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Erythropoietin should be part of congestive heart failure management

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Background. Up to 64% of patients referred to nephrologists with chronic kidney insufficiency (CKI) have evidence of congestive heart failure (CHF), and most of these patients are also anemic. We have called this triad of anemia, CKI, and CHF the cardio renal anemia (CRA) syndrome. The 3 components of this syndrome form a vicious circle, with each one capable of causing or worsening the other 2. Anemia is found in one-third to one-half of CHF patients and can either cause or worsen the CHF, and can increase the mortality, hospitalization, and malnutrition in this condition. Anemia is also associated with a worsening of renal function in CHF and CKI, causing a more rapid progression to dialysis than is found in those without anemia. Uncontrolled CHF can cause rapid deterioration of renal function and may also cause anemia. Chronic kidney insufficiency can cause anemia and worsen the CHF.

Methods. Aggressive therapy of CHF with all the accepted CHF medications in the accepted doses will often fail to improve the CHF if anemia is also present but is not corrected. However, when the anemia was corrected with subcutaneous erythropoietin and, in some cases, with intravenous iron, the cardiac and patient function and quality of life improved, the need for hospitalization and for high-dose oral and intravenous diuretics was strikingly reduced, and renal function, which had previously been deteriorating, stabilized.

Results. Nephrologists should carefully assess the cardiac status of all CKI patients, including routinely getting an echocardiogram and possibly measuring B-type natriuretic peptide. Where CHF is present, the indicated CHF agents in the indicated doses should be used.

Conclusion. Studies show that most cardiologists and internists do not recognize, investigate, or treat the anemia frequently seen in their CHF patients. In our experience cooperation between nephrologists and these specialists has increased their awareness about anemia, resulting in its earlier correction, and thus preventing the deterioration of the CHF, the CKI, and the anemia itself.

Despite the fact that there have been many advances in the therapy of congestive heart failure (CHF), a recent Framingham Study showed that the age-corrected life expectancy for males has hardly changed in 50 years, having fallen from 30% in 1950 to only 28% in 1999 [1]. Part of this unfortunate state may be due to the striking underutilization of medications proven to be useful in CHF, especially beta blockers and angiotensin-converting enzyme (ACE) inhibitors. In a recent large study of treatment of CHF in the community it was found that only 20% of cases were receiving both medications [2]. But there may be other reasons for the persistent high mortality. One may be the high prevalence of untreated anemia in CHF. We propose that CHF and anemia form a vicious circle with chronic kidney insufficiency (CKI). We have called this triad the Cardio Renal Anemia (CRA) syndrome [3, 4] (Fig. 1).

We define anemia as a hemoglobin (Hb) of <12 g/dL, CKI as a creatinine clearance of <60 mL/min/1.73/m^2, and CHF as a condition diagnosed by accepted clinical, radiologic, and laboratory criteria.

In this vicious circle one can see that anemia can cause CHF, CHF can cause anemia, anemia can cause CKI, CKI can cause anemia, CHF can cause CKI, and CKI can cause CHF.

In the last few years we have found a large number of CHF patients with CKI who, despite treatment with maximally tolerated doses of all the recommended CHF medications, have not improved clinically [3–6]. The one thing they had in common was a Hb of <12 g/dL. When this was corrected with subcutaneous erythropoietin (EPO) and intravenous iron (Fe Sucrose; Venofer; Vifor International, St. Gallen, Switzerland) the CHF improved and the renal function stabilized or improved. We believe that this syndrome is a very common cause of progressive CHF and CKI and that, unless both the CHF and the anemia are adequately treated, all 3 will progress with time.

Is anemia recognized as a problem in CHF by specialists?

The role of anemia in CHF has generally been ignored by cardiologists. It is not mentioned at all in 2 recent

Key words: erythropoietin, iron, congestive heart failure, chronic renal insufficiency, anemia.

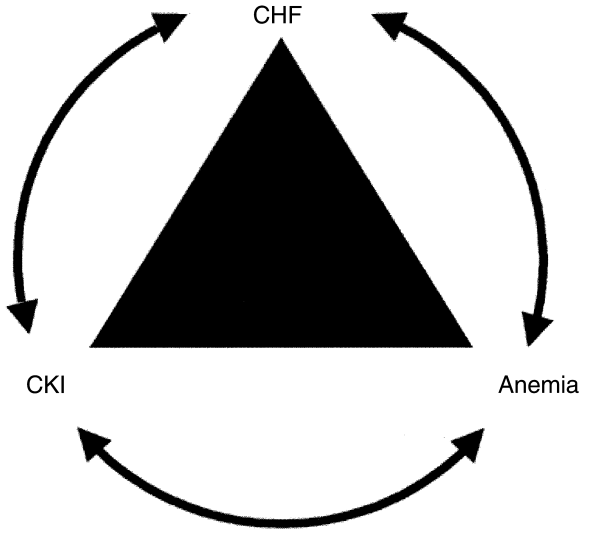

Fig. 1. The Cardio Renal Anemia Syndrome. CHF, congestive heart failure; CKI, chronic kidney insufficiency.

United States guidelines on the diagnosis and treatment of CHF [7, 8]. The attitude of physicians treating CHF patients to anemia (as defined as a Hb of ≤12 g/dL in men and ≤11 g/dL in females) has recently been studied in the United States [9]. Of 2011 consecutive patients with chronic stable heart failure seen at tertiary cardiology and internal medicine clinics, anemia appeared in 29% of cases during the follow-up period and, once it appeared, persisted in 93.4% of cases. When it was present, it was included among the patients' diagnoses, however, in only 11% of cases seen by internists and in only 4% of cases seen by cardiologists. A diagnostic evaluation was performed in only 6% of all these anemic CHF patients and only 10% received medical therapy for it. As stated by the investigators, anemia was under-recognized, under-diagnosed, and under-treated.

How common is anemia in CHF?

In the 142 cases of CHF we followed in our outpatient CHF clinic [5], we found that 55.6% of these ambulatory CHF patients were anemic, as defined by a hemoglobin (Hb) of less than 12 g/dL. In another study of 338 hospitalized patients with a primary diagnosis of CHF we found that the admission Hb was <12 g/dL in 52.4% [10]. As we recently summarized [11], while some investigators have reported a similar prevalence of anemia of about 40 to 60% [12–15], others have reported a prevalence of only about 15 to 30% [16–19]. In general one third to one half of CHF patients are anemic [11]. The reasons for the differences in prevalence in the various studies are probably the different definitions of anemia used, and the different nature of the populations studied. The prevalence rates of anemia have been higher in older than younger patients, higher in those hospitalized than in those seen in outpatient departments, and higher in those with more severe CHF and more severe CKI [11].

Anemia and the severity of CHF

We found that the worse the CHF, the more prevalent and severe the anemia, such that 9.1% of cases of mild CHF [New York Heart Association (NYHA) I] were anemic, the mean Hb of this group being 13.7 g/dL, while in contrast, in severe CHF, NYHA IV, 79.1% were anemic and the mean Hb had fallen to 10.9 g/dL [5].This inverse relationship between severity of CHF and Hb level has also been found by others [12, 17, 19, 20]. Indeed, in 13 studies in which this relationship was examined, it was confirmed in 12 of them [11].

Anemia and hospitalization for CHF

A relationship between severity of anemia and number of hospitalizations and rehospitalizations has been found in several studies [14, 21]. Of 5 studies that examined this, all of them showed this relationship [11]. This could be very important, since CHF is a very common cause of hospitalization in those aged 65 and older [22]. In addition, many of these are hospitalized again and again because of the CHF [22]. In fact, the major cost of the care of CHF patients is hospitalization costs [22]. A similar relationship between anemia and hospitalizations has been seen in chronic kidney insufficiency (CKI) [23, 24] and in patients on dialysis [25].

Anemia and mortality in CHF and coronary heart disease (CHD)

A relationship between severity of anemia and mortality has also been found in CHF [13–15, 18–20], that being the more severe the anemia, the greater the mortality. This relationship was found in 14 of 15 studies in which it was examined [11]. The anemia increased the mortality 50 to 100% independent of other factors [11]. The presence of CKI is additive and doubles the mortality [13, 20]. In patients with coronary heart disease (CHD), long-term studies have also found that anemia is associated with an increase in mortality of about 400% [26, 27] that is independent of renal function [27], although anemia and CKI have an additive effect on the mortality [27].

Is CKI common in CHF and what is its significance?

In our study of 142 cases of CHF mentioned above [5], 58 (40.8%) had CKI as defined as a serum creatinine ≥1.5 mg/dL. We also noted that the serum creatinine rose steadily as the CHF became more severe. The high prevalence of CKI in CHF, and the increase in its prevalence and severity with increasing severity of CHF have also been noted by others [28, 29]. Chronic kidney insufficiency has also been found to be an independent risk factor for mortality in CHF [28, 29]. The myocardium is

directly damaged in uremia [30]. There are probably many reasons for this, including anemia, hypertension, fluid retention, elevated homocysteine levels, hyperparathyroidism, and oxidative stress [30, 31].

Is anemia more common in CHF patients who also have CKI?

In a recent study of 338 patients hospitalized with CHF [10] we found that 161 (47.6%) had a serum creatinine >1.5 mg/dL, and 177 (52.4%) had a serum creatinine ≤ 1.5 mg/dL. One hundred fourteen (70.8%) of the former were anemic compared to only 63 (35.6%) of the latter. Thus, anemia was twice as common in those CHF patients with CKI as those without it.

Can anemia itself cause CKI?

While the CKI may be contributing to the production of anemia, the opposite may also be true. It is possible that anemia itself is contributing to the severity and progression of the CKI. In the RENAAL study, a randomized double-blind clinical trial that studied 1513 patients with type 2 diabetes and nephropathy over a mean of 3.4 years [32], patients were administered either losartan or placebo. By multivariate analysis the hazard ratio for doubling the serum creatinine or developing end-stage renal disease (ESRD) for Hb (g/dL) was 0.89 (CI, 0.84–0.95). This suggests that a normal Hb is protective against progressive CKI. This possible protective effect of Hb on renal function has been found in other studies of CKI as well [33].

CHF as a cause of progression of CKI

Congestive heart failure has been found in up to 64% of patients referred to nephrologists with moderate to severe CKI [34]. That CHF itself may be an important contributor to the production of CKI is suggested by a study of 11,192 patients with essential hypertension followed over 15 years [35]. One of the strongest predictive risk factors for reaching ESRD was the advent of CHF. It is known that the glomerular filtration rate falls at a rate of about 1 mL/min/month in patients who develop CHF after a myocardial infarction [36]. Studies have also shown that it may be possible to prevent this deterioration of renal function with a combination of beta blockers and ACE inhibitors [37] suggesting that good treatment of CHF can stabilize CKI. This is consistent with a study that showed that CKI patients with cardiovascular disease (CVD) progress to ESRD more rapidly than those without CVD [38]. The probable mechanism whereby CHF causes progressive CKI is the persistent renal vasoconstriction resulting in renal hypoxia, which can lead to renal cell death and fibrosis [39]. The direct toxic effects of angiotensin, aldosterone, and noradrenaline on renal tissue contribute to this destruction [39].

Can CHF itself cause anemia?

The main cause of the anemia in CHF is most likely the CKI produced by the prolonged renal vasoconstriction leading to prolonged renal ischemia. Renal damage causes reduced production of erythropoietin (EPO) in the kidneys [40]. However, as mentioned above, many anemic CHF patients have a normal serum creatinine, so that it is unlikely that CKI is the entire explanation for the anemia seen in CHF. Indeed, studies in animals have shown that CHF itself may cause anemia [41]. The damaged heart secretes cytokines such as tumor necrosis factor alpha (TNFα) [41, 42], which can cause anemia in three ways [43]: 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 iron from the reticulo-endothelial system so that it cannot get to the bone marrow to be utilized in Hb production. Studies in CHF have shown that the higher the blood levels of TNFα, the lower the Hb [44]. We recently studied the individual contribution of CHF and CKI to anemia in 3 groups of patients: (*1*) Group I, patients with CHF without CKI (serum creatinine <1.5 mg/dL); (*2*) Group II, patients with mild CKI (serum creatinine 1.5 to 2.5 mg/dL); and (*3*) Group III, patients with both CHF and mild CKI (M Blum et al, submitted for publication). The percentage with anemia (Hb <12 g/dL) was 32.1%, 22.4%, and 66.2%, respectively, in the 3 groups. This suggests that the effect of CHF and CRF are additive in production of the anemia.

There are other causes of anemia in CHF. Angiotensin-converting enzyme inhibitors themselves may cause anemia [45], and these are standard therapy in CHF. Many CHF patients take aspirin, which may cause blood loss in the gut. Congestive heart failure patients often have proteinuria, and both EPO, iron, and transferrin can be lost in significant amounts in the urine [46], also contributing to the anemia. The anemia may also be related to the increased plasma volume, causing hemodilution, but in the majority of cases there is also a reduced red cell volume [15].

Sensitivity of the damaged heart to anemia

The failing or ischemic heart may be very sensitive to even minimal falls in Hb, and anemia may worsen or precipitate severe CHF and/or ischemia in these patients at Hb levels that one might generally consider "normal," such as 11 g/dL. Certainly, there is much experimental evidence in animals to support this concept. When the coronary arteries of these animals were narrowed or their hearts damaged by other means, CHF developed at much higher Hb levels than in normal controls [47, 48]. In patients with ischemic heart disease (IHD) who were operated on but not given transfusions, their 30-day postoperative risk of mortality or serious morbidity was much

greater for each level of lower initial Hb than it was in those with normal hearts (i.e., the IHD patients showed increased susceptibility to anemia) [49]. Similarly, in a recent study of elderly patients with an acute myocardial infarction, their 30-day mortality was inversely related to the initial Hematocrit (Hct) up to an Hct of 33% [50]. In addition, transfusions in those with initial Hct levels of 33% or less reduced the mortality rate compared to those not transfused.

How does anemia cause CHF?

There are many ways in which anemia can cause CHF and CKI. The lack of oxygen supply to the heart in the face of the increased heart rate and stroke volume may cause ischemia and lead to myocardial cell death. The red blood cells contain many antoxidants, and therefore anemia is associated with increased oxidative stress [51, 52] that could cause damage to the myocardial cells. Treatment of the anemia with EPO can reduce the oxidative stress [51, 52]. There is even some evidence that EPO alone can reduce oxidative stress independent of its' effect on Hb [53].

Anemia causes tissue ischemia throughout the body, which causes peripheral vasodilatation and a lowering of the blood pressure [54]. The sympathetic system is activated, which, in addition to causing tachycardia and increased stroke volume, also 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 (ADH), causing further renal vasoconstriction and salt and water retention. This leads to peripheral edema and increased plasma volume (PV). The increased PV causes ventricular dilation, which puts a further stress on the already stressed heart. Under the influence of the RAAS and sympathetic activity, left ventricular hypertrophy (LVH) eventually occurs, which can lead to myocardial cell death from necrosis and apoptosis [55, 56]. This can lead to or worsen CHF.

Can EPO alone affect the heart unrelated to its effect on anemia?

In 2 recent in vitro studies EPO itself could directly reduce apoptosis in cardiac myocytes exposed to ischemia [57, 58]. In in vivo studies in rats [57] and rabbits [58] it was found that when a myocardial infarction was produced, the early addition of EPO reduced the size of the necrotic area and improved cardiac contractility and function, without any change in Hb. In our own laboratory (Y Wollman et al, in preparation), we studied the protective effect of pretreatment with Darbopoeitin alpha (ARANESP), a erythropoietin-stimulating protein closely related to erythropoietin, on anoxic-reoxygenation (AR)–induced damage inflicted on a culture of rat cardiac myocytes. Pre-treatment with ARANESP reversed the AR-induced necrosis of cardiac myocytes almost to the level of control.

Erythropoietin has also been found in animal studies to have a direct effect both on the development of cardiac muscle in utero [59] and on the degree of myocardial contractility [60].

What is the effect of correction of anemia on the CHF and the associated CKI?

Regular treatment with EPO in CKI in the predialysis period in patients who eventually required hemodialysis significantly reduced the incidence of hospitalization for CHF in the predialysis period, and in the dialysis period as well compared to those who received EPO sporadically or not at all [23]. Thus, it appears that treatment of anemia in CKD helps prevent CHF.

To assess the importance of this mild anemia in severely symptomatic (NYHA III-IV) CHF patients resistant to maximally tolerated doses of all the CHF medications, we corrected this anemia in both uncontrolled and controlled [3–6] studies in a joint nephrology-cardiology CHF program. We found that when their anemia was corrected to a Hb level of 12 to 13 g/dL with a combination of subcutaneous EPO and intravenous (IV) iron (Venofer), the CHF markedly improved. The patients had a marked improvement in their shortness of breath and fatigue as measured by the New York Heart Association (NYHA) functional class and by a self-administered visual analog scale. Their left ventricular ejection fraction (LVEF), [as measured by multiple gated radioactive angiography (MUGA)] also improved. In addition, the rate of hospitalization and dose of oral and IV diuretics fell with the correction of the anemia, and their glomerular filtration rate (GFR), which had been falling steadily at a rate of about 1 mL/min/month prior to therapy for their anemia, stabilized when the anemia was corrected.

In a recent randomized placebo-controlled study of EPO in severe CHF, the use of EPO was found to improve peak oxygen consumption during exercise, one of the most sensitive tests of cardiac function, and improved exercise duration and quality of life (QOL) [61]. This relationship between Hb level and peak oxygen consumption during exercise in CHF has recently been confirmed by others [62].

The role of anemia in CHF in the production of malnutrition and cardiac cachexia

Patients with CHF and anemia often have signs of malnutrition, such as a lowered body mass index (BMI), serum albumin, and cholesterol [19]. In a prospective study in 9 CRA patients (Vaisman N et al, submitted for publication), we found that correction of the anemia over 3 months was associated with a significant increase in caloric intake, which was reflected by a significant increase in resting energy expenditure, as measured by

Table 1. Two year mortality and incidence of ESRD in a random sample of 1.1 million US Medicare population (Reference 65)

	2 year mortality %	2 year incidence of ESRD %
No anemia, CHF or CKI	7.7	0.1
Anemia	16.6	0.2
CHF	26.1	0.2
CHF and anemia	34.6	0.3
CKI	16.6	2.6
CKI and anemia	27.3	5.4
CHF and CKI	38.4	3.4
CHF and CKI and anemia	45.6	5.9

ESRD is end-stage renal disease.

resting oxygen utilization. Thus, anemia may be responsible for part of the anorexia, weight loss, and cachexia seen in severe CHF. The defect in energy metabolism caused by the anemia and the associated tissue hypoxia (with a switch from aerobic to anaerobic metabolism) can lead to increased catabolism, wasting, and malnutrition [63]. The essential amino acids are channeled into energy production instead of into anabolism and cell growth. This can cause weight loss and malnutrition, and is reflected in a deficiency of essential amino acids in the body and reduced levels of essential amino acids in the blood [63]. Correction of the anemia with EPO and IV iron eliminates the tissue hypoxia and therefore returns the metabolism to the normal aerobic and anabolic state, which is reflected in a return of the plasma essential amino acid levels to normal and an improved nutritional state [63].

Use of IV iron as an adjuvant to EPO

In the studies we performed to treat the anemia of CHF with EPO, we maintained normal iron stores with IV iron (Venofer) [1–4]. This agent has been shown to have very few side effects, it increase the Hb even further than EPO alone, and it allows lower doses of EPO to be used, thus reducing cost of treatment [64].

The effect of the Cardio Renal Anemia Syndrome on mortality and ESRD

The above data all suggest that the combination of CHF, CKI, and anemia seems to have an additive effect on morbidity and mortality in CHF and CKI. This powerful interaction of the 3 is suggested by a recent study of a 5% sample of the Medicare population in the United States [65]. The 2-year risk of dying or of starting dialysis is shown in Table 1. Each of these 3 factors increase the risk of death or ESRD by 50 to 100% and the 3 together, increasing the chances by up to 300%. This interaction between the 3 factors is consistent with the presence of a vicious circle—the Cardio Renal Anemia Syndrome.

In a study we recently performed on 129 consecutive patients with CHF (Wexler D et al, submitted for publication) we measured the beta-type natriuretic peptide (BNP), which is considered to be one of the best tests for measuring the severity of CHF [66]. We found that left ventricular ejection fraction, the serum creatinine, and the Hb were all independent predictors of the BNP levels, again strengthening the concept of the additive effect of all three conditions.

The implications of the Cardio Renal Anemia Syndrome

The need for earlier and better evaluation of cardiac damage in every CKI patient. We suggest that, in many cases of CHF, anemia is a major contributing factor to progressive CHF and CKI. Both CHF and anemia cause renal vasoconstriction and renal ischemia, which can lead to renal fibrosis and progressive renal failure [39]. This is not to say that diabetes or hypertension is not contributing to the renal failure directly, but that in many cases these conditions, in addition to causing direct renal damage, cause cardiac damage and eventual CHF, and that the CHF itself is a major contributor to the progressive CKI. In studies we have done in both diabetics and nondiabetics with CHF [4], aggressive CHF treatment and treatment of the associated anemia in both groups resulted in a stabilization of renal function, as well as an improvement in the CHF. Therefore, it is possible that what is called diabetic nephropathy may, to some extent, be ischemic nephropathy resulting from uncontrolled CHF. Thus, it behooves nephrologists to carefully assess the heart early in every patient with CKI. Cardiac assessment in the routine evaluation of any CKI patient, in addition to including an EKG and chest x-ray, should include an echocardiogram. On echocardiogram, many may have signs of ventricular dilation, LVH, and evidence of systolic and/or diastolic dysfunction, even without clinical evidence of CHF [67].

There is a growing agreement among cardiologists that routine measurement of B-type natriuretic peptide is also useful in diagnosing CHF [66]. This peptide is released from the ventricles in response to increased ventricular volume and pressure, which results in increased ventricular wall stress. B-type natriuretic peptide has now been shown to be a very useful adjuvant to the diagnosis of CHF [66]. It has a high degree of sensitivity, since about 95% of CHF patients have moderately elevated to very high BNP values (>500 pg/mL) [66]. B-type natriuretic peptide has been shown to have a high specificity, such that about 85% of patients with moderately to severely elevated BNP levels (>500 pg/mL) have CHF [66]. Importantly, BNP also has a strong negative predictive value, such that if the BNP is normal the chances of the patient having CHF are extremely unlikely. In the study mentioned earlier we performed BNP measurements on 129 CHF patients seen in our outpatient CHF clinic. All but 1 had elevated BNP levels (>100 pg/mL)

and the average value was 2888 pg/mL. The BNP test is relatively inexpensive and takes only a few minutes to do. It may become a very important test to include in the diagnostic workup of CKI patients [66]. Since many CHF patients may not have a clear clinical picture of CHF, a high BNP would help confirm the diagnosis in questionable cases, and a normal BNP would almost certainly rule it out [66].

The need for better medical treatment of CHF. Although nephrologists treating CKI patients are aware of the benefits of ACE inhibitors in patients with associated CHD or CHF, they seem to be less aware of the benefits of beta blockers. In CKI patients, only about 34% of those with associated CHD are on beta blockers [68], despite their proven marked cardioprotective effect in CHF [7, 8] and possible renoprotective effect [37]. In hemodialysis patients, use of beta blockers was associated with the greatest reduction in mortality of all the antihypertensive agents used and were the only agents that retained this association with lower mortality rates in comorbidity adjusted models [69]. Furthermore, in a randomized placebo-controlled study of hemodialysis patients with severe dilated cardiomyopathy, the use of carvedilol over 2 years was associated with a lower mortality and rate of hospitalization than the placebo group [70]. All of this suggests that greater use of beta blockers, in addition to ACE inhibitors or angiotensin receptor blockers, should become an important aim in the treatment of CKI patients with evidence of CHF, dilated cardiomyopathy, or ventricular dysfunction.

The need for a common effort with cardiologists and other physicians. In our hospital, about 50% of the patients that we see with the combination of CHF, CKI, and anemia (i.e., the CRA syndrome) are being sent to us for treatment of the anemia by cardiologists. This is in contrast to the findings of the Pre Dialysis Survey on Anemia Management (PRESAM) survey of 4333 patients who started dialysis in 779 dialysis centers throughout the world [71]. In this study, only 3% of all consults to nephrologists for management of CKI and anemia come from cardiologists. This means that our patients with CKI are starting treatment with Hb levels of 11 g/dL and not 8 g/dL as they previously were, with serum creatinine values of 2 mg/dL and not 5 mg/dL as they previously were, and with CHF that is not severe and almost irreversible, as was frequently the case previously. The close cooperation between nephrologists and cardiologists has taught us how synergistic such a relationship can be. The cardiolgists have learned the value of correction of anemia in CHF and now refer such anemic CHF patients early. Nephrologists are greatly aided by the cardiologists' wide knowledge of CHF. The cardiologists may discover and treat reversible causes of CHF, such asynchronous cardiac contraction (which can be corrected with a biventricular pacemaker), or ischemic heart disease with a hibernating heart, which could respond to coronary artery bypass graft or angioplasty.

Other major sources of patients with the CRA syndrome are medical and geriatric wards where many patients have CHF and CKI, are anemic, and often are being hospitalized again and again. Indeed, in a study of 46,788 consecutive admissions to medical wards, 24% had CHF [72]. Discussion with the attending physicians will improve the possibility of early referral to nephrology for treatment of their anemia, as well as for other renal problems. Another major source of CRA may be diabetic clinics. In a recent study in a diabetic clinic, 23% of diabetics were found to be anemic [73], the prevalence and severity being related to the degree of proteinuria and renal damage.

CONCLUSION

A vicious circle appears to be present in CHF (Fig. 1), in which CHF causes both anemia and CKI. The CKI causes more anemia. The anemia and CKI act back to further worsen the CHF, which then further worsens the anemia and the CKI and so on. We suggest calling this relationship the Cardio Renal Anemia (CRA) syndrome, and we consider it to be very common. The condition is under-recognized, underdiagnosed, and undertreated. The importance of the concept of CRA is that if the anemia is not treated in CHF patients there will likely be resistant to any other form of CHF therapy, and there will be progression of the CHF, the CKI, and the anemia. On the other hand, if the patient does not get maximal cardioprotective medications, the CHF and CKI will progress, even if the anemia is treated. Thus, both correction of anemia and the adequate detection and treatment of CHF are crucial in stabilizing or improving both the CHF and the CKI. The management of the CRA syndrome will involve interdisciplinary cooperation between nephrologists, cardiologists, diabetologists, other internists, and family physicians.

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