The importance of iron deficiency in heart failure

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Iron deficiency and anaemia are common in patients with heart failure and independently associated with worse outcomes, including higher morbidity and reduced quality of life. All patients with heart failure should be screened for these conditions. If present, anaemia may be managed acutely with a restrictive red blood cell transfusion, whereas intravenous iron supplementation is the standard of care for iron deficiency in this population.

Heart failure (HF) currently affects 0.5 to 2% of Australian adults and is responsible for 2% of all deaths.[1,2] Anaemia is common in patients with HF, with rates of up to 27% reported in recent studies.[3] The prevalence of anaemia increases with worsening functional class, with the highest rates seen in patients with New York Heart Association (NYHA) class IV impairment and among patients with HF who are hospitalised.[4] Age, female gender and vascular comorbidities such as diabetes mellitus are associated with a greater risk of anaemia in patients with HF. Prevalence is equal in patients with reduced (HFrEF) and preserved ejection fraction phenotypes.[5]

The aetiology of anaemia in HF is often multifactorial and includes:

- anaemia of chronic disease related to cardiorenal syndrome, chronic kidney disease and/or chronic inflammation
- nutritional deficiencies, particularly in developing countries and remote areas
- hepatic dysfunction in patients with pronounced right HF
- iron deficiency (ID), an important emerging prognostic and therapeutic factor in HF.

ID in HF occurs due to a number of factors, as shown in the Flowchart,[6-9] including:

- malnutrition related to anorexia
- malabsorption due to gut oedema
- haemodilution with fluid retention
- medication side effects related to angiotensin II inhibition.

HF also results in functional ID wherein a reduction in erythropoiesis and increase in hepatic iron retention occur due to chronically elevated inflammatory cytokines and upregulation of hepcidin.[6] In advanced stages of the disease, increased catabolism from cardiac

Key points

- **Iron deficiency (ID), even in the absence of anaemia, in patients with heart failure (HF) is common, multifactorial and associated with worse outcomes.**
- **Anaemia should be thoroughly investigated and other common causes including blood loss, nutritional deficiencies and chronic renal failure considered.**
- **ID in HF is confirmed with iron studies showing a ferritin level less than 100 mcg/L or a ferritin level 100 to 299 mcg/L with a transferrin saturation below 20%.**
- **Oral iron supplementation has not shown consistent benefit in HF cohorts to be recommended in lieu of intravenous (IV) iron.**
- **IV iron supplementation in patients with HF and ID has numerous benefits including reduction in HF hospitalisations, reduction in symptoms, improved functional capacity and improved quality of life.**

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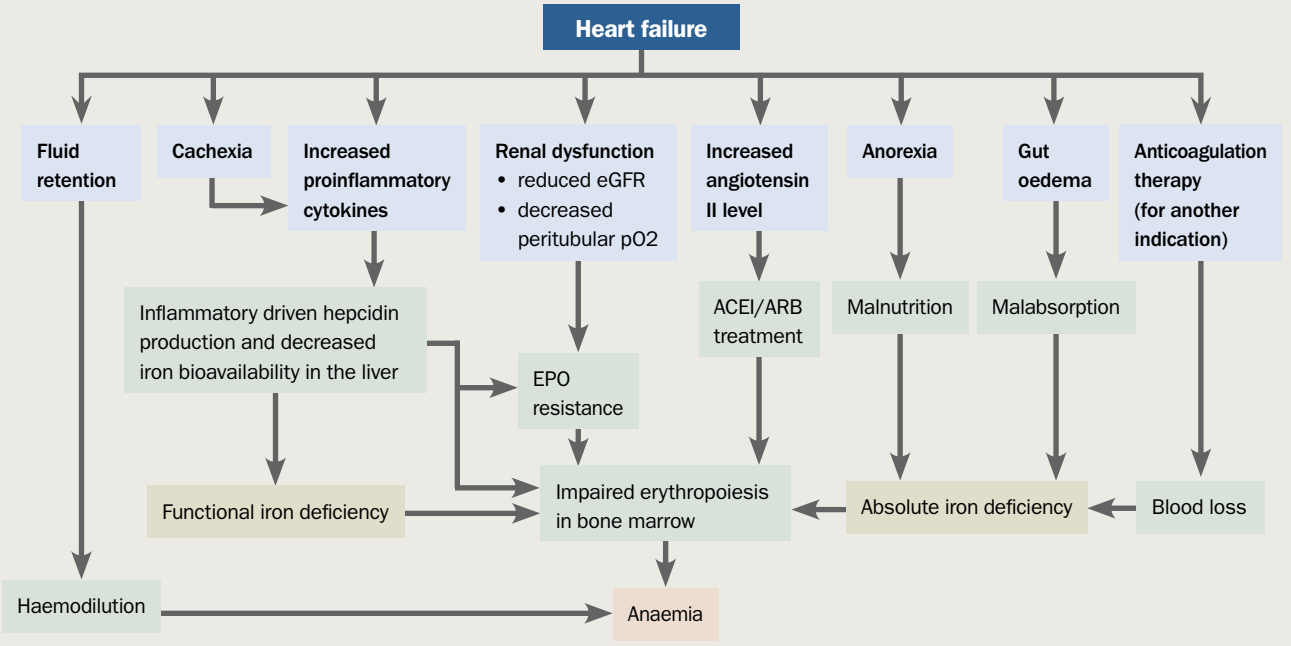
Causes of iron deficiency and anaemia in heart failure[6-9]



Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; EPO = erythropoietin; eGFR = estimated glomerular filtration rate; pO2 = partial pressure of oxygen.

cachexia can also contribute to ID.[10] Additionally, blood loss causing ID may be unmasked or exaggerated by the presence of anticoagulation, which is much more prevalent in the HF cohort than in the general population.

ID is present in nearly 50% of patients with HF and often without clinical or biochemical evidence of anaemia.[11] The presence of anaemia is prognostically important and increases rates of HF-related hospitalisations, healthcare-related costs and mortality in both acute and chronic HF cohorts.[12,13] Even among patients with HF without anaemia, ID is independently associated with higher mortality, reduced exercise capacity and worse quality of life.[14]

Screening recommendations

Knowledge of these important associations has resulted in class I guideline recommendations to screen all patients with HF for anaemia and ID with full blood count, red cell indices and haematinics including ferritin and transferrin saturation (TSat) levels.[15] Biochemically, ID is suggested by a hypochromic, microcytic anaemia (haemoglobin level less than 120 g/L in women or less than 130 g/L in men and mean corpuscular volume less than 80 fL) and evidence of reduced iron stores but may be diagnosed on haematinics alone, with a ferritin level less than 100 mcg/L or a ferritin level 100 to 299 mcg/L with TSat less than 20%.[16]

Iron studies are also important to check in patients with HF to exclude haemochromatosis, a rare but important cause of HF. Other important investigations to undertake in these patients are renal and liver function tests, coagulation studies and nutritional haematinics (vitamin B12, folate and 25-hydroxyvitamin D levels). Bone marrow assessment should be undertaken if suspicion exists for a neoplastic or myelodysplastic cause of anaemia. If undertaken, bone marrow iron stores depletion is most specific for ID and the gold standard for definitive diagnosis in otherwise ambiguous cases.[17]

Management strategies for iron deficiency in patients with heart failure

Acutely, anaemia may be managed with red blood cell transfusions; however, a restrictive strategy (haemoglobin threshold <70 to 80 g/L) is recommended. Among other advantages, such a strategy obviates the risk of transfusion-related circulatory overload to which patients with HF are particularly prone.[18]

Iron supplementation forms the backbone of managing ID in HF with class II guideline recommendations.[19] Oral iron is poorly absorbed, especially in patients with HF and gut oedema; associated with bothersome side effects including constipation and nausea; and often therapeutically inadequate due to slow correction of iron stores and increased likelihood of poor patient compliance.[20] Oral iron trials have not demonstrated consistent benefit in HF cohorts.[20]

Intravenous (IV) iron now represents the standard of care in this space. In Australia, therapeutic options include ferric carboxymaltose, iron polymaltose and iron sucrose. The latter of these has limited use and is reserved for use in patients with chronic kidney disease and allergy to the other agents. Although initial costs may

be higher than oral iron, compliance is guaranteed, and overall costs are lower with IV iron supplementation.

The recent randomised controlled trial (RCT), AFFIRM-AHF, demonstrated benefit of IV ferric carboxymaltose in 1132 individuals with HFrEF hospitalised with acute HF and concomitant iron deficiency. Heart failure hospitalisations were significantly lower and haemoglobin incrementation greater in the ferric carboxymaltose compared with placebo group. Overall mortality and serious adverse events were similar between groups.[16] Before this trial, an international meta-analysis representing 10 RCTs and 1404 patients demonstrated reduction in HF hospitalisations, improved NYHA class, improved six-minute walk test performance and reductions in levels of biomarkers (serum N-terminal pro-B-type natriuretic peptide and C-reactive protein). The analysis failed to show improvement in overall mortality between iron supplementation and placebo groups.[21]

Caution

Despite initial compelling evidence from small studies, erythropoietin (EPO) therapy in patients with HF is not recommended following results from the RED-HF study. This large RCT of 2278 patients with systolic HF and mild-to-moderate anaemia (haemoglobin 90 to 120 g/L) assigned to darbepoetin alfa or placebo showed no improvement in cardiovascular clinical outcomes but a significantly increased rate of thromboembolism and nonsignificant but numerically higher rate of ischaemic strokes in the EPO group.[22]

Iron infusions should be avoided in patients during periods of severe infection and potential bacteraemia, as the iron can act as an energy source for pathogens and potentiate worsened infection and sepsis. Despite advances in pharmaceutical manufacturing and agent preparation, iron infusions are still associated with a low but significant rate of serious allergic reactions. In patients with severe atopy or multiple drug allergies, it is reasonable to premedicate with corticosteroids before IV iron administration.

Conclusion

Anaemia and ID are common problems in HF populations. They are independently associated with worse outcomes, including higher mortality and reduced quality of life. Elucidation of the aetiology of anaemia is an important step in management and is best accomplished with thorough clinical history and examination of patients and basic and haematinic bloodwork. ID in HF is multifactorial but is suggested by a ferritin level less than 100 mcg/L or a ferritin level 100 to 299 mcg/L with TSat less than 20%.

Correction of ID with IV iron supplementation, preferably with ferric carboxymaltose, is feasible in both inpatient and outpatient settings and is associated with improvements in multiple key clinical outcomes. **CT**

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