Current perspectives

The cardiorenal syndrome: recognition and treatment

Francesco Fedele, Leonardo De Luca, Mihai Gheorghiade*

Department of Cardiovascular and Respiratory Sciences, "La Sapienza" University, Rome, Italy,
**Division of Cardiology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA*

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The term "cardiorenal syndrome" has been applied to the presence or development of a renal dysfunction in heart failure patients. Renal function that worsens during hospitalization is a major precipitant of decompensation and cause for admissions in heart failure patients and is a more important predictor of adverse outcome than baseline renal function.

Despite growing recognition of the frequent presentation of this combined cardiac and renal dysfunction, its underlying pathophysiology has not been well described and its management remains even less well understood.

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Address:

Prof. Francesco Fedele

Dipartimento di Scienze Cardiovascolari e Respiratorie Università degli Studi "La Sapienza" Policlinico Umberto I Viale del Policlinico, 155 00161 Roma
E-mail: francesco.fedele@uniroma1.it

Introduction

Renal dysfunction is a common and progressive complication of heart failure (HF), and may be a major precipitant of decompensation and cause for admissions in HF patients.

Importantly, most patients with acute HF syndrome (AHFS) are admitted with fluid overload, very high filling pressures, but normal cardiac output. Therefore, it is likely that the relatively insidious development of congestion is related more to the renal abnormalities rather than a decrease in cardiac function. The renal hypoperfusion that occurs with cardiac injury can lead to sodium and water retention and activation of the renin-angiotensin-aldosterone (RAA) system and neurohormonal pathways with consequent deleterious effects on the myocardium. A vicious cycle may then ensue and be associated with increased cardiovascular complications. In this regard, renal dysfunction is of a functional nature and thus any means to intervene with this vicious cycle need to be sought.

Despite growing recognition of the frequent presentation of combined cardiac and renal dysfunction, or "cardiorenal syndrome," its underlying pathophysiology has not been well described and its management remains even less well understood[1].

Etiology of renal dysfunction during heart failure

The mechanisms that cause decline of kidney function are still controversial[1]. One hypothesis is that cardiac pump failure may secondarily lead to diminished renal function and thus early renal failure may only be a marker of impaired cardiac function (Table I). Alternatively, more recent evidences suggest that even mild or moderate renal dysfunction, due to long-standing hypertension or diabetes, might contribute to the pathogenesis of progression of functional cardiac deterioration.

Other causes of renal dysfunction include a very high central venous pressure[2], renal vascular disease and decreased glomerular filtration rate (GFR) induced by neurohormonal activation (Table II) or certain classes of drugs, including nonsteroidal anti-inflammatory drugs, cyclosporine, and angiotensin system blockers.

Several clinical features are more common among HF patients who develop worsening renal function: on average, they are older and have a greater prevalence of prior HF, renal dysfunction, and diabetes. Surprisingly, these patients are not more likely to have systolic dysfunction; in fact, 37 to 55% have left ventricular ejection fractions > 40%. In addition, worsening renal function does not appear to be char-

Table I. Renal hemodynamics in heart failure.

Glomerular filtration rate
Normal in early or mild heart failure
Reduced as cardiac performance becomes more severely impaired
Renal blood flow
Decreased in proportion to the decrease in cardiac performance
Renal vascular resistance
Increased with a concomitant decrease in renal blood flow
A consequence of efferent arteriolar constriction
Filtration fraction (glomerular filtration rate/renal blood flow ratio)
Usually increased

Table II. Renal effects of neurohormonal activation in heart failure.

Vasoconstrictor systems
Promote efferent > afferent arteriolar constriction
Enhance sodium and water reabsorption in proximal and distal tubules
Increase water reabsorption in the collecting duct
Co-activate other vasoconstrictor systems
Vasodilator systems
Improve/maintain glomerular filtration rate
Promote renal vasodilation
Diminish tubular sodium and water reabsorption
Inhibit vasoconstrictor systems

acterized by a "low-output state" because a greater proportion of these patients present with elevated blood pressure[3]. In contrast, the findings that accompany worsening renal function have been those of fluid retention (tachypnea, rales, and elevated jugular venous pressure)[3,4].

Effects of renal dysfunction on heart failure patient prognosis

Renal dysfunction carries a grim prognosis in patients with HF and is at least as powerful an adverse prognostic factor as most clinical variables, including ejection fraction and New York Heart Association functional class.

In a multivariate analysis from the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME-II trial)[5,6] estimated GFR was the most powerful predictor of mortality, exceeding functional status and ejection fraction. A retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial and SOLVD Prevention Trial also found that estimated GFR was an important determinant of survival[7].

Worsening renal function signifies a poorer prognosis also in patients hospitalized for an AHFS. Gottlieb et al.[4] examined outcomes in 1002 patients admitted for AHFS, including many with preserved systolic function. Any increase in creatinine levels was significant, but an increase of 0.3 mg/dl had a sensitivity of 81 and 64%, and a specificity of 62 and 65% for predicting death or a length of stay of ≥ 10 days, respectively. Similarly, in a series of 412 patients, Smith et al.[8] reported that an increase of 0.2 mg/dl of creatinine predicted a worse outcome during hospitalization. Even recent data from the ADHERE registry[9,10] have convincingly demonstrated the important role of renal dysfunction in the pathophysiology and adverse outcomes associated with hospitalization for worsening chronic HF. In fact, a classification and regression analysis from ADHERE showed that blood urea nitrogen (BUN) (at a cut-off of 43 mmHg), creatinine (at a cut-off of 2.75 mg/dl) and systolic blood pressure (at a cut-off of 115 mmHg) discriminate between low and high-risk patients. This analysis identified four subgroups of patients at low, intermediate, high and very high-risk, with an in-hospital mortality of 2, 6, 13 and 20%, respectively[9,10]. Retrospective analyses from other studies have shown that high BUN and BUN/creatinine ratio on admission are associated with a 2-fold increase in 1-year post-discharge mortality[11,12]. Even minor abnormalities in renal function were associated with increased 60-day mortality and readmission rates.

Other studies have reported this degree of worsening renal function to be associated with a 2.3-day longer length of stay[13], a 67% increased risk of death within 6 months after discharge, and a 33% increased risk for hospital readmission[8].

Treatment of heart failure patients with renal dysfunction

Unfortunately, no data from clinical trials on which to establish the treatment for patients with significant renal dysfunction are available[14], largely because these studies predominantly recruited populations with relatively preserved renal function. As a result, treatment is largely empirical.

Inotropic agents and vasodilators. Positive inotropic agents are often used in this setting to facilitate diuresis with preservation or improvement in renal function. Randomized controlled trials failed to show a benefit with the acute, intermittent, or continuous use of inodilators. Moreover, the available data suggest that stimulating contractility of hibernating myocardium with dobutamine or dopamine appears to increase short-term myocardial contractility at the expense of myocyte necrosis, and myocardial recovery[15-17]. In spite of these findings, dobutamine, dopamine and milrinone are often given to improve cardiac performance and to relieve congestive symptoms of AHFS, even in patients with normal blood pressure and relatively preserved cardiac output.

Intravenous vasodilators can improve hemodynamics, but they are less likely to improve renal function. Cardiac afterload reduction with vasodilators may enhance cardiac index[18] and thereby improve renal function, including the capacity of maintaining sodium and water balance. However, overly aggressive arterial vasodilation can cause relative arterial underfilling, and thus decrease renal perfusion pressure, in spite of a rise in cardiac index. In this regard, a decrease in renal perfusion pressure has been shown to increase tubular sodium reabsorption[19] and thus potentially can worsen the deleterious effects of volume overload in the patient with HF. Excessive arterial vasodilation to decrease cardiac afterload also will further activate the RAA and sympathetic systems.

Angiotensin-converting enzyme inhibitors. Inhibitors of the RAA system are the cornerstone of the management of patients with left ventricular systolic dysfunction, and they also prevent progressive renal dysfunction in diabetic nephropathy and other forms of chronic kidney disease. To date, there have been no efficacy studies of angiotensin-converting enzyme (ACE) inhibitors in AHFS.

Recent guidelines of the European Society of Cardiology on acute heart failure[20], stated that ACE-inhibitors are not indicated in the early stabilization of patients with AHFS (class IIb recommendation, level of evidence C). However, as these patients are at high risk, ACE-inhibitors have a role in early management of patients with AHFS and acute myocardial infarction. Importantly, the trials which selected high-risk post-infarction patients with HF found that ACE-inhibitors led to large relative and absolute reductions in mortality[21].

There is still debate on the selection of patients and the timing of initiation of ACE-inhibitor therapy.

In the presence of underlying renal disease, use of ACE-inhibitors and other RAA inhibitors may be associated with elevations in creatinine, thereby creating a therapeutic dilemma. It is still unknown if a short-term increase in creatinine levels after initiating treatment with an ACE-inhibitor is associated with long-term clinical events.

Diuretics. A considerable controversy in the management of the cardiorenal syndrome relates to the role of diuretics. Controlled outcome studies have not and could not be conducted with loop diuretics for ethical reasons. As a consequence, the absence of a controlled survival trial for diuretics has been cited as reason for concern about their safety.

Numerous studies have found that aggressive diuresis can be associated with worsening renal function, especially in the presence of ACE-inhibitors[22,23]. High diuretic doses have been associated with increased mortality rates[24-26], leading some clinicians to conclude that the diuretics are causally related to increased mortality risk. In a retrospective analysis of 6797 patients with an ejection fraction < 36% enrolled in the SOLVD trial, patients receiving a diuretic at baseline were more likely to have an arrhythmic death than those not receiving a diuretic[25]. On univariate analysis, diuretic use was associated with an increased risk of arrhythmic death[25].

An emerging paradigm in the treatment of AHFS is to minimize the use of intravenous loop diuretics. This shift is due to the recognition that the kidney plays a vital role in the prognosis of patients presenting with AHFS. As previously discussed, increases in serum creatinine or BUN are known predictors of mortality. It is also widely recognized that diuretics often worsen renal function. Thus, a working hypothesis exists to suggest that diuretics may have adverse outcomes on mortality because of their effects on renal function. Perhaps a better approach to managing these patients in order to avoid worsening renal function and activation of neurohormones is to administer low doses of vasodilators or calcium sensitizers, which may allow lower diuretic doses to be given. This strategy has not been tested in randomized controlled trials, but this research is warranted.

In such patients who present with the combination of worsening renal function, volume overload, and diuretic refractoriness, the management of cardiorenal dysfunction is extremely challenging, and effective therapies are lacking[27].

Natriuretic peptides. In the absence of an effective therapy for patients with cardiorenal dysfunction, recent attention has focused on treatment with natriuretic peptides[28].

Wang et al.[29] studied 15 patients with a recent mean baseline creatinine of 1.5 ± 0.4 mg/dl and serum creatinine of 1.8 ± 0.8 mg/dl on admission and examined the effects of nesiritide on GFR, renal plasma flow, urinary sodium excretion, and urine output in a double-blind, placebo-controlled, crossover study. Patients received nesiritide (2 μg/kg intravenous bolus followed by an infusion of 0.01 μg/kg/min) or placebo for 24 hours on consecutive days to the study. There were no differences in GFR, effective renal plasma flow, urine output, or sodium excretion for any time interval or for the entire 24-hour period between the nesiritide and placebo study days. For 24 hours, urine output was 113 ± 51 ml/hour with placebo and 110 ± 56 ml/hour with nesiritide. GFR during placebo was 40.9 ± 25.9 ml/min and with nesiritide was 40.9 ± 25.8 ml/min[29].

Recently, Sackner-Bernstein et al.[30] determined the frequency of worsening renal function (defined as an increase in serum creatinine > 0.5 mg/dl) from five randomized studies comparing nesiritide with either placebo or active control for AHFS. Use of standard or low doses of nesiritide significantly increased the risk of worsening renal function compared with non-inotrope-based control or any control therapy, including non-inotrope- and inotrope-based therapies[30]. The same authors also analyzed the data from three randomized double-blind studies of patients with AHFS, evaluating

nesiritide and reporting 30-day mortality[31]. Compared with non-inotrope-based control therapy, nesiritide has been associated with an increased risk of short-term death after treatment for AHFS[31]. These findings raised the need for a large-scale, adequately powered, controlled trial before routine use of nesiritide for AHFS patients.

An ongoing randomized, placebo-controlled trial of nesiritide, administered as once or twice weekly at 4-hour infusions (Follow-Up Serial Infusions of Nesiritide-II [FUSION-II]), is evaluating the effect of this treatment in high-risk patients, including many with cardiorenal dysfunction, on the risk of death and repeat hospitalization.

Future treatments. Potentially promising pharmacological approaches include selective adenosine A_1 receptor blockers, which have a variety of effects on intrarenal hemodynamics and tubular function[32], vasopressin antagonists[33], which have shown promising results in animal studies and small-scale clinical trials, and new inodilators therapies, such as levosimendan.

Other interventions include the earlier use of dialysis and ultrafiltration and, ultimately, left ventricular assist devices to manage these patients effectively, at least in the short term.

Conclusions

The cardiorenal syndrome represents an ominous and frequent development in the natural history of HF and is recognized as a major long-term prognostic factor. The underlying mechanisms whereby even mild deterioration of renal function has been associated with a major cardiovascular risk are unknown.

The interaction between the heart and the kidney will be a major focus of new therapeutic development. It is hoped that new and effective therapies will be identified for the treatment and prevention of this challenging syndrome.

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