Anaemia in congestive heart failure

Anaemia is common in patients with congestive heart failure, and has an adverse effect on prognosis. This article discusses the advances in understanding of the pathophysiology of the anaemia, the treatment options including transfusion, and highlights areas in need of further development.

Our understanding of anaemia associated with congestive heart failure is improving. Several studies have described an association with anaemia and congestive heart failure (Komajda, 2004), and that the overall prognosis of compensated and decompensated congestive heart failure is adversely affected by the presence of anaemia (He and Wang, 2009). Alongside the improved understanding of the pathophysiology of anaemia new treatment options can be considered for this complex group of patients. This review outlines the underlying aetiology of anaemia in congestive heart failure, describes in detail the pathophysiology, and discusses the evidence base for treatment options and how this evidence informs the need for future studies.

Table 1. Common causes of anaemia classified according to mean cell volume

Mean cell volume	Cause
Microcytic anaemia (mean cell volume <80 fl)	Iron deficiency
	Anaemia of chronic disease
	Thalassaemia
Normocytic anaemia (mean cell volume 80–100 fl)	Anaemia of chronic disease
	Acute blood loss
	Chronic renal failure
	Combined deficiencies, e.g. folate and iron deficiency
	Bone marrow impairment, e.g. following chemotherapy
Macrocytic anaemia (mean cell volume >100 fl) megaloblastic	Folate or vitamin B_{12} deficiency
	Medication, e.g. hydroxycarbamide
	Pregnancy
Macrocytic anaemia (mean cell volume >100 fl) non-megaloblastic	Myelodysplastic syndromes
	Multiple myeloma
	Haemolytic anaemia (reticulocytosis)
	Alcohol
	Hypothyroidism
	Cirrhosis

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Aetiology of anaemia in congestive heart failure

Anaemia is conventionally classified according to red cell size (mean cell volume). A microcytic anaemia is most frequently caused by iron deficiency, although thalassaemia trait is common in some ethnic groups. A normocytic, normochromic anaemia may be secondary to the anaemia of chronic disease and a macrocytic anaemia is often secondary to cobalamin or folate deficiency although there are many other possible explanations (*Table 1*).

In a very large study of over 12 000 patients with congestive heart failure, anaemia was found in 17% (Ezekowitz et al, 2003). In these patients, the anaemia was attributed to anaemia of chronic disease in 58% and iron deficiency in 21%. On multiple logistic regression analysis, anaemia was more common in older patients, women, patients with chronic renal insufficiency and in those with hypertension. Anaemia is commoner in those with more advanced heart failure (New York Heart Association (NYHA) class III–IV compared to those with NYHA classes I–II.

In another important study, Parikh et al (2011) found that in the large prospective NHANES (National Health and Nutrition Examination Survey) III cohort study in congestive heart failure, iron deficiency was present in 352 of the 574 participants, with 20.2% of the iron-deficient individuals being anaemic compared with 10.7% of those with normal iron stores. Interestingly, iron deficiency was also associated with a higher C-reactive protein level (0.95 *vs* 0.63 mg/dl, P=0.04). In this study, there was an association with decreases in haemoglobin and increased cardiovascular mortality, but not all-cause mortality.

Table 2 summarizes the possible causes of anaemia in patients with congestive heart failure and indicates potential underlying mechanisms. These mechanisms are possible explanations for patients with congestive heart failure but it is important to remember that the patient may have other health problems and that appropriate investigation to determine the underlying cause of anaemia should always be carried out.

Iron deficiency

The patient is usually, but not always anaemic. Common causes include bleeding from the gastrointestinal or genitourinary tract, iron malabsorption from disorders such as coeliac disease or gastric achlorhydria and, just

occasionally in the western world, inadequate dietary intake. In addition to these causes, patients with congestive heart failure may malabsorb iron because of oedema of the small intestinal wall or from chronic blood loss contributed to by treatment with antiplatelets and/or anticoagulants (Silagy et al, 1993). Heavy proteinuria, in patients with renal disease, may also contribute to iron deficiency.

Anaemia of chronic disease

Anaemia of chronic disease is the second most common cause of anaemia worldwide, following iron deficiency. It is highly prevalent among unwell, hospitalized inpatients and is typically associated with an inflammatory, infective or malignant disorder. It is characterized by a hypoproliferative normochromic, normocytic anaemia. It reflects a state of functional iron deficiency caused by the defective use of existing reticuloendothelial iron for red cell production, co-existing alongside reticuloendothelial iron overload, reduced erythropoietin production, a blunted response of red cell precursors to endogenous erythropoietin, and reduced red cell life span in the circulation. Such changes are often driven by inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6).

Anaemia of chronic disease has been associated with congestive heart failure. In the NHANES (Parikh et al, 2011) epidemiological study, one third of cases of anaemia of chronic disease were associated with chronic kidney disease and 12% were associated with underlying congestive heart failure. This study also found that raised C-reactive protein levels, a marker of inflammation, were associated with an increased all-cause and cardiovascular mortality in congestive heart failure. The NHANES study therefore demonstrated the association between inflammation, anaemia and congestive heart failure.

Opasich et al (2005) studied 148 consecutive patients with congestive heart failure with haemoglobin <13 g/dl (if males) or <12 g/dl (if females) that was not caused by other comorbid conditions. Their cohort study found that 57% of patients presented with features typical of anaemia of chronic disease, defined in the study as a normocytic, normochromic anaemia with reduced serum iron concentration, transferrin, and total iron binding capacity co-existing with a normal or raised ferritin and normal or slightly increased soluble transferrin receptor. Of the anaemia of chronic disease patients 92% displayed defective endogenous erythropoietin production. A C-reactive protein level >0.50 mg/dl was found in 62% and co-existent chronic kidney disease was also common.

The cytokine profile of the patients with anaemia of chronic disease and congestive heart failure was also compared to normal healthy controls. TNF-α, IL-1 receptor and IL-6 levels were substantially higher in those with anaemia of chronic disease and congestive heart failure *vs* healthy controls. TNF-α has previously been shown to inhibit erythrocyte development. Bone marrow erythroid colony growth from patients with active rheumatoid arthritis was significantly reduced when compared with normal controls in proportion to increased TNF-α levels (Papadaki et al, 2002).

There is also clear evidence that IL-6 (Wrighting and Andrews, 2006) is a key upregulator of hepcidin, a hepatic peptide (Ganz, 2011) known to reduce iron

Table 2. Aetiology of anaemia in congestive heart failure

Cause of anaemia	Proposed mechanism	Reference
Iron deficiency (absolute)	Reduced iron absorption	Parikh et al (2011)
	Chronic blood loss as a result of antiplatelet agents and anticoagulation	Silagy et al (1993)
	Nutritional insufficiency	Witte and Clark (2002)
Anaemia of chronic disease (functional iron deficiency)	Reduced erythropoietin production	Opasich et al (2005)
	Reduced sensitivity of the developing erythrocyte to erythropoietin	
	Defective iron use in the developing erythrocyte	
	Reduced red blood cell survival	
	Above abnormalities induced by inflammatory cytokines: interleukin-1, interleukin-6, tumour necrosis factor-α	
	Chronic kidney disease, known to be associated with congestive heart failure	
Haemodilution	Renin–angiotensin–aldosterone pathway stimulation causing sodium and water resorption	Androne et al (2003)
Drug-induced anaemia	Anaemia induced by angiotensin-converting enzyme inhibitors	Leshem-Rubinow et al (2012)
Microangiopathic haemolysis	Valve-induced intravascular haemolysis	Nitter-Hauge (1979)
Unrelated causes	Haematinic deficiency	
	Haemolysis (immune and non-immune)	
	Bone marrow failure syndromes, e.g. myelodysplastic syndrome	n/a

absorption and reduce the export of macrophage storage iron from the reticulo-endothelium to the developing erythrocyte. Opasich et al (2005) showed that in those with anaemia of chronic disease and congestive heart failure, erythropoietin levels significantly correlated with NYHA classification, C-reactive protein levels and strongly with IL-6. Erythropoietin resistance has also been associated with raised TNF-α levels in congestive heart failure (Okonko and Ankers, 2004).

Other mechanisms of anaemia in congestive heart failure

In addition to absolute iron deficiency and anaemia of chronic disease, there are other potential mechanisms associated with anaemia in congestive heart failure. It is likely, in some patients, that overstimulation of the renin–angiotensin–aldosterone system contributes to a reduction in haemoglobin concentration via haemodilution (Androne et al, 2003). Co-existent chronic kidney disease, which is common in congestive heart failure, can cause a blunting of erythropoietin secretion (Ezekowitz et al, 2003). It is quite plausible that mechanisms overlap in these complex patients.

Treatment of anaemia in patients with congestive heart failure

Packed red cell transfusion

Providing a red cell transfusion to individuals with congestive heart failure is a relatively common challenge faced by hospital trainees across all specialties. Data have been collected and reported by the Serious Hazards of Transfusion working group regarding the prevalence of, and risk factors for, transfusion-associated circulatory overload. The 2010 Serious Hazards of Transfusion report (Knowles and Cohen, 2011) describes a number of recent cases of inadequate medical assessment before transfusion. The report highlights a lack of careful monitoring of fluid balance and a lack of appreciation that the rate (ml/minute) of red cell transfusion should consider patient weight and other risk factors for transfusion-associated circulatory overload, such as patient age, left ventricular systolic dysfunction, hypoalbuminaemia and renal impairment.

These findings subsequently led to the British Committee for Standards in Haematology (2012) producing national guidelines on this issue. These recommendations highlight the importance of:

1. Considering the absolute necessity of transfusion
2. Careful clinical assessment regarding the optimum rate of transfusion by taking into account the patient factors listed above
3. Increased frequency of clinical observations and fluid balance in at-risk patients
4. Calculating the red cell dose required based on the knowledge that 4 ml/kg gives rise to a haemoglobin increment of 1 g/dl. This is opposed to the old mantra that supposes that one unit of packed red cells gives rise to a haemoglobin increment of 1 g/dl in all patients, which is only true for stable, non-bleeding patients weighing 70–80 kg
5. Using single unit packed red cell transfusions when that dose is considered adequate.

New treatment options

Intravenous iron in congestive heart failure

Anker et al (2009) studied patients with congestive heart failure and iron deficiency. Eligible patients had NYHA functional class II or III and reduced left ventricular ejection fraction (40% or less for NYHA class II or 45% or less for NYHA class III). All patients had iron deficiency defined as a serum ferritin less than 100 μg/litre, or 100–299 μg/litre if transferrin saturation was <20%. This landmark study included those with or without anaemia – all patients included had haemoglobin 9.5–13.5 g/dl. Patients were randomized in a 2:1 fashion to either intravenous ferric carboxymaltose or placebo and treated over a 24-week period.

Intravenous iron significantly improved NYHA class, distance on the 6-minute walk test and quality of life compared with placebo. Results were similar in both the anaemic and non-anaemic subgroups and the mortality and morbidity rates were similar in the placebo and treatment arms of the trial. These findings suggest that treatment of iron deficiency is important in congestive heart failure and can result in functional improvement. Whether oral iron might have been as effective as intravenous iron is uncertain.

The findings are in keeping with other data from smaller randomized control trials. For example, Okonko et al (2008) found that 16 weeks of intravenous iron improved exercise tolerance (treadmill exercise duration) and NHYA class in those with congestive heart failure and abnormal iron status, although benefits in this smaller trial were more evident in anaemic patients. Toblli et al (2007) performed a double-blind, randomized, placebo-controlled study to investigate whether intra-venous iron in individuals with congestive heart failure and chronic kidney disease reduces NT-pro brain natriuretic peptide (NT-proBNP) and C-reactive protein levels. At 6-month follow up, those treated with intravenous iron sucrose had significantly improved haemoglobin and ferritin concentrations, increased transferrin saturation, and lowered NT-proBNP levels and C-reactive protein levels. Left ventricular ejection fraction percentage, Minnesota Living with Heart Failure Questionnaire score, 6-minute walk test, and hospitalization rates were all improved in the intravenous iron sucrose group ($P<0.01$).

Intravenous iron allows direct provision of plasma iron to the developing erythron, bypassing the impaired absorption in functional iron deficiency. It is intriguing that non-anaemic iron-deficient individuals with congestive heart failure can gain substantial symptomatic benefit from intravenous iron replacement. Cytochromes and

oxidative enzymes within the mitochondria require iron for normal function. It is postulated that symptomatic responses in non-anaemic, iron-deficient patients may be an effect of correcting otherwise iron deplete metabolism within skeletal muscle. This theory is supported by the fact that iron supplementation has been previously shown to improve endurance and exercise tolerance in both rats and humans (Willis et al, 1990; Brutsaert et al, 2003). These results consistently show that intravenous iron improves exercise tolerance, NYHA class, overall cardiac function and quality of life for congestive heart failure patients with iron deficiency.

Erythropoiesis-stimulating agents in congestive heart failure

Erythropoiesis-stimulating agents have been extensively studied in patients with anaemia associated with chronic kidney disease and the anaemia of cancer. Studies have also been reported in patients with anaemia of chronic disease and congestive heart failure. It is likely that some of these patients will have had impaired renal function. Ngo et al's (2010) systematic Cochrane review included eleven studies that examined erythropoiesis-stimulating agent use in congestive heart failure. Nine of these studies were placebo-controlled and five were double-blinded. The meta-analysis found that erythropoiesis-stimulating agents produced an improvement in left ventricular ejection fraction, NYHA class, exercise tolerance and quality of life scores. The benefits were mainly seen in those with mild anaemia (haemoglobin >10 g/dl). Mortality and hospitalizations were reduced and the findings were not at the expense of increased cardiovascular events, thromboembolism or stroke. Ngo et al concluded by stating that these interesting findings require large, prospective randomized trials to answer questions regarding dosage, haemoglobin target, and long-term outcome benefits.

Recent data have emerged from the RED-HF trial (Swedberg et al, 2013) which was initiated in 2006. RED-HF is the largest randomized controlled trial to date designed and powered to answer whether morbidity and mortality is improved with erythropoiesis-stimulating agents (darbepoetin) in anaemic patients with congestive heart failure. A total of 2278 anaemic patients with symptomatic left ventricular systolic dysfunction were randomized to either darbepoetin or placebo. The target haemoglobin was >13 g/dl in the erythropoiesis-stimulating agent arm. The results were recently published in the *New England Journal of Medicine* (Swedberg et al, 2013). There was no significant difference in the primary end point – a composite of time to all-cause mortality or first hospital admission for worsening congestive heart failure – in patients with congestive heart failure and anaemia (hazard ratio 1.01, 95% confidence interval 0.90–1.13). While darbepoetin may have symptomatic benefit, the role of single agent erythropoiesis-stimulating agent in congestive heart failure and anaemia is now in doubt.

Combination therapy

Given the multiple, complex underlying mechanisms of anaemia in congestive heart failure, and the knowledge that anaemia of chronic disease is common, the question of dual erythropoiesis-stimulating agent and iron therapy has been raised. This combination has proven effective in anaemia of chronic disease associated with chronic kidney disease (Coyne et al, 2007).

Erythropoietin and intravenous iron

Silverberg et al (2001) compared placebo with intravenous iron and erythropoiesis-stimulating agent combination, and showed that combination treatment in moderate to severe congestive heart failure resulted in marked improvement in NYHA class, left ventricular ejection fraction, need for diuretics and hospitalization rates. Following the study it was unclear which of the two agents provide the additional benefit.

Terrovitis et al (2012) published results of a small randomized control trial which aimed to assess the magnitude of haematological and symptomatic response to either intravenous iron combined with erythropoiesis-stimulating agents or intravenous iron alone. Forty three consecutive patients with anaemia (haemoglobin <12 g/dl in men and haemoglobin <11.5 g/dl in women) associated with advanced congestive heart failure were recruited following a recent admission for decompensated congestive heart failure. Thirty participants were found to have absolute iron deficiency, based on a negative Perl's stain on bone marrow aspirate. They were randomized to subcutaneous darbepoetin 50 μg with intravenous 300 mg iron sucrose once weekly (n=14) or intravenous 300 mg iron sucrose once weekly alone for a total of 6 weeks. Haemoglobin levels improved significantly in both groups compared to baseline, but there was no difference in response when comparing the groups at any time point.

The authors cited the 'unique mechanisms' of anaemia in congestive heart failure as the rationale for using erythropoiesis-stimulating agents. It was postulated that any response to iron alone could, in theory, be blunted by underlying erythropoietin resistance typical of anaemia of chronic disease. However, anaemia of chronic disease patients often display increased iron on a Perl's stain on a marrow aspirate and this might explain why addition of the erythropoiesis-stimulating agent was ineffective. This small study shows that, for now, short-term intravenous iron is first-line standard therapy in those with iron deficiency and advanced congestive heart failure.

Larger, adequately powered studies, in congestive heart failure participants with clearly defined anaemia of chronic disease, with precise laboratory and clinical primary outcomes are required to establish whether combination therapy is beneficial. It would be helpful to define, if possible, the major precipitant underlying the anaemia in the participants of such a trial as the pathophysiology and likely treatment response may be quite variable.

The risks of treatment with iron and erythropoiesis-stimulating agents

Although the FAIR-HF study (Anker et al, 2009) suggested that parental iron repletion in congestive heart failure with functional iron deficiency improves exercise capacity and quality of life independently of the presence of anaemia, it is important to cautiously titrate replacement. There is evidence that iron overload confers an increased risk of cardiovascular events. Iron loading can lead to excess labile plasma iron which can contribute to the formation of free hydroxyl radicals and subsequent tissue damage (Kruszewski, 2004). Although not a consistent finding in the literature, there is some evidence that increased labile plasma iron may increase the risk of carcinogenesis and atherosclerotic disease (Gey, 1993). Interestingly, the cardiovascular theory is indirectly supported by epidemiological studies in blood donors. Three of four studies (Meyers et al, 1997, 2002; Ascherio et al, 2001) found a substantial reduction in cardiovascular risk in the donor population, and the other study (Tuomainen et al, 1997) showed a significant reduction in the risk of fatal myocardial infarction. These results, however, are likely to be confounded by the altruistic nature of the 'healthy donor' and the strict health questionnaire screening pre-donation.

Erythropoiesis-stimulating agents are safe when used in accordance with current guidelines in chronic kidney disease and cancer. However, in chronic kidney disease three studies (Drüeke et al, 2006; Singh et al, 2006; Pfeffer et al, 2009) demonstrated that a higher target haemoglobin concentration (around 13.5 g/dl) resulted in more complications and an inferior outcome compared to a lower target (around 11.5 g/dl). In patients with anaemia and cancer, meta-analyses have shown an increased risk of venous thromboembolism in erythropoiesis-stimulating agent-treated patients and an increase in all-cause mortality. Guidelines from the American Society of Hematology support the use of erythropoiesis-stimulating agents in cancer to maintain the haemoglobin concentration high enough to avoid transfusion but not to increase the haemoglobin >12.0 g/dl (Rizzo et al, 2010). At present there are insufficient safety data available in patients with congestive heart failure and this requires more careful study.

KEY POINTS

- Anaemia in congestive heart failure is common, worsens New York Heart Association class and increases mortality.
- Anaemia is multifactorial, with functional and absolute iron deficiency playing major roles in the pathophysiology of anaemia in congestive heart failure.
- Intravenous iron improves New York Heart Association class, exercise tolerance and quality of life when compared with placebo in both anaemic and non-anaemic iron-deficient patients with congestive heart failure.
- Cochrane meta-analysis has shown that erythropoiesis-stimulating agents in congestive heart failure with anaemia produce an improvement in left ventricular systolic function, New York Heart Association stage, exercise tolerance and quality of life scores.
- A large recent randomized control trial suggests that erythropoiesis-stimulating agents have no clear mortality benefit in the treatment of anaemia in the context of congestive heart failure.
- There is no high quality evidence to suggest that combined erythropoiesis-stimulating agent and intravenous iron therapy is better than intravenous iron alone in congestive heart failure with absolute iron deficiency anaemia.
- Transfusion-associated circulatory overload is a major risk in those with impaired left ventricular systolic function, renal impairment, hypoalbuminaemia and increased age. Measures to reduce transfusion-associated circulatory overload have been summarized in British Committee for Standards in Haematology national guidelines.

Conclusions

Anaemia is a common and treatable association with congestive heart failure. The anaemia may be multifactorial, or have a single aetiology, such as iron deficiency. Over recent years, clear data have shown that short-term intravenous iron replacement in patients with iron depletion (functional or absolute) in congestive heart failure with and without anaemia, and erythropoiesis-stimulating agents in those with anaemia in congestive heart failure, improve symptoms and functional performance. A recent large randomized trial suggests that erythropoiesis-stimulating agents alone do not improve overall mortality rates in anaemia and congestive heart failure.

It is reasonable at present to treat functional or true iron deficiency anaemia with short-term intravenous iron replacement; however, it is not clear what dose of intravenous iron or erythropoiesis-stimulating agent is optimal, or what is the ideal target haemoglobin. At present, there is minimal clear evidence supporting the use of dual therapy in anaemia associated with congestive heart failure. Large, prospective randomized trials are needed to answer questions regarding dosage, haemoglobin target, and long-term outcome benefits and risks of erythropoiesis-stimulating agent or intravenous iron therapy in these challenging patients. **BJHM**

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