The cardio–renal anaemia syndrome: does it exist?

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Abstract

Many patients in our nephrology department who have anaemia and chronic kidney insufficiency (CKI) show evidence of congestive heart failure (CHF). This triad of anaemia, CKI and CHF is known as the cardio–renal anaemia syndrome. The three conditions form a vicious circle, in which each condition is capable of causing or being caused by another. Anaemia can increase the severity of CHF and is associated with a rise in mortality, hospitalization and malnutrition. Anaemia can also further worsen renal function and cause a more rapid progression to dialysis than is found in patients without anaemia. Uncontrolled CHF can cause rapid deterioration of renal function and anaemia. CKI can also cause anaemia, as well as worsen the severity of CHF, and is associated with increased mortality and hospitalization in patients with CHF. Aggressive therapy against CHF with all the conventional medications at the accepted doses often fails to improve the CHF if anaemia is also present but is not treated. In studies in which the anaemia was corrected with s.c. erythropoietin and, in some cases, with i.v. iron, however, the cardiac function improved, as assessed by measurement of the left ventricular ejection fraction and oxygen utilization during maximal exercise. Symptomatic patient functioning improved, as monitored by shortness of breath and fatigue on exertion, and the need for hospitalization and oral and i.v. diuretics markedly decreased. The quality of life, as judged by different criteria, also improved. The glomerular filtration rate, which fell rapidly when the anaemia was untreated, stabilized in patients when their anaemia was treated. Nephrologists need to assess the cardiac status of all patients with CKI carefully, and this includes an echocardiogram along with possibly measuring the levels of B-type natriuretic peptide. Nephrologists also need to use the indicated agents for CHF at the recommended doses, while cardiologists and internists need to be more aware of the importance and lethal effects of even mild anaemia and the benefits of its treatment in CHF and CKI. Cooperation between these specialists will allow better and much earlier treatment of the anaemia, CHF and CKI, and prevent the deterioration of all three conditions.

Keywords: anaemia; cardio–renal anaemia syndrome; chronic kidney insufficiency; congestive heart failure; erythropoietin; i.v. iron

The cardio–renal anaemia syndrome

No one will argue that conditions such as diabetes mellitus, hypertension and glomerulonephritis are important and common contributors to progressive chronic kidney insufficiency (CKI) and end-stage renal disease (ESRD). Yet, in addition to their direct effect on the kidneys, these conditions can all cause renal damage in other ways: (i) by causing ischaemic, metabolic and hypertensive cardiac damage they may lead to congestive heart failure (CHF), which could then itself cause or worsen CKI; (ii) through causing anaemia they can further worsen the CHF and CKI.

We propose that CHF and anaemia are themselves major contributors to the deterioration of renal function and that CHF, CKI and anaemia form a vicious circle (Figure 1). We have termed this the cardio–renal anaemia (CRA) syndrome [1]. The interaction between these three conditions causes deterioration of the cardiac function, the renal function and the anaemia. In this circle, CHF can cause CKI and anaemia, CKI can cause CHF and anaemia and anaemia can cause CHF and CKI. Approximately 80% of patients referred to our nephrology department with CKI and anaemia also have CHF, i.e. the CRA syndrome [1–4]. Around 50% have diabetes mellitus, 50% have hypertension and 50% have hypercholesterolaemia [1–4]. In around 70% of patients with CHF, coronary artery disease is the major cause of CHF. Approximately 15% of CHF cases result from long-standing hypertension, ~10% is caused by cardiac valve damage.
and \(\sim\) 5% arises from other causes, such as idiopathic hypertrophic cardiomyopathy [1–4]. The possibility that early and optimal therapy of CHF and anaemia could prevent the progression of both the CHF and the CKI is tantalizing. Yet, there is growing evidence that this is indeed the case.

### The effect of the CRA syndrome on mortality and ESRD

The importance of the interaction between CHF, CKI and anaemia was suggested by a recent study conducted in \sim\) 1.1 million elderly patients, a 5% sample of the Medicare population in the USA [5]. The 2-year risk of dying or starting dialysis is shown in Table 1. Individually, each of these three conditions increases the risk of death or ESRD by 50–100\%, and the three together increase the probability by up to 300\%. This interaction is consistent with the presence of the vicious circle — the CRA syndrome.

In a recently performed study on 129 consecutive patients with CHF, we measured the levels of B-type natriuretic peptide (BNP), which is considered to be one of the most accurate tests for measuring the severity of CHF [6]. We found that the left ventricular ejection fraction (LVEF), serum creatinine and haemoglobin (Hb) were all independent predictors of the BNP levels, which again strengthened the concept of the additive effect of these three conditions (Silverberg et al., submitted).

### The frequency of CKI in CHF and its significance

In a study comprising 142 patients with CHF from our CHF out-patient clinic [3], 58 patients (40.8\%) had CKI as defined by a serum creatinine concentration of \(\geq\) 1.5 mg%. We also noted that the serum creatinine concentration rose steadily as the CHF became more severe. The high prevalence of CKI in patients with CHF and the increase in its prevalence and severity with the rise in severity of CHF have also been noted by other researchers [7,8]. CKI has also been found to be an independent risk factor for mortality in CHF [7,8]. Uraemia may give rise to cardiac fibrosis and structural alterations of the intramyocardial microcirculation, including a reduction in the number of myocardial capillaries [9]. Uraemia may also increase renal arteriosclerosis and atherosclerosis [9]. All of these changes could result from a combination of volume overload, hypertension, dyslipidaemia, inflammation, hyperhomocysteinaemia, oxidative stress and other factors [10].

### CHF in the development of CKI, and prevention of CKI with aggressive CHF treatment

CHF can be an important contributor to the onset of CKI as suggested by a study of 11 192 patients with essential hypertension followed over 15 years [11]. The strongest predictive risk factor for acquiring ESRD was the presence of CHF. Another recent study showed that patients with CKI and cardiovascular disease (CVD) progress to ESRD at a more rapid rate than those without CVD [12]. It is known that the glomerular filtration rate (GFR) falls at a rate of \sim\) 1 ml/min/month in patients who develop CHF after a myocardial infarction [13]. We found a similar rate of fall in GFR in patients with uncontrolled CHF [1–3]. Studies have shown that it may be possible to prevent this deterioration of renal function in patients with CHF using a combination of \(\beta\)-blockers and angiotensin-converting enzyme (ACE) inhibitors [14], suggesting that good treatment of CHF can help to stabilize CKI. Thus, it appears that CHF alone can be an important cause of progressive CKI.

### The prevalence of anaemia in CHF and its relationship to the severity of CHF

Many of the 142 patients followed in our out-patient CHF clinic failed to respond to therapy and suffered...
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from severe CHF with frequent hospitalizations, despite being seen frequently by specialists and treated with the maximally tolerated doses of all CHF medications [3]. One characteristic that was common to the great majority of these severely resistant CHF patients was that they had anaemia (an Hb level of <12 g%). Anaemia was present in 55.6% of all patients with CHF. The prevalence of anaemia in CHF varies widely in the literature and ranges from 10–25% in some studies [15–19] to 40–60% in others [20–22,24]. The differences in prevalence in the various studies probably result from the different definitions of anaemia used and the different composition of the populations studied. For example, prevalence rates of anaemia have been higher in older than younger patients, higher in hospitalized patients than in those seen in out-patient departments, and higher in patients with more severe CHF and CKI [15–25].

In our study of anaemia in CHF, anaemia was more prevalent and more severe as the severity of the CHF increased [3]. Of patients with mild CHF (New York Heart Association — NYHA I), 9.1% were anaemic and the mean level of Hb in this group was 13.7 g%, whereas in severe CHF (NYHA IV), 79.1% of patients were anaemic and the mean level of Hb had fallen to 10.9 g%. This inverse relationship between the severity of CHF and Hb level has also been reported by other researchers [15,17,19,20,23–25].

The role of anaemia in mortality and hospitalization in CHF

Many studies have now been published of CHF in which the association of anaemia and mortality in CHF was evaluated [15,17–19,21–25]. All but one [17] of these studies showed that as the level of Hb lowered, patient mortality increased. In some studies, this association was found to be independent of other confounding factors such as CKI [21,23], and, indeed, CKI and anaemia were additive in increasing the risk of death [21,23]. Hospitalization and re-hospitalization occurred extremely frequently in patients with severe CHF, and anaemia was also found to be a risk factor for hospitalization [15,22,26].

Can treatment of anaemia in CKI prevent CHF?

Regular treatment for CKI with erythropoietin (EPO) in the pre-dialysis period in patients who eventually required haemodialysis significantly reduced the incidence of hospitalization for CHF in the pre-dialysis and dialysis periods compared with patients who received EPO sporadically or not at all [27]. Thus, it appears that the treatment of anaemia in patients with CKI helps to prevent CHF.

The association between anaemia and the progression of CKI

The prolonged renal vasoconstriction caused by both anaemia and CHF, and the direct toxic effects of angiotensin, aldosterone and noradrenaline on renal tissue can cause renal ischaemia, renal cell destruction and renal fibrosis [28]. Several recent studies have shown that anaemia is an independent risk factor for progression to ESRD [29,30].

Can treatment of anaemia in patients with CHF and CKI improve both conditions? Results of uncontrolled and controlled studies of EPO and i.v. iron in resistant CHF

We selected 26 patients from our CHF out-patient department who had not responded to maximally tolerated doses of CHF therapy [including high doses of β-blockers (mainly carvedilol), ACE inhibitors, spironolactone, digoxin, nitrates and high doses of oral and i.v. furosemide] and who had a Hb level of <12 g/dl [3]. With a regimen of s.c. EPO and i.v. iron, we treated the patients for a mean of 7.2 ± 5.5 months. We maintained normal iron stores with i.v. iron [iron sucrose (Venofer®)] [1–4]. This agent has been shown to increase the levels of Hb to a value higher than that achieved with EPO alone, thus allowing lower doses of EPO to be used, and therefore reducing the cost of treatment [31–33]. In addition, Venofer® has very few side effects.

The levels of Hb increased from a mean of 10.2 ± 1.0 to 12.1 ± 1.2 g/dl, the NYHA class improved from 3.7 ± 0.5 to 2.7 ± 0.7, and the LVEF improved from 27.7 ± 4.8 to 35.4 ± 7.6%. There was a marked reduction in hospitalizations (91.9%) compared with the same period before the intervention, and there was a marked decrease in the need for oral and i.v. furosemide. The calculated mean creatinine clearance, which had been falling at a rate of ~1 ml/min/month before the correction of the anaemia, stabilized when the anaemia was treated. We then performed a randomized, but not double-blind, study of the correction of anaemia in 32 similar patients, 16 of whom received the EPO + i.v. iron combination and 16 of whom did not [4]. Over a mean of 8.2 ± 2.6 months, four patients died in the control group, all from progressive CHF. In the treated group, however, no patient died. The NYHA class and LVEF improved and the number of days of hospitalization, and doses of oral and i.v. furosemide administered, all fell in the treated group. On the other hand, all these parameters worsened in the control group. The serum creatinine concentrations did not change in the treated group, but increased in the control group. We subsequently broadened our experience to 179 patients [2] and obtained similar results. We also added a Visual Analogue Scale where patients marked on a 10 cm scale their level of fatigue and shortness of breath at the...
beginning of the EPO + i.v. iron treatment and after they had reached the target Hb level of 13–14 g/dl. A score of 10 indicated the worst they could possibly feel and 0 was the best. The patients went from a mean score of 8.9 ± 1.4 to 2.7 ± 1.9 cm. In a condition such as severe resistant CHF, in which these parameters generally worsen markedly with time [34], such an improvement is striking.

In a recent, randomized, placebo-controlled study of EPO use in patients with severe CHF, EPO was found to improve peak oxygen consumption during exercise (one of the most sensitive tests of cardiac function) [35]. Exercise duration and quality of life also improved. In those patients who had an increased plasma volume, correction of the anaemia was associated with a decrease in plasma volume of ~50%.

The role of anaemia in CHF

There are many ways in which anaemia can cause CHF and CKI.

Direct cardiac hypoxia

The lack of oxygen supply to the heart in the face of increased heart rate and stroke volume (increased cardiac work) may cause ischaemia and lead to myocardial cell death.

Increased oxidative stress

Erythrocytes contain many antioxidants and anaemia is, therefore not surprisingly, associated with an increase in oxidative stress [36,37], which can cause damage to the myocardial cells. Treatment of anaemia with EPO may reduce the oxidative stress [36–38] and there is even some in vitro evidence that EPO itself may reduce oxidative stress by a direct effect on cells unrelated to the effect on anaemia [38].

Increased fluid retention, sympathetic activity and renin—angiotensin and aldosterone activity

Anaemia causes tissue ischaemia throughout the body, which causes peripheral vasodilatation and a lowering of blood pressure [39]. The sympathetic system is activated and, in addition to causing tachycardia and increased stroke volume, this causes renal vasoconstriction, which can lead to salt and water retention. The reduced renal blood flow activates the renin–angiotensin–aldosterone system (RAAS) and antidiuretic hormone, causing further renal vasoconstriction, and salt and water retention. This leads to peripheral oedema and increased plasma volume. The increased plasma volume causes ventricular dilatation, which places further stress on the already strained heart. Under the influence of the RAAS and the increased sympathetic activity, left ventricular hypertrophy (LVH) eventually occurs, which can result in myocardial cell death from necrosis and apoptosis [40,41]. This can lead to, or worsen, CHF.

Direct effect of EPO on the heart

EPO itself also has a direct effect both on the development of cardiac muscle [42] and on the degree of cardiac contractility [43,44]. Therefore, the lack of EPO could possibly worsen cardiac function further.

The role of CHF in causing anaemia

There are many possible causes for anaemia in CHF.

Renal failure

Anaemia in CHF probably and mainly results from the CKI produced by the prolonged renal vasoconstriction caused by the CHF. This leads to prolonged renal ischaemia, which can cause renal damage [28] and reduced production of EPO in the kidneys. As discussed previously, however, many anaemic CHF patients have a normal serum creatinine level, so it is unlikely that CKI is the entire explanation for the anaemia seen in CHF.

Cytokines

Studies in animals have shown that CHF may cause anaemia [45]. When the heart is damaged, it can secrete cytokines such as tumour necrosis factor-α [45,46], which can cause anaemia in three ways [47]: by reducing EPO production in the kidneys, by interfering with EPO activity in the bone marrow, and by inhibiting the release of iron from the reticulo–endothelial system so that iron cannot reach the bone marrow and be utilized in Hb production. Thus, CHF can be listed along with other inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease as a cause of ‘the anaemia of chronic disease’.

ACE inhibitors

ACE inhibitors are standard therapy in the treatment of CHF and may, themselves, cause anaemia [48].

Aspirin

Many patients with CHF take aspirin, which may cause blood loss in the gut.

Proteinuria

Patients with CHF often have proteinuria, and EPO, iron and transferrin can be lost in significant amounts
Malnutrition

Patients with severe CHF often lose appetite and, consequently, show signs of malnutrition such as weight loss, anaemia and hypoalbuminaemia [19]. The converse may also be true, namely that anaemia itself could cause lack of appetite and malnutrition.

Haemodilution

The anaemia may also be related to the increase in plasma volume in CHF, which causes haemodilution, but in the majority of cases, the anaemia is also caused by a reduction in erythrocyte volume [24].

The importance of early detection and treatment of CHF and anaemia

If CHF is an important factor in the progression of CKI and anaemia, it would mean that early detection and treatment of cardiac damage and CHF would not only cause an improvement in cardiac function and CHF, but would also improve the anaemia and CKI. It also means that treating CHF without treating the associated anaemia will not stop the progression of CHF or CKI. This, indeed, has been our experience. Similarly, treating the anaemia without providing optimal medical therapy for CHF would also not be effective.

Optimal medical therapy for CHF includes: the use of the specific β-blockers that have been proven to be effective in CHF — carvedilol, metoprolol or bisoprolol; ACE inhibitors and/or ARBs; and where possible, spironolactone [50,51].

Optimal therapy for CHF would also require an accurate assessment of cardiac function, including a routine echocardiogram, as many patients with CKI would show evidence of cardiac abnormalities, such as LVH and dilatation, systolic and/or diastolic dysfunction or valvular disease, even if they do not have apparent signs of CHF. In light of the high mortality and morbidity in both CHF and CKI, these changes require treatment with the cardioprotective agents discussed above. Measurement of serum levels of BNP may also be very helpful in diagnosing or excluding CHF [6].

Cooperation between cardiologists, internists, family physicians and nephrologists

In our nephrology department, ~50% of referrals of patients with anaemia and CKI are from cardiologists. This is in sharp contrast to a study investigating referrals for CKI into nephrology departments in 21 countries, in which only 3% of referrals were from cardiologists [52]. The percentage of referrals to our department is much higher because we have held many joint sessions with cardiologists on the role of anaemia in CHF and the cardiologists saw for themselves the profound improvement in health in their previously extremely resistant CHF patients once the associated anaemia was treated. We have held similar sessions with other hospital internists who treat hospitalized patients with CHF, and their awareness of the importance of anaemia in CHF has also led to a marked increase in referrals of these patients with CRA syndrome. One very noticeable advantage of this cooperation, in our experience, is that patients with CHF are now being referred to our nephrology department much earlier for treatment of anaemia, when the patient’s level of Hb is 11–12 g/dl, and not at 8 g/dl as was the case previously, and when their serum creatinine levels are ~1.5 mg% and not 4 mg%. In our experience, the gratifying results of correcting the anaemia, in particular the patients’ often striking improvement in quality of life, fatigue, shortness of breath and need for hospitalization, as well as the stabilization or improvement in renal function, have proved to be a source of satisfaction, not only to the patients but to all the physicians who treat them.

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