Anaemia in heart failure: the clinical perspective

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Anaemia is common in heart failure and is a risk factor for increased mortality but whether it has a causative role has not been established. Iron supplementation and erythropoietin replacement improve exercise capacity and well-being scores but have not been shown to reduce hospitalisation or mortality.

Anaemia is very common in heart failure. Although anaemia of chronic disease is probably the dominant cause, often related to renal dysfunction, iron deficiency is also common, and recent studies suggest active iron replacement and bone marrow stimulants may have a symptomatic benefit in patients with severe heart failure.

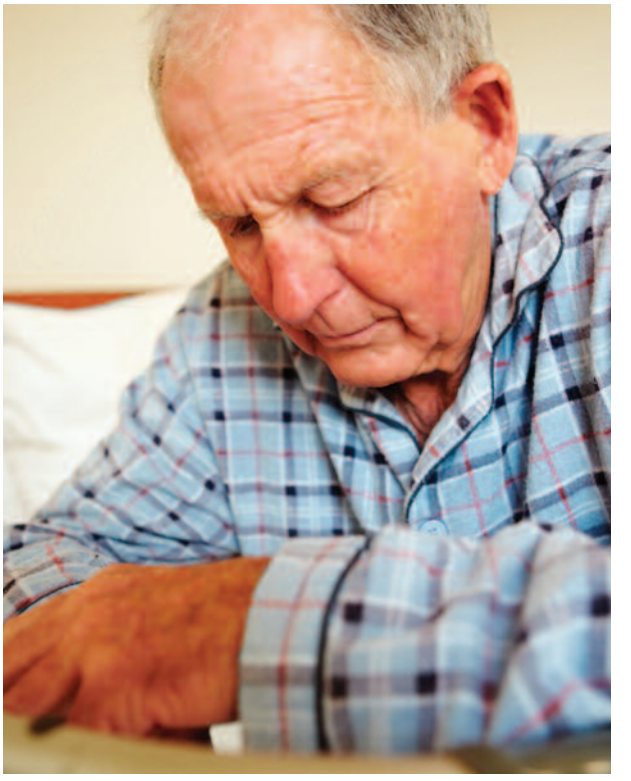
Understanding the aetiology of anaemia helps to inform the results of a number of randomised clinical trials that are starting to report results.

Why check for anaemia in heart failure?

The main reason for checking for anaemia in patients with heart failure is that it is surprisingly common, probably twice as common as in the age-matched general community population.[1] Evidence of excess anaemia was seen in the first heart failure mega-trial investigating the effectiveness of ACE inhibitors (SOLVD [Studies of Left Ventricular Dysfunction] and has been confirmed in multiple subsequent heart failure studies and population registries.[2,3] The prevalence of anaemia is independent of the degree of left ventricular dysfunction in heart failure (systolic or diastolic).[4] Depending on the definition used (usually haemoglobin level below 130 g/L for men and below 115 g/L for women), subsequent studies have shown the prevalence of anaemia to vary from 9.3% to 17.2% to 45%, with a typically higher prevalence of anaemia in women.[4-7]

Three-quarters of patients with heart failure are on either oral anticoagulation or antiplatelet agents, and are therefore at much higher risk for gastrointestinal blood loss than individuals not taking these drugs.[8] Having said that, anaemia is often normochromic and normocytic, sometimes associated with lymphopenia, which suggests a more general failure of haematopoiesis.[7]

Related to the finding of nonspecific impaired haematopoiesis,



Key points

- **Anaemia occurs in more than 10% of patients with heart failure.**
- **Anaemia is associated with decreased survival and increased hospitalisation in patients with heart failure.**
- **Anaemia is multifactorial, including not only iron deficiency but also bone marrow paresis and haemodilution.**
- **Alternative causes for anaemia should be sought and corrected in patients with heart failure.**
- **Iron replacement improves symptoms in anaemic or non-anaemic patients with heart failure – even without a change in haemoglobin concentration.**
- **Correction of anaemia by erythropoiesis stimulants is associated with improved symptoms in heart failure.**

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it is recognised that cardiac failure is associated with inflammatory cytokine activation and also with defective iron supply and/or blunted erythropoietin production, both of which may contribute to the anaemia.[1,9] It has been suggested that the anaemia of heart failure is similar in many ways to the anaemia of chronic disease.[10]

A recent large Australian study (959 patients hospitalised with heart failure) confirmed these large-scale clinical trial results in a community population, with 38% defined as anaemic (haemoglobin level below 120 g/L).[11] In the vast majority of these patients (88%), the anaemia was normocytic and normochromic and iron deficiency was only demonstrated in 15% of anaemic patients. This understanding may contribute to the incomplete success for current anaemia treatment trials,[12] and emphasise the importance of defining aetiology of anaemia as completely as possible.

Which haematological tests to use in heart failure?

It is understandable, but concerning nonetheless, that cardiologists tend to investigate patients with anaemia far less thoroughly than do generalists.[6] Primary care practitioners are probably more likely to look for alternative causes, particularly in the context of alcohol consumption and nutritional deficiencies. Iron studies (ferritin, serum iron, transferrin saturation and transferrin) are important to check in patients with heart failure – not least to exclude haemochromatosis, in which the iron overload may be a rare cause of cardiac impairment.

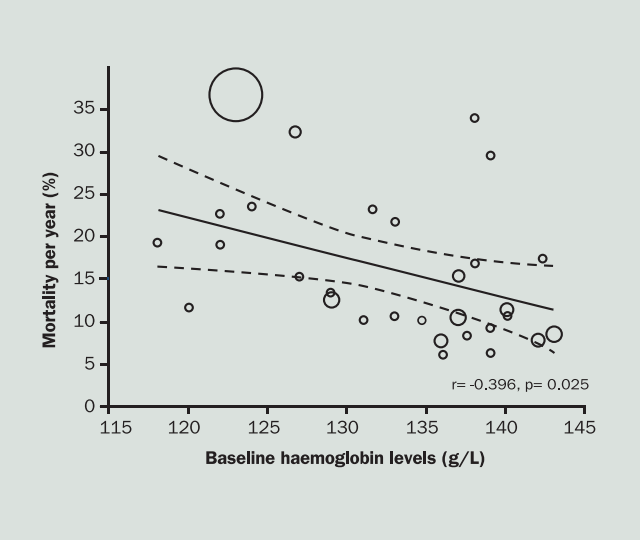

Figure. Relation between baseline haemoglobin level and annual mortality in a meta-analysis of 32 studies of heart failure patients with anaemia. The area of each circle is proportional to the sample size in each cohort. The centre line shows the estimated mortality risk per year of lower baseline haemoglobin values on a continuous scale. The dotted lines represent the 95% confidence intervals. Reproduced from: Groenveld HF, Januzzi JL, Damman K, et al. Anemia and mortality in heart failure patients: a systematic review and meta-analysis. *J Am Coll Cardiol* 2008; 52: 818-827, with permission from Elsevier.

Iron deficiency is commonly defined as a ferritin level below 30 µg/L, or a ferritin level below 100 µg/L with transferrin saturation below 20%. When bone marrow stores are examined for evidence of iron deficiency, rather than relying just on blood markers, rates of nearly 75% have been found in patients with heart failure.[13]

Another very important comorbidity with heart failure is concomitant renal impairment. Anaemia is closely associated with renal dysfunction, also affected by poor cardiac function.[7,14,15] Renal dysfunction may also be related to heart failure treatment, particularly diuretics and ACE inhibitors/angiotensin receptor blockers. Low blood pressure and low cardiac output are major risk factors, and both are associated with worsening of outcomes.[16]

What is the impact of anaemia in heart failure?

Patients with heart failure and anaemia have a significantly higher risk of subsequent death. In a meta-analysis of studies totalling more than 150,000 patients with heart failure, anaemia (variably defined according to each study) was associated with a subsequent risk of death of 47%; compared with 30% in patients without anaemia.[4] Even after adjusting for age and renal function, both of which are strong predictors in cohort studies of survival in heart failure, anaemia was associated with a nearly 50% increase in mortality.[4,17] A decrease of haemoglobin concentration even within the normal range increases mortality; for example, a decrease from 140 g/L to 120 g/L increases mortality from 12.5% to 22%, as shown in the Figure.[4]

The Australian study mentioned previously showed the complex interaction of risk factors, and even treatment.[11] In this study, patients with anaemia were more likely to have more severe heart failure, as manifest by higher heart failure readmission rates, a worse degree of hyponatraemia, more impairment of renal function, lower ACE inhibitor use, higher nonheart failure admission as well as higher all-cause mortality.

Trials of haematinic replacement therapy in heart failure

Iron replacement

Iron is essential for the transport and storage of oxygen in the blood and is also involved in oxidative metabolism in the skeletal and heart muscle.[18] As a result, it has been suggested that improving iron availability through iron supplementation or erythropoiesis support may benefit patients with heart failure.

There have been several recent studies examining iron replacement in heart failure. A small pilot study (observer-blinded) – the Effect of Intravenous Ferrous Sucrose on Exercise Capacity in Chronic Heart Failure study (also known as the Ferric Iron Sucrose in Heart Failure [FERRIC-HF] trial) – examined the effect of intravenous iron sucrose in 17 anaemic and 18 nonanaemic patients with heart failure.[19] As expected, there was an improvement in ferritin levels and transferrin saturation, but haemoglobin levels

did not change. Despite this lack of change in haemoglobin concentration, there was still an improvement in aerobic exercise capacity (weight-corrected peak oxygen consumption), associated with a significant decrease in venous distension, body weight and symptomatic scores of heart failure (New York Heart Association and fatigue score).

Improvement in surrogate endpoints for heart failure, such as B-type natriuretic peptide, has also been demonstrated with iron replacement in patients with heart failure.[20] Interestingly, this study also showed significant improvements in inflammatory markers (C-reactive protein) in patients treated with iron, possibly related to improvements in oxidative status.

A further large multicentre study – the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial – confirmed beneficial symptomatic responses to iron supplementation in patients with evidence of iron deficiency.[21] Patients were given an average of six injections of iron (ferric carboxymaltose) over a period of three to seven weeks, based on the degree of iron deficiency from laboratory calculations. Quality of life, patient global assessment scores and six-minute walk distances were improved, again in the absence of any significant change in haemoglobin levels.

The largest ongoing international multicentre trial of iron replacement – the Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Iron Deficiency and Chronic Heart Failure (EFFECT-HF) study – is with intravenous ferric carboxymaltose, using standardised cardiopulmonary stress testing. This phase III trial will use more objective measures of heart failure severity (change in maximum oxygen consumption at six months) to assess response to iron replacement in a targeted population.

The Iron Supplementation in Heart Failure Patients With Anemia (IRON-HF) study is a large multicentre placebo-controlled study examining the short-term (three-month) effect on peak oxygen consumption of combination intravenous iron (iron sucrose) loading with supplemental oral iron (ferrous sulfate) in iron-deficient patients with heart failure.[22] Secondary endpoints in this study are the effects on left ventricular function, natriuretic peptides and clinical outcomes. Results are not yet available. As yet, there are no studies showing a benefit for routine oral iron replacement in heart failure patients.

Erythropoietin replacement

The great majority of patients with heart failure have defective endogenous erythropoietin production.[9] The first study to show a beneficial role for supplemental erythropoietin on exercise capacity was in 12 patients less than 10 years ago.[23] The results of this study were confirmed in a slightly larger study with darbopoetin.[24] A more recent pivotal trial with darbopoetin – the Study of Anemia in Heart Failure Trial (STAMINA-HF) – did not confirm symptomatic improvement, despite a slight improvement in haemoglobin levels.[25]

A recent Cochrane meta-analysis of 734 patients with heart failure across 11 studies (nine of which were placebo-controlled) suggested improvements in six-minute walk distance and in maximum oxygen consumption as well as tendencies to lower hospitalisations and mortality with treatment with erythropoiesis-stimulating agents.[26] Across those study populations, the mean increase in haemoglobin concentration was nearly 20 g/L.

Enthusiasm has been curtailed and caution highlighted by the recent trial of darbopoetin in patients with type 2 diabetes, chronic kidney disease and anaemia – the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study.[27] This trial was stopped early because of an increased risk of stroke, despite a tendency to lower fatigue, in this group of patients without heart failure. An important difference between patients with heart failure and those with kidney failure is blood pressure, which is a major contributor to stroke, as seen with a strong tendency to higher blood pressure in the darbopoetin group in the TREAT study. Patients with heart failure, who typically have low blood pressure, may not be exposed to such a risk.

A further large scale placebo-controlled clinical trial examining the effects of targeted darbepoietin (to a haemoglobin concentration of 130 g/L, but not exceeding 145 g/L) on all-cause mortality and heart failure hospitalisation in patients with impaired ventricular function is under way – the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial.[28]

Summary

Anaemia is common in patients with heart failure. It has repeatedly been confirmed as a risk factor for increased mortality, but whether this is through a causative role or it is an innocent bystander, particularly in the setting of concomitant renal impairment, has not been established. The most common causes of anaemia are anaemia of chronic disease with blunted erythropoietin response and/or iron deficiency.

Replacement studies with both iron supplementation and erythropoietin replacement have been encouraging in terms of symptomatic improvement in exercise capacity and well-being scores; however, improvements in hard endpoints such as hospitalisation or mortality have not been demonstrated. Symptomatic improvement may occur without a change in haemoglobin concentration with intravenous iron supplementation, confirming nonhaematological benefits of iron on body metabolism.

Several large studies are ongoing and will clarify whether there is a role for iron or erythropoietin replacement in patients with heart failure. **CT**

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A list of references is available on request to the editorial office.

COMPETING INTERESTS: Associate Professor Hayward is a co-investigator in the EFFECT-HF trial, a study of intravenous iron replacement in iron deficient heart failure patients, administered through St Vincent's Hospital, Sydney. There are no commercial interests to declare.

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