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REVIEW ARTICLE

Cardiorenal syndrome: still not a defined entity

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Abstract Because of the increasing incidence of cardiac failure and chronic renal failure due to the progressive aging of the population, the extensive application of cardiac interventional techniques, the rising rates of obesity and diabetes mellitus, coexistence of heart failure and renal failure in the same patient are frequent. More than half of subjects with heart failure had renal impairment, and mortality worsened incrementally across the range of renal dysfunctions. In patients with heart failure, renal dysfunction can result from intrinsic renal disease, hemodynamic abnormalities, or their combination. Severe pump failure leads to low cardiac output and hypotension, and neurohormonal activation produces both fluid retention and vasoconstriction. However, the cardiorenal connection is more elaborate than the hemodynamic model alone; effects of the renin-angiotensin system, the balance between nitric oxide and reactive oxygen species, inflammation, anemia and the sympathetic nervous system should be taken into account. The management of cardiorenal patients requires a tailored therapy that prioritizes the preservation of the equilibrium of each individual patient. Intravascular volume, blood pressure, renal hemodynamic, anemia and intrinsic renal disease management are crucial for improving patients' survival. Complications should be foreseen and prevented, looking carefully at basic physical examination, weight and blood pressure monitoring, and blood, urine urea and electrolytes measurement.

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Introduction

Cardiorenal syndrome is a pathophysiological condition in which combined cardiac and renal dysfunction amplifies the progression of failure of the individual organs and has an extremely bad prognosis. Recently, Ronco et al. subdivided cardiorenal syndrome into five classes in order to provide better characterization and management of patients: type 1 reflects a rapid worsening of cardiac function leading to acute kidney injury (acute renal syndrome); type 2 comprises chronic abnormalities in cardiac function causing progressive chronic kidney disease (chronic cardiorenal syndrome); type 3 consists of a rapid worsening of renal function causing acute cardiac dysfunction (acute renocardiac syndrome); type 4 describes a condition referring to a state of chronic kidney disease contributing to decreased cardiac function (chronic renocardiac syndrome); type 5 reflects combined cardiac and renal dysfunction caused by systemic diseases (e.g., sepsis) (secondary cardiorenal syndrome) [1] (Fig. 1).

Cardiorenal insufficiency is more than a simultaneous cardiac and renal disease. Atherosclerosis, renal vascular disease, diabetes mellitus, and hypertension are significant precursors of both heart failure and renal failure. Patients with cardiorenal syndrome live in a fragile environment challenged by the interaction of neurohumoral, hemodynamic, and other less known factors [2].

The overall goals of management of these patients should be to normalize volume status while avoiding overdiuresis and attendant renal dysfunction, and to

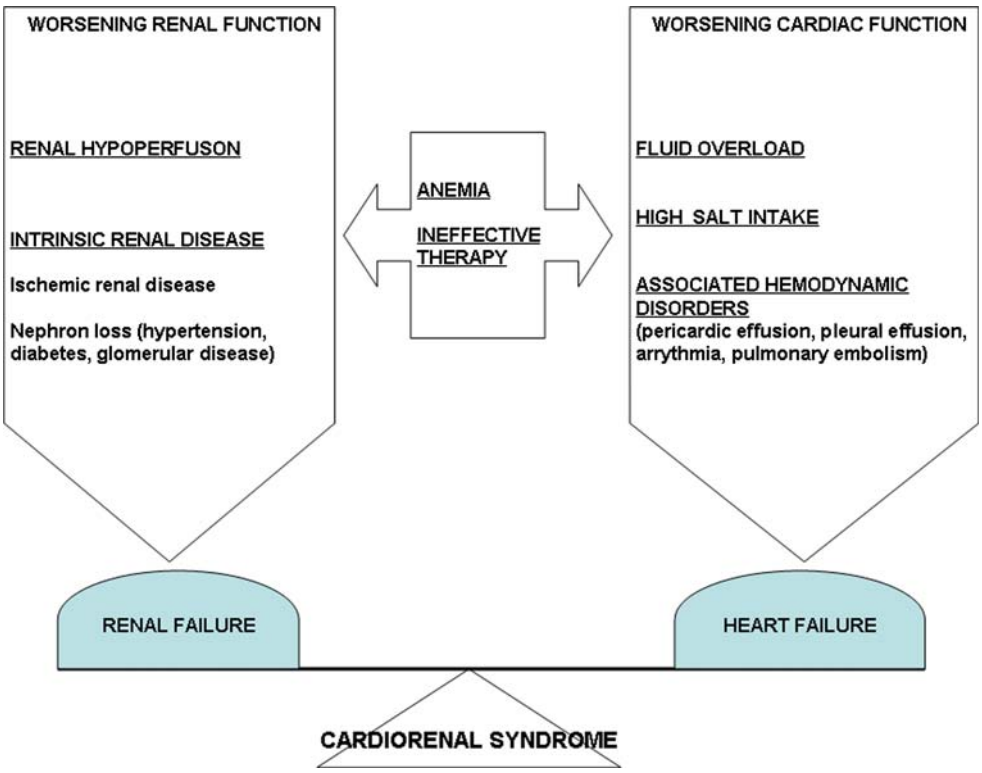

Fig. 1 Physiopathology of cardiorenal syndrome balance

implement pharmacological and device therapy to improve patient outcomes [3].

Epidemiology and prognosis

Despite increasing recognition of the prevalence and importance of renal disease in patients with cardiovascular diseases [4–6], the exclusion of subjects with renal disease from cardiac trials has remained high over the past 20 years.

In an evaluation of data from a study sample including 1,681 patients aged more than 65 years who were admitted at hospitals for acute decompensated heart failure, 21% of patients had baseline renal failure, and 41% had a baseline serum creatinine level >1.5 mg/dl [8]. Similarly, renal dysfunction complicated acute heart failure management in 18% of the 11,327 patients admitted to 115 hospitals in the EuroHeart Failure survey program [9]. Finally, 30% of hospitalized patients with acute heart failure had a history of chronic renal failure (serum creatinine level >2 mg/dl in 20% of patients) in an evaluation of 105,388 hospitalization episodes at 274 hospitals from the Acute Decompensated Heart Failure National Registry (ADHERE) [10]. Moreover, these data probably underestimate the true prevalence of renal failure in these patients since serum creatinine concentration alone may not accurately reflect renal function. Comorbid renal dysfunction can complicate the management of acute heart failure, even when it is not present at the time of admission. Between 27 and 45% of patients hospitalized for acute heart failure develop an acute worsening of renal function (increase in serum creatinine level >0.3 mg/dl) during hospitalization [11]. In a classification and regression tree analysis of more than 33,000 patients from the ADHERE registry, results showed that admission serum creatinine and blood urea nitrogen levels were among the strongest independent risk predictors for in-hospital mortality [12].

As far as chronic heart failure (CHF) is concerned, in a prospective cohort study of 6,427 patients with CHF and coronary artery disease, the prevalence of chronic kidney disease (creatinine clearance <60 ml/min) was 39%. A clear gradient of mortality was observed as renal function worsened, with 1-year mortality increasing by 0.2% for every μmol/l increase in serum creatinine [13]. In a review of 16 studies focused on the association between renal impairment and mortality in 80,098 hospitalized and non-hospitalized heart failure patients, all-cause mortality risks associated with any renal impairment and moderate-to-severe impairment were estimated. A total of 63% of the patients had some renal impairment, and 29% had moderate to severe impairment; adjusted all-cause mortality was increased for patients with any impairment (hazard ratio, HR = 1.56) and moderate to severe impairment (HR = 2.31); mortality worsened incrementally across the range of renal function, with 15% increased risk for every

0.5 mg/dl increase in creatinine and 7% increased risk for every 10 ml/min decrease in eGFR [14]. In the study of Grigorian Shamagian et al. [15] including 552 consecutive CHF patients admitted to hospital, renal failure was a common and strong predictor of mortality in those with either depressed (RR = 3.8) or preserved (RR = 2.9) systolic function.

Pathophysiology of cardiorenal syndrome

In patients with heart failure, renal dysfunction can result from intrinsic renal disease, hemodynamic abnormalities, or their combination. Diminished renal perfusion is frequently a consequence of the hemodynamic changes associated with heart failure and its treatment. Severe pump failure leads to low cardiac output and hypotension [16]; neurohormonal activation produces fluid retention, increasing central venous pressure, and vasoconstriction, increasing afterload and diminishing cardiac output [17]. Overdiuresis can cause hypovolemia, reducing preload, and use of intravenous vasodilators can lead to hypotension. In addition, agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARBs) all can decrease renal perfusion [18, 19].

In patients with heart failure, there is a correlation between renal dysfunction and circulating levels of neurohormones. Activation of the renin-angiotensin-aldosterone system (RAAS) leads to renal hypoxia, vasoconstriction, intraglomerular hypertension, glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria [20, 21]. Similarly, sympathetic nervous system activation causes proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall of intrarenal blood vessels [22]. High central venous pressure is another cause of renal dysfunction [23].

In addition to the adverse effects of heart failure on renal function, renal dysfunction adversely affects cardiac function, producing a vicious circle in which renal insufficiency impairs cardiac performance, which then leads to further impairment of renal function. As a result, renal insufficiency is a major determinant of the progression of heart failure, congestion, and recurrent decompensation [24–26]. Both heart failure and renal insufficiency produce neurohormonal activation, and this activation increases the volume and pressure load on the heart, reduces myocardial oxygen supply, promotes deleterious myocardial remodeling, and accelerates atherosclerosis [27]. Neurohormonal activation is thus a key component of the links between renal insufficiency and heart failure.

The cardiorenal connection is more elaborate than the hemodynamic model alone suggests, taking into account the extended cardiorenal effects of the RAAS [28–30], the balance between nitric oxide (NO) and reactive oxygen species (ROS), inflammation, and the sympathetic nervous system [31, 32].

Moreover, many patients are affected by cardio-anemia-renal syndrome [33]. Anemia is frequently observed in patients with CHF: the incidence of anemia increased from 9% for patients with New York Heart Association (NYHA) class I to 79% for NYHA class IV, as reported by Silverbeg [34]. It has been reported that each 1-g/dl decrease in serum hemoglobin was associated with increases in LV dilatation and LVH, which in turn were associated with worsening renal function [35].

Managment of patients with cardiorenal syndrome

The management of cardiorenal patients requires a precise understanding of the clinical features of the patient and the design of a tailored therapy that prioritizes the preservation of the equilibrium of each individual patient and often uses a multidisciplinary approach.

Cardiorenal syndrome can be difficult to manage because both cardiac and renal functions are strictly dependent on circulating volume: the avoidance of oscillations between overfilled-decompensated and emptied-overtreated states becomes of critical importance [3]. Drugs that have demonstrated their utility in heart failure, such ACEI, beta-blockers, and spironolactone, are rather underused in cardiorenal syndrome despite recent studies suggesting that the effect of these drugs in chronic renal insufficiency is at least equivalent to that observed in isolated heart failure [36]. Because patients with heart failure and renal insufficiency have been underrepresented in the trials, little evidence is available to guide clinicians in the optimal management of patients with both conditions [7].

An initial consideration is the identification of potentially reversible factors that may be contributing to cardiorenal dysfunction. In this regard, it is important to evaluate fluid status, blood pressure (hypotension) and cardiac output, aneamia and evidence of intrinsic renal disease.

Intravascular volume management

Concerning a patient with cardiorenal syndrome, the first problem to deal with is to ascertain whether the patient is hypovolemic.

Since diuretics are an integral part of heart failure therapy, an overaggressive use or their use in combination with other factors, such as an intercurrent illness, with reduction both of cardiac output and GFR is frequently observed [37]. The resultant extracellular fluid contraction increases the adverse renal effects of therapeutic agents

used in the treatment of heart failure, including ACEI, ARBs, and natriuretic peptides [18, 38], and enhances the risk of radiocontrast agents [39].

Moreover, diuretics stimulate adverse neurohormonal activation [40]. Both heart failure and renal failure influence the dose-response curve for diuretics; renal failure shifts the curve to the right, while heart failure shifts the curve both downward and to the right. This not only increases the dose required to produce a diuretic response, but also decreases the maximum response that can be achieved, creating a state of relative diuretic resistance. Moreover, this increasing dose requirement and diminished responsiveness intensify as heart failure progresses [41]. It is also important to remember that diuretics have an S-shaped dose-response curve: for any individual patient there is a maximum dose above which nothing is gained by using larger doses. It is essential to carefully assess the therapeutic response to these increases of doses to make sure that one remains on the steep part of the dose-response curve [42]. Diuretics, especially when employed at high doses, have been shown to increase the mortality risk in patients with heart failure and/or renal insufficiency [43].

In synthesis the use of diuretics involves a delicate balance; the dose must be sufficient to achieve effective relief of fluid overload and its ensuing symptoms without stimulating adverse effects. A careful physical examination and estimation of right and left atrial pressures with echocardiography can usually answer this question, although invasive assessment of filling pressures will occasionally be necessary.

Novel agents for the treatment of heart failure are under investigation. They include arginine vasopressin (AVP) receptor antagonists, also termed 'vaptans.' AVP is a neuropeptide hormone that plays an important role in circulatory and sodium homeostasis and serum osmolality. Three receptor subtypes that mediate the actions of AVP have been identified (V-1A, V-2, and V-1B). The cardiovascular and renal effects of AVP are mediated primarily by V-1A and V-2 receptors: antagonism of V-1A receptors results in vasodilatation and antagonism of V-2 receptors results in aquaresis, an electrolyte-sparing water excretion [44].

The drugs targeting the V1AR-V2R (conivaptan) or the V2R (mozavaptan, lixivaptan, satavaptan, and tolvaptan) are now being tested. They not only decrease congestion and correct hyponatremia but, in contrast with other neurohormonal modulators, also prevent left ventricular remodeling and progression of left ventricular dysfunction [45].

In data analysis of 319 patients with left ventricular ejection fractions of less than 40% and hospitalized for heart failure, 60-day mortality was lower in tolvaptan-treated patients and decrease in body weight was not associated with changes in heart rate or blood pressure, hypokalemia, or worsening renal function, in contrast to diuretic use [46]. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), a large trial, investigates whether tolvaptan improves survival in patients with CHF; 4,133 patients were randomly assigned to receive oral tolvaptan, 30 mg once per day, or placebo, for a minimum of 60 days, in addition to standard therapy. Tolvaptan initiated for acute treatment of patients hospitalized with heart failure had no effect on long-term mortality or heart failure-related morbidity [47].

However, long-term follow-up studies are needed to determine if theoretical concerns are problematic in patients with heart failure and if the efficacy of dual V1A and V2 receptor antagonists may have some advantage versus that of selective V2 receptor antagonists.

Blood pressure and cardiac output management

The next step is to consider the adequacy of renal perfusion. Renal perfusion depends on both blood pressure and cardiac output. If hypotension is present, pressures should be used to maintain a systolic blood pressure at least >80 mmHg and a mean blood pressure >60 mmHg [48].

Inotropic drugs augment ventricular contractility and are an important component of the treatment of low-output heart failure manifested by cardiogenic shock. However, they improve short-term hemodynamics, but increase the risk of adverse events and mortality [49–51]. These effects may, in part, be due to augmentation of the deleterious neurohormonal activation that is already present in patients with decompensated heart failure.

In a multicenter evaluation of patients with stable heart failure, treatment with levosimendan or dobutamine was associated with a significant increase in plasma renin levels compared with baseline [52]. The Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study is a trial comparing the efficacy and safety of intravenous levosimendan or dobutamine in 1,327 patients hospitalized with acute decompensated heart failure who required inotropic support; all-cause mortality at 180 days was the main outcome measure. Despite an initial reduction in plasma B-type natriuretic peptide level in patients in the levosimendan group compared with patients in the dobutamine group, levosimendan did not significantly reduce all-cause mortality [53].

If hypotension is not present, then cardiac output should be evaluated. In the absence of hypotension, cold extremities are frequently an indication of excessive vasoconstriction leading to low cardiac output and elevated systemic vascular resistance. These patients often respond favorably to vasodilators [54], which decrease preload and

afterload, thus reducing ventricular work, increasing stroke volume, and augmenting cardiac output. They are indicated in patients with acute heart failure who have signs of congestion and hypoperfusion with adequate blood pressure. Nitrate dosing must be carefully titrated to produce optimal vasodilation because excessive or inappropriate vasodilation causes a rapid decline in blood pressure with resultant reflexive sympathetic activation and tachycardia, RAAS activation, and fluid retention [55]. In addition, tolerance to nitrates develops quickly, especially when they are given intravenously in high doses, generally limiting the duration of effectiveness to 24–48 h and often necessitating central hemodynamic monitoring in an intensive care unit setting. In patients with heart failure B-type natriuretic peptide (BNP), a counterregulatory hormone produced by the ventricles in response to pressure and volume load, produces balanced vasodilation, improves cardiac output, and inhibits activity of the RAAS, sympathetic nervous system, and endothelin system [56]. BNP is released from the myocardium depending on wall stress, and the precursor peptide pro-BNP is cleaved into two peptides, BNP and NT-proBNP. BNP is a 32-amino acid peptide that is biologically active, and its half-life is about 20 min. NT-proBNP is a 46-amino acid peptide that is biologically inert, and its half-life is 1–2 h. Assays for BNP and NT-proBNP are approved by the US Food and Drug Administration for evaluating, estimating prognosis, and monitoring therapy of congestive heart failure [57]. Nesiritide, a recombinant form of BNP, in a small study, exerted a renal vasodilatory effect, which maintained renal blood flow despite a significant decrease in renal perfusion pressure [58]. In a meta-analysis including over-therapeutic doses of nesiritide, risk of acute serum creatinine elevation paralleled the prevalence of symptomatic hypotension [59].

In an analysis of data from the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, the risk of acute serum creatinine elevation was significantly increased in patients treated with nesiritide who received high-dose diuretics [38]. It is not yet clear whether the observed increase in creatinine is associated with adverse outcomes. In a pooled analysis of five randomized nesiritide trials, increases in serum creatinine (>0.5 mg/dl) that occurred in patients treated with nesiritide were not associated with an increased risk of mortality at 30 days [60]. Recently, in a randomized, double-blind, placebo-controlled clinical trial, nesiritide (0.01 μg/kg/min with or without a 2-μg/kg bolus or placebo 5% dextrose in water for 48 h in addition to their usual care) had no impact on renal function (a rise in serum creatinine by ≥20%) in patients with acute decompensated heart failure and baseline renal dysfunction (mean serum creatinine 1.82 mg/dl) [61]. There were no significant differences in the secondary end points of change in weight, intravenous furosemide use, discontinuation of the infusion due to hypotension, or 30-day death/hospital readmission.

Although data are emerging that low doses of nesiritide are potentially renal protective in patients with cardiorenal syndrome, studies addressing the effect of nesiritide on renal function in patients hospitalized for decompensated heart failure are limited, with conflicting results. Larger randomized, placebo-controlled trials, such as the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) [62], are required to further elucidate the effect of nesiritide on renal function in patients hospitalized for decompensated heart failure.

Adenosine antagonists are novel agents that have the effect of activating adenosine A1 receptors and promoting diuresis. Adenosine antagonists have the potential to improve renal blood flow and increase sodium excretion. The safety and efficacy of adenosine antagonists are currently being evaluated in larger clinical trials to determine their net effect on renal function and cardiovascular function [63].

Renal hemodynamic management

Another important issue is to examine the feasibility of discontinuing drugs that interfere with renal function.

Agents such as NSAIDs, cyclosporine, ACEI, and ARBs all can decrease renal perfusion. While the angiotensin-induced vasoconstriction of the efferent glomerular arteriole helps to preserve GFR in patients with heart failure and renal insufficiency [64], the ACEI and/or ARBs impede this vasoconstriction, reducing glomerular capillary pressure and hence, GFR leading to an acute, small increase in serum creatinine level. Although initially worrisome, the resultant decrease in glomerular hyperfiltration seems to be renoprotective over the long term, and supports continuation of these therapies in the absence of renal artery stenosis [65–67]. Because patients who are volume-depleted may be especially sensitive to this efferent arteriolar vasodilation, restoring and maintaining a normal volume status before and throughout therapy with a neurohormonal blocking agent may help alleviate the initial acute decline in renal function [68].

In synthesis ACEI and ARBs should be discontinued only in patients with renovascular disease who develop a significant increase in their serum creatinine level; these agents may need to be temporarily reduced or discontinued in patients who have excessive vasodilation. However, given their long-term beneficial effects in both heart failure and renal insufficiency, therapy with an ACEI or ARB should be continued or reinstituted whenever possible.

Nonsteroidal anti-inflammatory drugs are the most commonly used class of medications for the treatment of pain and inflammation, and represent one of the most common classes of medications used worldwide [69]. Nonselective NSAIDs inhibit both constitutive cyclooxygenase-1 (COX-1) and inducible cyclooxygenase-2 (COX-2), the rate-limiting enzymes that are involved in production of prostaglandins and thromboxane. In addition to their role in inflammation, prostaglandins are important regulators of vascular tone, salt and water balance, and renin release, and nonselective NSAIDs exhibit adverse effects, including salt retention and reduced GFR, which may elevate BP or make pre-existing hypertension worse [70]. Risk factors that predispose to NSAID-induced renal functional alterations include age more than 65 years, cardiovascular disease, diabetes, male gender, high NSAID dosage, and concurrent use of other nephrotoxic drugs [71].

Anemia management

Anemia is a frequent feature of cardiorenal patients. The clinical utility of blood transfusions in anemic cardiovascular disease is controversial, and erythropoietin treatment has been introduced as a new approach to the global care of heart failure [72]. Anemia in CHF may be responsive to an exogenous erythropoietin supplementation due to inhibition of apoptosis of bone marrow erythrocyte progenitors [73].

Silverberg et al. first reported the effect of recombinant human erythropoietin (rHuEpo) treatment on anemic patients with CHF. In an open-label study design, 26 anemic CHF patients (NYHA class III–IV and hemoglobin <12 g/dl) were treated with subcutaneous rHuEpo (mean dose, 5,277 IU/week) and intravenous iron sucrose (mean dose, 185 mcg/monthly) with mean follow-ups of 7 months' duration. The mean hemoglobin value increased from 10.2 to 12.1 g/dl and was associated with improved NYHA function class, left ventricular ejection fraction (28.5% at baseline to 35.8%), and reduced need for diuretic therapy [34]. The same investigators subsequently reported similar results in a randomized open-label trial with a mean follow-up duration of 8 months to compare the effects of partial correction of anemia (4,000 IU 1–3 times weekly subcutaneously plus intravenous iron sucrose 200 mg every 2 weeks) versus usual care in 32 patients with severe CHF and anemia (NYHA class III–IV and hemoglobin <11.5 g/dl) [74]. In a trial of rHuEpo therapy in 26 patients with advanced CHF and anemia (hematocrit <35%), the rHuEpo therapy was associated with significant increases in hemoglobin, peak oxygen uptake, and treadmill exercise duration [75].

The pharmacokinetic and pharmacodynamic profile of darbepoetin-α (a long-acting N-linked supersialylated analog of human erythropoietin with greater in vivo biologic activity than recombinant human erythropoietin) was compared in 33 anemic CHF patients (hemoglobin <12.5 g/dl) [76]. A number of small-scale studies have examined the effect of darbepoetin alfa in the treatment of anemia in CHF patients concerning various clinical outcomes [77–79]. In these studies the authors showed that, through amelioration of symptoms, darbepoetin alfa improved the quality of life with a parallel increase in exercise capacity. The 'Study of Anemia in Heart Failure Trial' (STAMINA-HeFT) is a recent, multicenter, randomized, double-blind, placebo-controlled study that evaluated the effect of treatment with darbepoetin-α on hemoglobin value, exercise tolerance, symptoms, and quality of life in 319 anemic patients with symptomatic CHF. Patients were randomized to placebo or subcutaneous darbepoetin alfa administered every 2 weeks for 1 year, with a target Hb level of 14.0. At the target range of Hb, treatment did not significantly improve exercise duration, NYHA class, or quality of life score compared with placebo, and a non-significant trend was observed towards a lower risk of all-cause mortality or first hospitalization due to heart failure in darbepoetin alfa-treated patients compared with placebo [80].

Only a few studies, mainly in predialytic chronic kidney disease, have examined this issue in patients with cardiorenal syndrome [81, 82].

Threshold and target hemoglobin concentrations for treatment initiation and treatment goals, respectively, still need to be established [83]. Erythropoietic agents are associated with increased risk of thrombosis and increased blood pressure. These side effects may be partly attributable to effects of increased hemoglobin levels on blood viscosity, platelet-erythrocyte interactions, or direct effects of erythropoietin in platelets or vascular endothelial cells [84–86]. To optimize the clinical response to erythropoietic agents, the National Kidney Foundation recommends the use of intravenous iron to maintain serum ferritin levels of 100–800 ng/ml and a transferrin saturation of 20–50% [87]. Although intravenous iron sucrose and iron gluconate preparations are not associated with anaphylaxis and are generally well tolerated, there are concerns that excess iron stores may be associated with increased risk of infection and cardiovascular events [88].

In synthesis for the patients with CHF with moderate-to-severe anemia (hemoglobin <11 g/dl) and concomitant moderate to severe chronic kidney disease (eGFR <60 ml/min), current guidelines of the National Kidney Foundation recommend treatment with erythropoietic agents and supplemental iron to a target hemoglobin of 12 g/dl [87]. The effects of treating anemia with erythropoiesis-stimulating proteins are well documented in the setting of chronic kidney disease [89, 90], and the results and findings from

initial interventional trials in heart failure patients are encouraging, although more data are required concerning the optimal threshold for initiation of treatment and target hemoglobin during therapy, the optimum dosing regimen and choice of erythropoietic agent, the role of intravenous or oral iron supplementation, and the long-term safety of erythropoietic agents in anemic patients with CHF. Publication of the results from CREATE [91] and CHOIR [92], the largest cardiovascular outcomes studies in non-dialysis CKD patients, which aimed to determine the impact of early versus late anemia correction or the degree of anemia correction, respectively, on mortality and cardiovascular morbidity in patients with CKD, generated much discussion and controversy in the field. Both tested the hypothesis that higher Hb levels would lead to improved patient outcomes; however, in contrast to expectations, the results from both studies were negative [93]. The Reduction of Events with Darbepoetin Alfa in Heart Failure (RED-HF), a randomized, double-blind, placebo-controlled study, evaluated the effect of two darbepoetin alfa dosing regimens on hemoglobin rate of rise and clinical effects in CHF patients with anemia [94]; the study is in progress and is likely to provide definitive answers.

Intrinsic renal disease management

Finally, intrinsic renal disease should be suspected if renal dysfunction persists after abnormalities in volume status, cardiac output, and systemic vascular resistance have been corrected. Typically, this is owing to nephron loss secondary to diabetes, hypertension, or renovascular disease. The presence of proteinuria usually indicates intrinsic renal disease and is associated with an increased risk for the development of chronic, progressive renal insufficiency. Depending on the degree of renal impairment, these patients may benefit from ultrafiltration or hemodialysis [1, 95–97].

Intrinsic renal disease should be taken into account in the management of ischemic heart disease patients with reduced GFR or with microalbuminuria because of the risk of contrast-induced nephropathy (CIN). Patients with normal renal function are at exceptionally low risk for CIN; on the contrary, chronic kidney disease and congestive heart failure are risk factors for its development [98, 99]. Patients with cardiorenal syndrome are, therefore at high risk for CIN, a hospital-acquired renal failure, with adverse effects on prognosis and health care costs.

Kistorp et al. [100] assessed the prognostic value of NT-proBNP, C-reactive protein (CRP), and the urinary albumin/creatinine ratio in 598 subjects aged 68 years at baseline and without left ventricular systolic dysfunction. They found that plasma NT-proBNP levels predicted the development of heart failure; in contrast there were no associations between CRP or urinary albumin/creatinine ratio and heart failure. On the other hand, Silverberg et al. [81] investigated 179 patients with severe resistant congestive heart failure, of whom 95 were non-diabetics and 84 were diabetics, and their mean serum creatinine was 2.1–2.3 mg/dl. Although mean urinary protein excretion was 1.3–1.4 g/24 h in diabetics, the same parameter was 0.5–0.6 g/24 h in non-diabetics, suggesting that proteinuria should be evaluated in all subjects with cardiorenal syndrome. Interestingly, all the patients, diabetics and non-diabetics, were being treated by cardiologists with maximally tolerated doses of ACEI, beta-blockers, and aldosterone antagonists, the same medications recommended by nephrologists for slowing renal function decline.

Conclusion

The incidence of cardiac failure and chronic renal failure is increasing, and the co-existence of the two problems carries an extremely bad prognosis. The progressive aging of the population, the extensive application of cardiac interventional procedures, and the improved prognosis of diseases with a poor outcome have generated the rising number of patients who have combined heart and kidney failure. Patients with renal dysfunction are often excluded from cardiovascular trials; in this setting, the prognosis, management, and treatment may substantially differ compared with those described in younger and less comorbid populations. Increased activity of the renin-angiotensin system, oxidative stress, inflammation, increased activity of the sympathetic nervous system, and anemia may partially explain several pathophysiological aspects of cardiorenal syndrome such as accelerated atherosclerosis, structural myocardial changes, and a further decline of renal function. Patients with cardiorenal syndrome live with a fragile homeostatic adaptation. Special attention should be paid to recognizing the presence of renal failure coexisting with heart failure with estimation of creatinine clearance. The management of this syndrome requires a good understanding of the particular hemodynamic and homeostatic conditions of the patient to be treated, and reversible complications should be foreseen and prevented. The early recognition and follow-up of complications can be detected by means of a basic physical examination, weight and blood pressure monitoring, and blood and urine urea and electrolytes measurement. There is, however, a need to develop better strategies to manage existing and prevent future renal dysfunction, including alternative methods for fluid removal and the development of renal-protective medications.

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