Anaemia and heart failure: aetiology and treatment

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Abstract

Heart failure (HF) is a common disease associated with poor prognosis. Anaemia is commonly associated with HF due to bone marrow depression, reduced availability of iron and haemodilution, and is sometimes aggravated by too frequent blood testing. Low haemoglobin is very detrimental to the haemodynamic state of the patient with decreased cardiac output as it further diminishes the oxygen supply to the tissues. When anaemia is associated with HF and renal failure, the patient enters a vicious cycle called cardio renal anaemia syndrome. The prognosis of patients with HF is worse as the haemoglobin is lower and even mild anaemia is associated with <1 year survival. Aggressive correction of the anaemia by subcutaneous injections of erythropoeitin and intravenous iron has been shown to improve the functional capacity and quality of life of patients with cardio renal anaemia syndrome and to reduce the need for hospitalization. However, intravenous iron can be detrimental because of increased formation of free radicals, oxidative stress and risk of infection. The level of haemoglobin needed to be achieved is not clear, but it seems indicated to maintain it above 12 g%.

Keywords: anaemia; heart failure; prognosis; renal failure; treatment

Leviticus 17:11: ‘For the life of the flesh is in the blood’

Heart failure (HF) is a common and costly clinical condition, associated with grave outcome. It is estimated that the 1-year mortality rates for patients with New York Heart Association (NYHA) class II, III and IV are 10, 20 and 40%, respectively. Ischaemic heart disease (IHD) and hypertension account for most cases of HF in developed countries. HF is the most common cause for hospitalization in patients >65 years old, and its frequency increases with increased age [1]. Several clinical and laboratory markers identify patients with HF with worse outcome; amongst them are advanced age, reduced ejection fraction, presence of IHD, elevated filling pressure, reduced exercise capacity [2] and elevated levels of several inflammatory cytokines such as tumour necrosis factor (TNF)-α, C-reactive protein (CRP), interleukin-6 [3], naturietic peptides [4,5] and neurohormones [6]. In recent years, the presence of anaemia has emerged as one of the important predictors of poor outcome in HF patients. Anaemia is one of the most common causes of increased cardiac output and, when extremely severe, may result in HF due to a high output state even in the absence of intrinsic heart disease. Normally, 1 g of haemoglobin (Hb) binds 1.34 ml of O2. When the Hb level is 15 g/dl, 100 ml of arterial blood contains 20 ml of O2, while during ‘mild to moderate anaemia’ of 10 g/dl, the O2 content of 100 ml of blood falls to 13.3 ml. A physiological compensation can be achieved by an increase in cardiac output, enhanced oxygen unloading from the Hb by a shift to the right of the Hb–O2 dissociation curve, or by increased erythropoietin production [7]. In the presence of anaemia, when the need for greater cardiac output is combined with decreased systolic and/or diastolic performance, the clinical state of congestive HF may develop or become aggravated.

The World Health Organization’s definition of anaemia is Hb <13 g/dl in men and <12 g/dl in women. Horwich et al. [8] studied 1061 patients with advanced HF (functional capacity III or IV) and left ventricular ejection fraction (LVEF) <40%. The patients were divided into four quartiles according to their Hb levels <12.3, 12.3–13.6, 13.7–14.8 and >14.8 g/dl. Even a small decrease in the Hb level was associated with worsening of prognosis, with a 1-year survival of 55.6, 63.9, 71.4 and 74.4% in the different Hb quartiles. On multivariate analysis, adjusting for known HF prognostic factors, low Hb proved to be an independent predictor of mortality with a relative risk of 1.13 for each decrease of 1 g/dl in Hb. It seems, therefore, that...
even an Hb of 12–13.6 g/dl should be considered abnormal in patients with reduced cardiac function.

The aetiology of anaemia in HF is multifactorial, including bone marrow depression and reduced availability of iron and haemodilution secondary to sodium and water retention. As discussed by Lewis et al. and Wexler et al. in the current supplement, HF is accompanied by bone marrow depression, probably due to chronic inflammation with production of proinflammatory cytokines and induced erythropoietin resistance [9]. The low iron level, due to reduced content of iron in the diet and also reduced iron absorption, is often present in patients with HF [10,11]. Witte et al. [12] explored the relationship between levels of iron, B12 and folic acid levels. They measured the Hb levels and exercise tolerance in 173 patients with systolic dysfunction, 123 patients with diastolic HF and 58 control patients. Thirty-five percent of the patients with systolic dysfunction, 33% of the patients with diastolic dysfunction and four control patients were anaemic. Exercise tolerance and peak oxygen consumption during effort correlated with Hb levels. There was no difference in the levels of iron, B12 and folic acid among the different groups of patients. Altogether, 6% had vitamin B12 deficiency, 13% had iron deficiency and 8% folate deficiency.

Anaemia can be also iatrogenic due to repeated blood testing. Smoller et al. [13] studied 50 HF patients who were hospitalized in intensive care units and found that a volume of 762 ml of blood was withdrawn during their hospitalization. It is clear that every blood test should be ordered only if necessary and not only by routine!

IHD is the most common cause of HF. Zeidman et al. [14] compared 317 anaemic IHD patients with 50 anaemic patients without IHD and 50 IHD patients without anaemia (control). Patients with combined IHD and anaemia had more severe clinical presentations, with 44% presenting with acute coronary syndrome and 36% with acute myocardial infarction, compared with 26 and 20% in the group of IHD patients with normal Hb levels. HF was more common in IHD patients with anaemia compared with IHD patients without anaemia (31 vs 18%). Mortality was also significantly higher in IHD patients with anaemia (13 vs 4%). In their discussion, the authors raise the possibility that the more severe clinical manifestation is due to more severe chronic inflammation, leading both to anaemia and to more advanced atherosclerosis.

Recently, Iversen et al. [15] demonstrated a decreased haematopoiesis in the bone marrow of mice with HF. The HF mice had a 60% reduction in the amount of progenitor cells compared with control mice. A 3-fold increase in apoptosis was probably the reason for the paucity in progenitor cells. As measured in vitro, the proliferative capacity of progenitor cells in mice with HF was only 50% of the control. The authors also found that the expression of TNF-α was markedly increased in bone marrow natural killer cells and T cells and these lymphocytes exhibited increased cytolytic activity against progenitor cells in vitro, indicating that anaemia is related to increased inflammatory activity.

Wexler et al. (this supplement), who performed several pioneering studies on the frequency and significance of anaemia in HF patients, found that anaemia is present in ~40% of HF patients. This is in concordance with the findings of Lewis et al. [16]. Lewis et al. [16], who reported an incidence of almost 50% of anaemia (defined as Hb < 12 g/dl) in HF patients. In the European Heart Failure Survey [16], an Hb of <11 g/dl was found in 23% of the women and 18% of the men. These authors suggest that in HF patients, the main cause of the anaemia is the renal damage caused by the reduced cardiac output. Several other reports have demonstrated reduced renal function in anaemic HF patients [3,17,18]. Ezekowitz et al. [18] analysed the data from a large cohort of 12065 patients hospitalized in Alberta, Canada with new onset HF. Seventeen percent of these patients were found to be anaemic, 58% of whom had anaemia of chronic disease, 21% of iron deficiency and 8% of other causes. Anaemia was more common in older patients, females, hypertensive or chronic renal failure patients. The hazard ratio for mortality was 1.34 in anaemic patients.

A major advance was made by Silverberg et al. [19–22] who corrected the anaemia of HF patients by subcutaneous (s.c.) erythropoietin and intravenous (i.v.) iron. In their first and second reports, which included 26 patients [19] and 179 patients [20], respectively, the functional capacity improved by 34% and the hospitalization numbers dropped dramatically by 96%. In their randomized trial [21], which included only 16 treated and 16 control patients, the improvement in exercise capacity, quality of life and renal function was nevertheless remarkable. The functional class improved by 42% in the treated patients and worsened by 11% in the control group. In the first 26 treated patients [22], an increase in LVEF from 27.7 to 35.4% was observed. The majority of these patients had advanced renal failure with a mean serum creatinine of 2.59 mg%. Wexler et al. (this supplement) suggest that treatment of anaemia in the HF patient can break the vicious cycle of the cardio renal anaemia syndrome [14] which in their opinion is crucial to the improvement in response to the treatment of HF. If the anaemia is not corrected, the extent of improvement, even with an optimal treatment of HF, is limited. The beneficial effect of the correction of anaemia is probably not related to protection from ischaemia, as silent ischaemia was as common in 15 haemodialysis patients treated with erythropoietin and normalized Hb compared with 16 control haemodialysis patients [23].

Slotki, in an extensive review in the current supplement, discussed the risk of iron supplementation in patients with HF and renal failure. The clinical studies reported [24–26] included only patients on haemodialysis and it is not clear whether the risk of the iron toxicity, namely free radical formation, oxidative
Anaemia and heart failure: aetiology and treatment

stress and infection, can be applied to patients not on haemodialysis.

Kurishev et al. [27] examined a model of iron overload in Mongolian gerbils given repeated injections of iron dextran. They noticed important electrophysiological changes: (i) the iron content of gerbil ventricular myocytes was increased to amounts similar to those found in patients with iron-induced cardiomyopathy; (ii) the overshoot and duration of the cardiac action potential were decreased; and (iii) sodium current was reduced and transient, outward potassium current was increased. Schwartz et al. [28] showed decreased cardiac conductivity in Purkinje fibre in iron-overloaded guinea pigs. A high incidence of sudden death was seen in the treated guinea pigs. Yang et al. [29], using the Mongolian gerbil model, demonstrated a bimodal effect of iron loading. At shorter duration, an initial state of high cardiac output was seen. The mean cardiac work, coronary flow and left ventricular dp/dt were significantly greater than control values. At longer durations of treatment, concentric hypertrophy developed and cardiac output and exercise capacity were impaired, with a low output failure similar to patients with transfusion iron overload. It is possible that treatment with erythropoietin by itself can be detrimental by worsening the left ventricular diastolic function, as described by Topuzovic [30], while systolic function at rest and during exercise remain unchanged.

In summary, anaemia is very common in HF patients. It is frequently associated with renal failure and, when present, it affects prognosis of these patients, their quality of life and their response to treatment. Aggressive correction of the anaemia with s.c. erythropoietin and i.v. or p.o. iron can improve the Hb levels of these patients, their quality of life, their response to medical therapy and, hopefully, though not yet demonstrated, improve their prognosis. While the level to which the anaemia should be corrected is not clear, Hb probably should exceed 12 g/dl.

Conflict of interest statement. None declared.

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