Cardiorenal-anemia syndrome - definition, epidemiology and management: The Cardiologist’s view

Farmakis D1, Filippatos G2
1First Dept of Internal Medicine, University of Athens Medical School, Laiko Hospital, Athens, Greece
2Second Dept of Cardiology and Heart Failure Unit, University of Athens Medical School, Attikon University Hospital, Athens, Greece

Abstract

The term “cardiorenal anemia syndrome” (CRAS) was introduced to describe the frequent coexistence of heart failure (HF), renal dysfunction and anemia as well as the close pathogenetic relationship between them. Up to two thirds of patients with acute heart failure (HF) and nearly one third of those with chronic HF have at least moderate renal dysfunction. Anemia, on the other hand, is detected in 10-60% of HF patients, depending on definitions and HF severity. Data on the coexistence of anemia and kidney disease in HF is quite variable and a prevalence of 3-22% is reported by various studies. Both renal dysfunction and anemia are independent predictors of adverse prognosis in HF and seem to have an additive effect on patients’ survival. Anemia pathogenesis in CRAS is multifactorial and among other factors includes reduced synthesis of and/or resistance to erythropoietin and iron deficiency. As a result, erythropoiesis stimulating agents (ESA) and iron supplementation have both emerged as potential therapeutic modalities for CRAS. Although the first small clinical trials on ESA were promising, the subsequent large-scale testing of those agents resulted in controversial findings. Recent studies on the use of iron therapy in HF patients with iron deficiency have shown beneficial effects regarding patients’ symptoms, functional status and quality of life, which seem to occur irrespectively of the presence of anemia. However, there are several issues that need to be clarified, including whether the correction of iron deficiency is followed by better long-term prognosis, what patients benefit the most and therefore need to be treated or what therapeutic targets should be pursued. Hippokratia 2011; 15 (Suppl 2): 9-14

Key-words: cardiorenal syndrome, anemia, iron deficiency, iron replacement therapy, review

Corresponding author: Gerasimos Filippatos, Second Dept. of Cardiology and Heart Failure Unit, University of Athens Medical School, Attikon University Hospital, 1 Rimini St, Haidari, Athens, Greece, email: geros@otenet.gr

Definition

Cardiorenal syndrome is defined as the coexistence of cardiac and renal dysfunction, in which an acute or chronic deterioration of one of the two organs leads to an acute or chronic worsening of the other. As a result, cardiorenal syndrome represents a wide range of conditions in acute or chronic setting, in which the primarily affected organ may be either the heart or the kidney. Other terms that have been used in this population but are not identical to cardiorenal syndrome include “diuretic resistance”, defined as congestion persistence despite treatment with intravenous furosemide in high dose or combination of loop, thiazides and/or aldosterone inhibitors and “worsening renal function” (WRF) defined as an increase in serum creatinine ≥0.3 mg/dL or ≥25% from baseline during hospitalization for acute heart failure (HF).

As both HF and chronic kidney disease (CKD) cause anemia, which in turn leads to both cardiac and renal deterioration, Silverberg expanded the term “cardiorenal syndrome” to also include anemia and therefore the term “cardiorenal anemia syndrome” (CRAS) was born in 2002. As a result, CRAS may be defined as the combination of HF, kidney disease and anemia, in which each one of the three conditions causes worsening of the other two, establishing a vicious circle of progressive deterioration.

Although questioned, the use of the term CRAS stresses on one hand the close epidemiologic and pathogenetic relationship of its three components and on the other the need for a comprehensive approach for their prevention and treatment.

Epidemiology

The epidemiology of CRAS is complicated as it depends on the prevalence of each one of its components, which in turn is largely dependent upon the applied definitions and the disease severity of the population studied. As a result, the reported data is considerably variable. Seen from the Cardiologist’s view, the majority of clinical trials in HF exclude patients with clinically important co-morbidities, such as moderate to severe renal dysfunction or significant anemia. HF registries in contrast provide a better picture of the prevalence of renal dysfunction and anemia in the real-world HF populations. In the Acute Decompensated Heart Failure National Registry (ADHERE), the largest registry on
acute HF including nearly 120,000 patients in U.S.A., normal renal function [estimated glomelural filtration rate (eGFR) ≥90 ml/min/1.73m²] was present in only 9% of patients; two thirds of patients (64%) had at least moderate renal dysfunction (eGFR <60 ml/min/1.73m²), while 20% of them had severe renal dysfunction (eGFR <30 ml/min/1.73m²). In the recent European Society of Cardiology – Heart Failure (ESC-HF) Pilot registry including more than 5000 patients, either hospitalized for acute HF or ambulatory ones with chronic HF, chronic renal dysfunction was present in 26% and 19% of acute and chronic HF patients, respectively, while severe renal dysfunction (eGFR <30 ml/min/1.73m²) was detected in 10% and 5% of patients, respectively. Moreover, nearly one fourth of patients hospitalized for acute HF develop WRF during their hospital stay, with an occurrence reported by different studies between 21 and 29%.

On the other hand, anemia is detected in 10-60% of HF patients, depending on the applied definition of anemia and the severity of heart failure. A meta-analysis of 34 trials including 150,000 patients reported a prevalence of 37%. In HF registries, anemia, defined as a hemoglobin level <12 g/dL, was encountered in 40% of patients in ADHERE, 33% in EuroHeart Failure Survey program, 31% and 19% of hospitalized and ambulatory patients, respectively, in the ESC-HF Pilot registry. Data on the coexistence of anemia and CKD in HF patients is quite variable. In a population-based cohort of 12,065 patients with new-onset HF in Canada, 3% had both anemia and chronic kidney disease, while in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial on 2653 HF patients the coexistence of both conditions was present in 14% of patients. Finally, in a single-center study on 955 HF patients, 22% had both anemia and chronic kidney disease.

Renal dysfunction leading to fluid retention and congestion is one of the mechanisms implicated in HF worsening and progression and represent a strong and independent predictor of adverse prognosis in those patients. A GFR <60 mL/min has been associated with a two fold increase in the risk of mortality in HF, while patients in the lowest GFR quartile (<44 mL/min) had almost a three fold increase (relative risk, 2.85). Moreover, WRF is

Table 1: Measures for the prevention and treatment of cardiorenal syndrome.

<table>
<thead>
<tr>
<th>General measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early and correct optimization of heart failure medication</td>
</tr>
<tr>
<td>Close monitoring of hemodynamics and renal function (clinical/biomarkers)</td>
</tr>
<tr>
<td>Correct usage of diuretics</td>
</tr>
<tr>
<td>• Diuretic combinations of different categories for sequential nephron blockade</td>
</tr>
<tr>
<td>• Avoidance of diuretic combinations of the same category</td>
</tr>
<tr>
<td>• Avoidance of thiazides when GFR &lt;15-20 ml/min</td>
</tr>
<tr>
<td>• Avoidance of extremely high doses</td>
</tr>
<tr>
<td>Avoidance of hypovolemia</td>
</tr>
<tr>
<td>Avoidance of excess salt and fluid intake</td>
</tr>
<tr>
<td>Avoidance of nephrotoxic agents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific measures in acute conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropes (dopamine, dobutamine, levosimendan)</td>
</tr>
<tr>
<td>Renal replacement therapy (ultrafiltration)</td>
</tr>
<tr>
<td>Mechanical circulatory support</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Novel/investigational agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesiritide</td>
</tr>
<tr>
<td>Vasopressin antagonists</td>
</tr>
<tr>
<td>Adenosine antagonists</td>
</tr>
</tbody>
</table>
also independently associated with worse prognosis in acute HF. Finally, markers of renal function such as BUN are independent predictors of adverse prognosis in HF. Anemia is also an independent predictor of survival and prognosis in HF as shown by several studies, registries and meta-analyses. The combination of anemia and kidney disease seem to have an additive effect on the prognosis of HF patients; according to data from a population of 1,136,201 individuals, the 2-year mortality risk rose from 27% in patients with HF alone to 35% in those with HF and anemia, 38% in those with HF and kidney disease and finally to 46% in those with all three conditions.

**Prevention and treatment**

**Worsening renal function and diuretic resistance**

Table 1 summarizes the strategies for the prevention and/or management of renal dysfunction in HF patients. The careful introduction and up-titration of HF medications, and especially of RAAS inhibitors and diuretics, and the close clinical and laboratory monitoring of patients is essential. The education of patients to avoid excess fluid and salt intake and nephrotoxic agents such as non-steroid anti-inflammatory drugs is also important. In acute settings, the proper use of inotropes and mechanical circulatory support may be beneficial while renal replacement therapy and particularly continuous venous-venous ultrafiltration, although not yet widely used, should be early considered in those patients. Some recently developed agents that are currently under investigation, including nesiritide, arginine-vasopressin antagonists and adenosine antagonists, as well as statins may also play a role in renal protection and management of diuretic resistance, but solid evidence on those agents is still missing.

**Table 2: Treatment options for anemia that have been used in cardiorenal-anemia syndrome.**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusions</td>
<td>In severe anemia or urgent conditions</td>
</tr>
<tr>
<td>Iron supplementation</td>
<td>In iron deficiency</td>
</tr>
<tr>
<td>• Iron sucrate - intravenous</td>
<td>Amelioration of functional status and quality of life</td>
</tr>
<tr>
<td>• Ferric carboxymaltose - intravenous</td>
<td></td>
</tr>
<tr>
<td>• Ferrous sulfate - per os</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 and /or folic acid supplementation</td>
<td>In B12 and /or folic acid deficiency</td>
</tr>
</tbody>
</table>

Erythropoiesis stimulating agents (with or without iron supplementation)

- Epoetin alpha - subcutaneous
- Epoetin beta - subcutaneous
- Darbepoetin alfa – subcutaneous

**Table 3: Causes and pathogenetic mechanisms of iron deficiency in cardiorenal-anemia syndrome.**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal ischemia and/or edema</td>
<td>Reduced iron absorption</td>
</tr>
<tr>
<td>Gastrointestinal bleeding due to antiplatelets or anticoagulants</td>
<td>Increased iron loss</td>
</tr>
<tr>
<td>Increased hepcidin release due to inflammatory activation</td>
<td>Reduced iron release from enterocytes and macrophages</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Reduced iron intake</td>
</tr>
<tr>
<td>Erythropoietin therapy without iron supplementation</td>
<td>Increased iron usage</td>
</tr>
</tbody>
</table>

also independently associated with worse prognosis in acute HF. Finally, markers of renal function such as BUN are independent predictors of adverse prognosis in HF. Anemia is also an independent predictor of survival and prognosis in HF as shown by several studies, registries and meta-analyses. The combination of anemia and kidney disease seem to have an additive effect on the prognosis of HF patients; according to data from a population of 1,136,201 individuals, the 2-year mortality risk rose from 27% in patients with HF alone to 35% in those with HF and anemia, 38% in those with HF and kidney disease and finally to 46% in those with all three conditions.
and most trials failed to show any benefit.\(^{36-39}\)

**Anemia**

Anemia in the context of the CRAS is multifactorial and several mechanisms have been implicated. These mechanisms include decreased erythropoietin synthesis due to renal dysfunction and renin-angiotensin-aldosterone system (RAAS) inhibitors, further inhibition of red cell production by RAAS inhibitors, bone marrow hypoperfusion due to low cardiac output, gastrointestinal blood losses due to antiplatelets and anticoagulants, iron deficiency, erythropoietin resistance and deregulation of iron metabolism due to inflammatory activation in the context of chronic disease and finally hemodilution, although this latter mechanism has recently been questioned.\(^{40-43}\) As erythropoietin and iron metabolism are believed to play an important role in the pathogenesis of anemia in CRAS, erythropoiesis stimulating agents (ESAs) and iron supplementation have emerged as potential therapeutic interventions in anemic patients with CKD and/or HF (Table 2).

The findings on the use of ESAs both in HF and CKD remain controversial. In chronic HF, several small trials showed improvement in functional status and/or quality of life or cardiac performance.\(^{44-46}\) However, evidence on patients’ prognosis remains inconclusive as large-scale testing of ESAs in HF is generally missing.\(^{41,42}\) The ongoing Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial designed to recruit 2600 HF patients may shed some new light on this issue.\(^{44}\)

In CKD, on the other hand, a series of large randomized trials showed that the aggressive correction of the generally mild anemia occurring in those patients has either neutral results or even negative effects on patients’ prognosis. More specifically, the CREATE trial in 603 CKD patients with mild anemia (hemoglobin 11.0-12.5 g/dL) showed neutral effects on the occurrence of cardiovascular events at 3 years.\(^{46}\) In the CHOIR trial in 1432 patients with CKD and mild to moderate anemia (hemoglobin <11.0 g/dL), erythropoietin increased the occurrence of death and cardiovascular events at 3 years, without having a significantly beneficial effect on quality of life.\(^{41}\) Finally, the TREAT trial in 4038 patients with CKD, diabetes mellitus and mild to moderate anemia (hemoglobin <11.0 g/dL) demonstrated an increase in the rate of stroke at 3 years in the darbepoetin arm.\(^{48}\)

**Iron deficiency**

Iron deficiency is frequently encountered in HF patients, both with and without anemia, especially in those with advanced disease.\(^{42,43}\) In a group of 546 patients with chronic HF of varying severity, the prevalence of iron deficiency was 37% in the whole cohort, 57% in anemic patients and 32% in non-anemic ones.\(^{35}\) Moreover, in a group of 37 patients with advanced chronic HF, iron deficiency, as indicated by the absence of iron stores in bone marrow, was present in 73% of cases.\(^{32}\) It has been shown that iron deficiency is independently associated with reduced exercise performance and worse prognosis in HF patients, irrespectively of the presence of anemia.\(^{33}\)

The etiology of iron deficiency in CRAS is also multifactorial (Table 3). Gastrointestinal losses, malabsorption, reduced iron intake, inflammatory activation and ESA therapy without iron supplementation may all be implicated.\(^{47-49}\) Iron deficiency is generally indicated by a serum ferritin concentration <100 ng/mL or a serum ferritin <300 ng/mL with transferrin saturation <20%.\(^{50}\) A number of clinical trials on the use of iron regimens in chronic HF patients with iron deficiency, with or without anemia, have shown beneficial effects mainly in terms of functional capacity and quality of life. Intravenous iron sucrose (200 mg once/week for 5 weeks) was compared with placebo in 40 chronic HF patients with mild anemia, iron deficiency and at least mild renal insufficiency (creatinine clearance <90 ml/min); iron repletion was followed by a significant decrease in natriuretic peptides and C-reactive protein, increase in 6-min walked distance and left ventricular ejection fraction (LVEF) and amelioration of quality of life at 6 months.\(^{31}\) In the subsequent FERRIC-HF trial, 35 chronic HF patients with iron deficiency were randomized to intravenous ferric carboxymaltose (at 200 mg/week until to iron repletion and then at 200 mg/month for a total of 4 months) or placebo.\(^{51}\) Iron supplementation was followed by a significant increase in peak VO\(_2\) (primary end point) as well as a significant amelioration of patients’ self-reported symptoms (Patient Global Assessment, PGA) and New York Heart Association (NYHA) class. However, those beneficial effects were mostly observed in patients with anemia at baseline. The most recent FAIR-HF trial, the largest study concerning iron repletion therapy in HF, randomized 459 NYHA II-III patients with impaired LVEF and iron deficiency to intravenous ferric carboxymaltose (at 200 mg/week till iron repletion followed by 200 mg/month) or placebo.\(^{50}\) The primary end point, PGA and NYHA class at week 24, was met and in addition 6-min walked distance and quality of life questionnaires were significantly improved by iron therapy at weeks 4, 12 and 24. Interestingly and in contrast to FERRIC-HF trial, the positive effects on primary end points were observed both in patients with and without anemia at baseline, defined as hemoglobin ≤12 g/dL. Finally, iron therapy was safe.

There are still several issues that require clarification regarding the management of anemia or iron deficiency in HF patients, with or without CKD. First, as previously stressed, the evidence on the role of ESAs is still inconclusive. Given the adverse effects caused by those agents in CKD patients, the safety issues regarding their use are the first that need to be properly addressed. Moreover, it is not yet known whether correction of either anemia or iron deficiency prevents the development of CRAS or affects beneficially patients’ prognosis. Other open issues include the profile of HF of CRAS patient who benefits the most of those therapies and therefore needs to be treated as well as the therapeutic targets that should be pursued (e.g., hemoglobin, serum ferritin) as well as its desirable target levels or rate of achieving these levels. Finally, confirmation of the promising results by large study populations will also be required.
References
13. 640.
22. 2007; 12: 149-156.
29. 2006: 48; 2485-2489.
47. Silverberg DS. The role of erythropoiesis stimulating agents and intravenous (IV) iron in the cardio renal anemia syndrome. Heart Fail Rev. 2010 2011; 16: 609-614.