement of dietary iron absorption might be the main driving force behind the fluctuations seen in iron status of HF patients. This is because the magnitude of depleted iron stores in these patients is so severe that up to a year would be needed to restore the depleted stores based solely on dietary iron absorption. Evidence about dietary iron absorption in HF and whether it might be improved as a result of optimal treatment is lacking. These explanations remain to be assumptions and therefore, further mechanistic studies should be conducted to reveal the exact pathophysiology underlying ID in HF.

The work by Graham et al. also illustrates the limitations of the ESC definition. The ESC definition is useful in selecting a patient cohort that might benefit from treatment with IV iron, but it also appears to include patients without true ID, and with a prognosis that is not worse than patients who do not fulfil these criteria. According to the ESC definition, outcomes in this study were similar amongst those in whom ID persisted, resolved or did not develop compared to those who never developed ID. These observations are likely attributed to the dependence on ferritin. Although ferritin provides a useful indirect estimate of iron stores correlating poorly with iron indices in HF, it is probably unrealistic to think that only improvement of dietary iron absorption might be the main driving force behind the fluctuations seen in iron status of HF patients. This is because the magnitude of depleted iron stores in these patients is so severe that up to a year would be needed to restore the depleted stores based solely on dietary iron absorption. Evidence about dietary iron absorption in HF and whether it might be improved as a result of optimal treatment is lacking. These explanations remain to be assumptions and therefore, further mechanistic studies should be conducted to reveal the exact pathophysiology underlying ID in HF.
similar to HF patients with normal iron status (ferritin ≥100 μg/ml and a TSAT ≥20%). Furthermore, re-analysis of the four randomized controlled trials comparing ferric carboxymaltose with placebo in HF patients showed that those with TSAT >19.8% or serum iron >13 μmol/L did not have improved outcomes after IV iron treatment. This questions if the ESC definition is still the preferred method to define ID in HF. It is not validated against the gold standard of bone marrow aspirates, but on a consensus after the clinically meaningful improvements observed in clinical trials. As such, our definition of ID is actually a combination of expert opinions and a pragmatic approach that allowed us thus far to identify a population of HF patients that benefit from iron replacement therapy.

This study by Graham et al. has also several limitations. Firstly, although several ID definitions were used, this comprehensive analysis did not include data on soluble transferrin receptor, which is a more reliable marker in accurately reflecting depleted iron stores when compared to bone marrow. Also, as acknowledged by the authors, only 33% (906 out of 2763 patients in whom HF was confirmed and survived 12 months) of the patients with available tests for iron status and haemoglobin at baseline and 1 year were included for the present analysis. This might make the results prone to selection bias as those included were more likely to have HFrEF, be men and have higher plasma N-terminal pro-B-type natriuretic peptide, thereby limiting the generalizability of the results.

In conclusion, the natural history of ID in HF is crucial; the results of Graham et al. provide rationale for annual follow-up of iron status. Although the ESC definition is a pragmatic approach that has performed reasonably well thus far at a population level, this work further shows its weakness as it does not identify patients with a worse prognosis. Accurately determining iron status is a prerequisite for correctly evaluating the role of ID in HF, diagnosing ID and monitoring response to interventions at an individual level. Prespecified subgroup analyses with more in-depth analysis of iron homeostasis of the ongoing trials will provide more evidence regarding the response to IV iron in relation to how ID should be defined.

Conflict of interest: N.G.B. reports speaker fees from Vifor Pharma. P.v.d.M. reports consultancy and/or research grants from Vifor Pharma, AstraZeneca, Servier, Pharmacosmos, Novartis, Pfizer, Ionis. R.I.S.A. has nothing to disclose.

References