Outcomes of anaemia management in renal insufficiency and cardiac disease

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Abstract
Cardiac disease represents a major cause of morbidity and mortality in dialysis patients, and is also a well-established feature of chronic kidney disease (CKD). Anaemia has also been shown to be a key component not only of dialysis and CKD but also of cardiac disease, including congestive heart failure (CHF). Furthermore, published clinical and laboratory data suggest that anaemia, CHF and CKD are interrelated, each causing the other to worsen and thus resulting in a 'vicious cycle' of disease progression which we have called the Cardio-Renal Anaemia syndrome. In this syndrome anaemia may cause CKD or be caused by CKD, anaemia may cause CHF or be caused by CHF and CHF may cause CKD or be caused by CKD. Numerous publications have borne out the fact that anaemia correction through epoetin treatment provides great benefit to CKD patients. Additionally, there is evidence to suggest that these benefits may be extended to patients with cardiac disease. Uncontrolled and controlled studies of the effect of subcutaneous epoetin treatment in anaemic patients with both CHF and CKD show significant improvements in both cardiac and renal function. Despite these findings, however, it is apparent that anaemia correction is not implemented rigorously within both CHF and CKD populations. Greater awareness of the need for early anaemia correction therapy is therefore required. Cooperation between nephrologists and others who are caring for CHF patients, especially cardiologists, is crucial.

Keywords: anaemia; cardiac disease; chronic kidney disease; congestive heart failure; education; epoetin; iron

Introduction
Cardiovascular disease accounts for almost half of all deaths in patients undergoing dialysis in the USA [1], and congestive heart failure (CHF), coronary artery disease (CAD) and left ventricular hypertrophy (LVH) are highly prevalent in patients with chronic kidney disease (CKD) [2]. Thus, cardiac disease represents a major concern in this patient group.

There is a wealth of clinical data demonstrating the positive benefits of anaemia correction in patients with renal disease, including improvements in cardiac function [3–5]. It has been found that impaired renal function and anaemia are common features in patients with CHF [6–8], and both have been identified as independent risk factors of mortality in CHF patients [7–9]. In addition, evidence is emerging to show that anaemia management produces positive outcomes in terms of cardiac and renal function in patients with severe CHF [6,10–12]. The three conditions (CHF, renal disease and anaemia) appear to be interconnected in a complex fashion, and this has been named the Cardio-Renal Anaemia syndrome (Figure 1a and b). This article discusses the data supporting the existence of a relationship between anaemia, cardiac disease and renal disease, and also outlines the proposed mechanisms by which these conditions interact.

Origins of anaemia in cardiac and renal disease
For some time, it has been recognized that an association between cardiac disease, CKD and anaemia may exist, but the underlying means by which anaemia exerts its effects remain unclear. Since the beginning of the 1990s, the mechanisms by which anaemia can induce cardiac and renal disease, and how they in turn can exacerbate anaemia, have gradually been elucidated (Figure 1a and b).

Using anaemia as the 'start point', associated hypoxia leads to peripheral vasodilation and decreased vascular
resistance, which in turn reduces blood pressure. To maintain blood pressure, peripheral vasoconstriction, heart rate and stroke volume are all increased through elevated sympathetic activity. However, increased sympathetic activity also causes renal vasoconstriction and a resulting reduction in renal blood flow and glomerular filtration rate (GFR) leading to renal ischaemia. The reduced renal blood flow is further aggravated by activation of the renin–angiotensin aldosterone system, coupled with release of antidiuretic hormone. All of this leads to fluid retention [13]. Excessive fluid retention causes the plasma volume to increase dramatically, which in turn causes LV dilatation and further increases the stress on an already stressed heart. LVH follows and leads to necrosis and apoptosis of myocardial cells, resulting in CHF. Furthermore, elevated levels of renin, angiotensin and aldosterone can destroy cardiac cells directly, exacerbating the damage already caused [14,15]. The levels of tumour-necrosis factor α (TNFα) are increased in CHF, and there is evidence that cardiac cells produce this cytokine in response to injury, which damages the heart further [16]. This increased production of cytokines such as TNFα has also been implicated in the development of the

Fig. 1. (a) The mechanism by which anaemia causes heart failure and renal failure. (b) The Cardio-Renal Anaemia syndrome.
anaemia of chronic disease [17], and may also worsen the anaemia in CKD and CHF patients, thus completing a ‘vicious cycle’ of disease progression (Figure 1a and b).

Supportive evidence for a link between CHF and anaemia was recently published by Iversen and colleagues [18]. In this study, the haematopoietic activity of the bone marrow was shown to be markedly depressed in mice in which CHF had been induced. There was a marked reduction in the proliferative capacity of the precursor red cells in the bone marrow and increased apoptosis of these cells, which may have resulted from an increase in TNFα expression. These results may help to explain why CHF patients are predisposed to anaemia.

**Anaemia, cardiac and renal disease—evidence for association**

Several major studies have emphasized the association between cardiac disease, renal disease and anaemia. Clinical support for a link between cardiac and renal disease comes from a study by Foley et al. [19], where an assessment of 433 patients at the start of end-stage renal disease (ESRD) therapy showed that 31% had CHF, 19% had angina and 14% had CAD. Furthermore, echocardiography also revealed the presence of LVH in 74% of patients. In another study of patients already receiving dialysis, a 1 g/dl fall in haemoglobin (Hb) levels increased the risk of LV dilatation by 42%, either de novo or recurrent heart failure by 18% and death by 14% [20]. Similarly, in renal transplant patients, multivariate analysis revealed that a 1 g/dl decrease in Hb was associated with a 24% increase in the risk of CHF [21].

As well as being a common feature of CKD, anaemia is also present in many patients with CHF. In a retrospective analysis of 142 ambulatory CHF patients attending our special CHF clinic, 55.6% were anaemic (Hb <12 g/dl), and more severe degrees of CHF [according to New York Health Association (NYHA) class] were associated with both lower Hb levels and higher creatinine levels [6]. In NYHA class IV patients (the most severely affected), 79.1% had Hb levels of <12 g/dl, compared with only 9.1% with the least severe CHF (NYHA class I). Similar associations between anaemia and severity of CHF have been reported by Wisniacki et al. [22]. In their study of hospitalized patients, using the same criteria for anaemia, 49.8% of all patients were anaemic, including 65.9% of patients in NYHA class IV. No patients in class I, however, had Hb levels of <12 g/dl. A similar prevalence of anaemia (46.8%) in hospitalized CHF patients was found by McClellan et al. [8].

Several studies have demonstrated that anaemia is associated with poor outcomes in patients with cardiac and renal disease. The Study Of Left Ventricular Dysfunction (SOLVD), involving 6563 patients with LV dysfunction with or without CHF, has demonstrated that survival rates are highest in patients with a haematocrit level of 40% or greater, with progressively poorer rates of survival in patients with lower haematocrit [9]. Low Hb was also shown to be an independent predictor of mortality in a study of 1061 ambulatory patients with advanced CHF [7] and in 665 hospitalized patients with CHF [8]. The Outcomes of the Prospective Trial of Intravenous Milrinone for Exacerbations (OPTIME) study, involving 949 patients hospitalized with CHF, demonstrated a 13% increase in risk of death or rehospitalization for every 1 g/dl fall in Hb level [23].

A comprehensive study of over 1 million US Medicare recipients aged 65 years or over has further emphasized the complex interaction of cardiac disease, renal disease and anaemia, and the impact of these conditions on patient outcomes [24]. In this study, 26.1% of patients with CHF but with no anaemia died over a 2-year period compared with 34.6% of CHF patients with anaemia. A similar pattern was observed in patients with CKD—16.4% of patients with CKD and no anaemia died over the same period compared with 27.3% of patients with CKD and anaemia. In patients with both CKD and CHF, the corresponding death rates were even higher, at 38.4 and 45.6% for non-anaemic and anaemic patients, respectively. The study also demonstrated the influence of anaemia and cardiac disease on progression of renal disease as well as on mortality. The number of CKD patients progressing to ESRD within 2 years was lower in non-anaemic subjects than in those with anaemia, 2.6 compared with 5.4% respectively (3.5 and 5.9% for patients with both CKD and CHF).

Several studies by Levin and colleagues have also demonstrated how anaemia, renal disease and cardiac disease can influence one another’s progression. Levin et al. [25] have shown that patients with cardiac disease had a 50% greater probability of needing renal replacement therapy (RRT) than patients without cardiac disease. Lower Hb concentrations have also been shown to be associated with an increased risk of progression to RRT [26]. A further study by this group has shown that cardiovascular risk appears to correlate with the extent of reduced Hb levels in CKD patients, with a 0.5 g/dl fall in Hb level increasing the risk of LV growth by 32% [27].

In summary, anaemia occurs frequently in CKD, with serious consequences for patients, as highlighted elsewhere in this supplement [28]. Recent evidence suggests that cardiac disease is also common in CKD, and that anaemia is prevalent in cardiac disease. The clinical association between cardiac disease, CKD and anaemia is supported by a mechanism of interaction, whereby the presence of anaemia influences the course of CKD and cardiac disease, whereas these two disease states also contribute to anaemia. This completes the ‘vicious cycle’ (Figure 1b), where both CKD and cardiac disease progress in severity unless managed appropriately. Adequate management of anaemia is one of the most direct methods of breaking the cycle, and is of utmost importance in both cardiac and renal disease patients.
Outcomes of anaemia treatment

Recombinant human erythropoietin (rh-EPO, epoetin) has been widely used in the correction of anaemia in CKD for some time, and its benefits are well established in this patient population [28]. There is also evidence to suggest that these benefits may be extended to patients with cardiac disease.

In our own studies, we have examined the effect of anaemia correction on cardiac and renal function in patients with established CHF. In an uncontrolled study, 26 anaemic patients with severe CHF (despite maximally tolerated CHF medication) and progressive loss of renal function were given subcutaneous (s.c.) epoetin and intravenous (i.v.) iron treatment (iron sucrose, Venofer) [6]. Achieving and maintaining Hb levels of >12 g/dl for an average of 7.2 ± 5.5 months produced improvements in cardiac and renal function in these patients (Table 1). In association with significant increases in Hb levels and ferritin saturation, mean NYHA class was reduced by 27%, and the significant increases in Hb levels and ferritin saturation, in these patients (Table 1). In association with significant increases in Hb levels and ferritin saturation, mean NYHA class was reduced by 27%, and the mean number of hospitalizations fell by 92%. In addition, creatinine clearance improved at a rate of 0.9 ml/min/month during epoetin treatment, compared with a fall at a rate of 1.0 ml/min/month before anaemia correction. The requirement for oral and i.v. diuretics (furosemide) was also significantly reduced.

These findings prompted a randomized controlled study in 32 patients with moderate/severe, treatment-refractory CHF [11]. Sixteen patients received s.c. epoetin i.v. iron to achieve and maintain Hb levels of at least 12.5 g/dl for an average of 8 months, whereas the remaining 16 patients did not receive epoetin or iron. No CHF-related deaths were reported in the treatment group, whereas four occurred in the control group. As expected, Hb levels increased in the epoetin/iron-treated group (from 10.3 to 12.9 g/dl), but were unchanged in the control group (10.9 to 10.8 g/dl). In addition, at the end of the study, LVEF, NYHA class and the number of hospitalization days were all significantly improved in the epoetin/iron group compared with both baseline and the control group (Figure 2). Conversely, all of these parameters were significantly worse in the control group at the end of the study compared with baseline.

The need for education and communication in anaemia treatment

Despite the benefits of anaemia correction in cardiac and renal disease, there is evidence that anaemia in these patients is under-recognized and under-treated. As many as 44% of patients entering dialysis already have CHF [29]. Unfortunately many patients do not receive epoetin treatment before entering dialysis [30].

There appears to be a need for improved education amongst the healthcare community concerning the importance of early anaemia treatment. From our own experience, there has been an 8-fold increase in referrals to our nephrology department from internal medicine and cardiac units following individual discussions with cardiologists and publication of the benefits of anaemia management in CHF patients. The range of patients now seen includes those with milder degrees of anaemia, CHF and CKD. Hb levels now range from 9 to 11 g/dl where previously they had been 6–8 g/dl.

### Table 1. Clinical trial of anaemia correction: parameter changes in patients with severe CHF at start and end of epoetin/iron treatment [6]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Start</th>
<th>End</th>
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<tr>
<td>Hb (g/dl)</td>
<td>10.16 ± 0.95</td>
<td>12.10 ± 1.21a</td>
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<tr>
<td>LVEF (%)</td>
<td>27.7 ± 4.8</td>
<td>35.4 ± 7.6a</td>
</tr>
<tr>
<td>NYHA class (0–IV)</td>
<td>3.66 ± 0.47</td>
<td>2.66 ± 0.7a</td>
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<tr>
<td>No. of hospitalizations per patient</td>
<td>2.72 ± 1.21</td>
<td>0.22 ± 0.65a</td>
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<tr>
<td>Oral furosemide (mg/day)</td>
<td>200 ± 120.4</td>
<td>78.3 ± 41.3a</td>
</tr>
<tr>
<td>Intravenous furosemide (mg/month)</td>
<td>164.7 ± 178.9</td>
<td>19.8 ± 47.0a</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.59 ± 0.77</td>
<td>2.73 ± 1.55</td>
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<tr>
<td>Change in estimated creatinine clearance (ml/min/month)</td>
<td>−0.95 ± 1.31</td>
<td>0.85 ± 2.77</td>
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*P < 0.05 study start versus end, paired Student’s t test.

*Before the onset of treatment and during the treatment period.
and serum creatinine levels now range from 2 to 3 mg/dl where previously they had been 5–8 mg/dl.

Conclusions

From the findings presented, there is considerable evidence of an association between anaemia, CHF and renal disease [dubbed the Cardio-Renal Anaemia syndrome (Figure 1b)]. In this concept anaemia can cause CKD and vice versa, anaemia can cause CHF and vice versa and CHF can cause CKD and vice versa. Clinical findings suggest that anaemia is common in cardiac and renal disease, contributing to increased mortality and morbidity. Furthermore, both cardiac and renal diseases are now believed to worsen anaemia, thus contributing to the ‘vicious cycle’ of disease progression.

Recent studies have confirmed that anaemia correction in patients with cardiac and renal disease may improve both cardiac and renal functions, slow disease progression and improve patient quality of life. Despite the proven benefits of anaemia management in these disease conditions, however, early recognition and treatment of anaemia in patients remains suboptimal. Greater physician and patient awareness of these benefits is needed if the current trend of increasing prevalence of renal disease is to be reversed.

References

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