Anaemia as a contributor to morbidity and mortality in congestive heart failure

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Abstract
Anaemia is present in ~40% of cases of congestive heart failure (CHF) and is associated with a higher mortality, a lower left ventricular ejection fraction, a lower cardiac functional status, a higher rate of hospitalization, signs of malnutrition, a lower exercise capacity, a progressive fall in renal function, an increased need for high dose diuretics, hyponatraemia, an increased plasma volume, a reduced red cell volume and a lower quality of life. In both uncontrolled and controlled studies, correction of the anaemia with subcutaneous erythropoietin and, in some cases, with the addition of intravenous iron, has been shown to improve these parameters. A vicious circle is present between CHF, chronic kidney insufficiency (CKI) and anaemia, each capable of causing or being caused by the other, the so-called cardio renal syndrome. If larger randomized, controlled, double-blind studies confirm these observations, correction of the anaemia may prove to be a useful addition to the prevention and progression of both CHF and CKI. Cooperation between nephrologists, cardiologists and other internists to identify and treat these anaemic CHF patients early will help prevent progression of both the cardiac and renal disease.

Keywords: anaemia, erythropoietin; heart failure; iron; kidney failure

CHF in the community
Congestive heart failure (CHF) is present in ~2% of the population, ~5% of the population above age 65 years and ~10% of the population above age 80 years [1]. Despite all the advances in the therapy of this disease, the 1-year mortality in men in the Framingham study fell from 30% in the period 1950–1969 to only 28% in the period 1990–1999 [2]. Although part of this disappointing result may be due to lack of an aggressive approach to therapy with CHF medications [3,4], it is possible that another factor is also contributing, i.e. lack of treatment of the anaemia which is often seen in CHF.

The relationship between anaemia and CHF manifestations
Anaemia (which is defined in different ways by different investigators) is found in 9–61% of CHF cases [5–15]. On average ~40% of CHF cases are anaemic. Anaemia is more common and more severe in the elderly, in those with more severe compared with milder heart failure, in those who are hospitalized compared with those in out-patient clinics, and in those with associated renal insufficiency. Anaemia in CHF is associated with a higher rate of hospitalization or rehospitalization [5–7] and mortality [5–13] than patients without anaemia and is an independent risk factor for these complications even when other factors such as age, sex and renal function have been taken into consideration [5–13]. Anaemia and chronic kidney insufficiency (CKI) have an additive effect on the mortality [8,9] and on the need for dialysis [16] in CHF. The anaemia in CHF has been associated with worsening New York Heart Association (NYHA) functional status [6,10,14], hyponatraemia [7], rapid progression of renal failure [5,6,17,18], signs of malnutrition such as a low body mass index (BMI) and serum albumin [10] as well as with more severe haemodynamic changes such as reduced oxygen utilization [10,14,19], reduced exercise capacity [10,14,19], lower blood pressure [10], higher heart rate [10], higher pulmonary capillary wedge pressure [10] and signs of peripheral hypoperfusion [20].
How does anaemia cause or worsen CHF?

Anaemia causes peripheral ischaemia which results in a fall in blood pressure that activates both sympathetic and renin–angiotensin, aldosterone and vasopressin activity, resulting in reduced renal blood flow, reduced glomerular filtration rate (GFR) and increased sodium and water absorption [21]. The expanded extracellular volume will cause haemodilution and a lower haemoglobin (Hb) concentration [13]. The increased plasma volume causes ventricular dilation which puts a further stress on the heart already stressed by tachycardia and increased stroke volume. Eventually, left ventricular hypertrophy (LVH) occurs, which can lead to myocardial cell death from necrosis and apoptosis [22,23]. All this may lead to CHF. Put simply, anaemia can cause or worsen oedema and CHF. There are also other ways by which anaemia can cause CHF. The lack of oxygen supply to the heart caused by the anaemia in the face of increased heart rate and stroke volume may cause ischaemia and lead to myocardial cell death. In addition, the red blood cells contain many antioxidants and, therefore, not surprisingly, anaemia is associated with an increase in oxidative stress [24,25] which could cause damage to the myocardial cells. mVO₂ (volume of oxygen) utilization during peak exercise is considered one of the most accurate tests of cardiac function [19]. In CHF patients, peak mVO₂ decreases significantly with lower Hb levels [14,19].

The aetiology of anaemia in CHF

The main cause of anaemia is most probably renal damage produced by poor cardiac function, with reduced cardiac output and renal vasoconstriction leading to prolonged renal ischaemia. This causes renal damage and reduced production of erythropoietin (EPO) in the kidneys. However, not all patients with anaemia and CHF have CKI [5–15]. Studies in animals have shown that CHF itself may cause anaemia [26]. The damaged heart may secrete cytokines such as tumour necrosis factor-α (TNF-α [27]) which can cause anaemia in three ways [28]: by reducing EPO production in the kidneys; by interfering with EPO activity at the level of the bone marrow; and by inhibiting the release of Fe from the reticuloendothelial system so that it cannot reach the bone marrow to be utilized in Hb production. It has been shown recently that the higher the TNF-α in CHF, the lower the Hb level [29]. Many patients with CHF take aspirin, which may cause mucosal irritation and blood loss. Patients with CHF often have proteinuria, and EPO, iron and transferrin can all be lost in significant amounts in the urine [30], also contributing to the anaemia. EPO production and utilization may be inhibited by angiotensin-converting enzyme (ACE) inhibitors, resulting in anaemia [31]. Finally, part of the anaemia in CHF may be due to haemodilution [13,21], but the majority of CHF patients with anaemia actually have, in addition to an increased plasma volume, a reduced red cell volume [13].

The effect of correcting the anaemia on CHF and the associated CKI

The most important way to assess the possible causal role of anaemia in CHF and CKI is to correct it. This has been examined by us in several recent studies [5,6,17,18].

We treated for several months 26 patients with NYHA class IV who were resistant to all CHF medications (given in recommended doses) with subcutaneous (s.c.) EPO and intravenous (i.v.) iron [Venofer (iron sucrose)] to correct the anaemia to a mean of 12 g% [6]. The treatment was associated with a marked improvement in CHF as judged by improved NYHA functional status and increased left ventricular ejection fraction (LVEF). Compared with the pre-treatment period, the rate of rehospitalization fell markedly and the dose of oral and i.v. diuretics needed was greatly reduced. In addition, the rate of fall of GFR as measured by 1/serum creatinine × 100 improved. Renal function, that had been falling at a rate of ~1 ml/min/month, stabilized when the anaemia was corrected, and the CHF improved.

In a subsequent randomized controlled (but not double-blind) study [17], we studied 32 such resistant anaemic CHF patients. They were assigned to two groups. 16 received the EPO–i.v. iron combination for several months and the other 16 were not treated. In the 16 who were treated, the NYHA and LVEF improved significantly, the mean serum creatinine did not change, and the rate of hospitalization fell significantly, as did the doses of oral and i.v. furosemide. In the control group, the NYHA, LVEF, hospitalization rate and needed dose of diuretics worsened and the serum creatinine increased significantly. No deaths occurred in the treated group; four occurred in the non-treated group, all from progressive CHF. We have now increased our experience to 179 such patients, including both diabetics and non-diabetics, and our results were similar [18]. Our patients were asked on their first visit and at the completion of the study when they had reached and maintained the target Hb of 12.5 g% to assess their fatigue and NYHA class IV who were resistant to all CHF medications (given in recommended doses) with subcutaneous (s.c.) EPO and intravenous (i.v.) iron [Venofer (iron sucrose)] to correct the anaemia to a mean of 12 g% [6]. The treatment was associated with a marked improvement in CHF as judged by improved NYHA functional status and increased left ventricular ejection fraction (LVEF). Compared with the pre-treatment period, the rate of rehospitalization fell markedly and the dose of oral and i.v. diuretics needed was greatly reduced. In addition, the rate of fall of GFR as measured by 1/serum creatinine × 100 improved. Renal function, that had been falling at a rate of ~1 ml/min/month, stabilized when the anaemia was corrected, and the CHF improved.

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and diabetics suggests that it was not only the diabetes itself that is causing the deterioration in renal function but also the anaemia and uncontrolled CHF.

Another argument for the causative effect of anaemia in CHF is the response to EPO of other cardiovascular parameters. In a placebo-controlled trial, patients with severe CHF who received EPO for 3 months had a significant improvement in peak VO₂, VO₂ at the anaerobic threshold, exercise duration in seconds and distance walked in 6 min [19]. In the control group, none of these parameters changed significantly. In the treated group, the quality of life based on a questionnaire showed improvement in the treated group and a deterioration in the placebo group. As in the study mentioned above [14], a significant positive linear correction was observed between the change in Hb level and the change in peak VO₂. In addition, in those patients who initially had had excessive plasma volume, correction of the anaemia reduced the plasma volume to normal.

**Why does CHF damage the kidneys?**

In several studies of CHF, about half the patients have CKI defined as a serum creatinine of 1.5 mg% or higher [5,6,9,17,18]. The reduced renal blood flow in CHF activates angiotensin, aldosterone and the sympathetic activity. All these factors cause progressive renal ischaemia as well as toxic effects on the renal tissue [32,33]. All these hormones as well as other factors also activated by ischaemia can cause damage to the glomerulus, the mesangium, the tubular cells and the interstitial cells, with progressive renal fibrosis [32,33].

**Why would renal failure worsen CHF?**

The heart can be damaged in many ways in renal failure. There is a high prevalence of atherosclerotic lesions in uraemic patients as well as a high frequency of coronary lesions and events. This has been documented by retrospective and prospective clinical observations and has been confirmed in animal models [34]. Heavily calcified plaques are found much more often in uraemic patients than in controls, and atherosclerotic plaques grow faster in an uraemic environment. This process occurs early in renal disease. It has been suggested that there is also excessive angiogenesis in the adventitial layer of the coronary arteries leading to intramural haematoma formation and rupture of the fibrous cap [34].

**What causes the vascular and cardiac damage in uraemia?**

In addition to the classical risk factors seen in renal failure—hypertension, dyslipidaemia, diabetes and increased insulin resistance, obesity and smoking—other risk factors also play a role in the vascular and cardiac damage of uraemia [34–38]. These include: anaemia, hypervolaemia, malnutrition, elevated nocturnal blood pressure, high sympathetic activity and high blood levels of noradrenaline, renin, angiotensin and aldosterone, inflammation, elevated C-reactive protein, reduced fibrinolysis, low high-density lipoprotein (HDL), increased serum Lp(a), elevated \( \beta_2 \)-microglobulin, hyperphosphataemia, calcium, elevated calcium phosphate product, parathyroid hormone, vitamin D, homocysteine, advanced glycation end-products (AGEs), oxidative stress and advanced oxygen protein products, cytokines, including tumour necrosis factor (TNF), interleukin-6 and asymmetric dimethyl arginine (ADMA), with loss of nitric oxide-mediated endothelial cell vasodilatation leading to endothelial cell dysfunction.

**Ischaemic tolerance of the heart**

As a result of all the factors listed above, the heart in uraemia has an abnormal reaction to ischaemia [34,39]. This explains the devastating coronary prognosis of uraemic patients when they develop a myocardial infarction [40]. Coronary ligation causes greater infarct areas in uraemic rats compared with sham-operated control rats [34,39]. There are many cardiac abnormalities seen in the heart in CKI [34,39].

(i) Microvessel disease. It appears that the growth of capillaries in uraemia does not keep pace with the hypertrophy of the cardiomyocytes. This mismatch between cardiomyocytes and capillaries increases the distance through which oxygen must diffuse from the capillary lumen to the interior of the myocyte.

(ii) Failure of vasodilatation of the coronary arteries due to endothelial dysfunction.

(iii) Studies of the metabolism of the heart in uraemia have shown a decay of energy-rich nucleotides, especially ATP. There is thus a reduction in energy stores coupled with an increased energy demand.

(iv) Increased sympathetic activity. Chemoreceptors and baroreceptors in the damaged kidney are activated, sending signals to the hypothalamus causing sympathetic efferent traffic and increased sympathetic tone. Besides increasing heart rate and cardiac contraction, this predisposes to the development of arrhythmias. Excessive sympathetic activity will lead to pump failure. Compared with sham-operated rats, the hearts of rats subjected to subtotal nephrectomy contain fewer myocytes in the left ventricle. In other words, there is cardiocyte drop-out in the uraemic animals even in the absence of ischaemia. This is probably due primarily to excessive apoptosis.

(v) In uraemia, there are numerous abnormalities of cardiomyocyte function, including abnormal cardiomyocyte calcium cycling and contractile function.
The vicious circle of CHF, CKI and anaemia—the cardio renal anaemia (CRA) syndrome

A vicious circle therefore appears to be present in CHF, where CHF itself causes both anaemia and CKI. The CKI causes more anaemia, and the anaemia and CKI act back to further worsen the CHF, which then further worsens the anaemia and CKI, and so on. In other words, each condition can cause or be caused by the other. We suggested calling this relationship the cardio renal anaemia (CRA) syndrome [5].

\[ \text{heart failure} \]
\[ \uparrow \uparrow \]
\[ \text{anaemia} \leftrightarrow \text{renal failure} \]

The importance of this concept is that if the anaemia is not treated in CHF patients, there will probably be resistance to any other form of CHF therapy and there will be progression of both the CHF and the CKI. Thus, correction of anaemia may therefore be crucial in the prevention of the progression of both CHF and CKI. It also follows that the failing heart needs maximal protection with all the CHF medications in the recommended doses.

Attitude of cardiologists and internists to anaemia in CHF

In a preliminary report from the Cleveland Clinic [41], 2011 consecutive ambulatory patients with chronic stable heart failure seen in tertiary care cardiology or internal medicine clinics were studied. Anaemia was defined as a Hb \( \leq 12 \text{g}\% \) in men and \( \leq 11 \text{g}\% \) in women; 29% of the patients had or developed anaemia at some time. Yet anaemia was only recognized as a diagnosis in 11.1% of these cases by the internists and in 4.4% of the cases by cardiologists. Diagnostic evaluation was only performed in 6% of these patients and only 10% received medical therapy for the anaemia. The conclusion of the investigators was that anaemia in ambulatory patients with CHF is under-recognized, under-diagnosed and under-treated by cardiologists and internists.

The challenge of interdisciplinary cooperation

This lack of awareness of the importance of anaemia in CHF among internists and cardiologists is a major challenge to the one group of physicians who are most experienced in anaemia correction in patients with CKI and CHF, i.e. nephrologists. Another advantage that will be accrued to nephrologists by cooperation with them will be that CHF itself may be better treated. Cardiologists are much more likely to find reversible causes of CHF and are more likely to treat CHF aggressively with proven \( \beta \) blockers (carvedilol, metoprolol and bisoprolol) and other CHF agents in the correct doses than other specialties. As suggested above, the aggressive treatment of the CHF including correction of the anaemia may cause a slowing or arrest of the progression of both CHF and CKI. Randomized double-blind, placebo-controlled studies of EPO in CHF are now in progress which will further clarify the role of anaemia and its correction in CHF.

Conflict of interest statement. None declared.

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