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The Clinical Challenge of Cardiorenal Syndrome

Michael G. Shlipak, MD, MPH; Barry M. Massie, MD

Renal dysfunction is a common and progressive complication of chronic heart failure, with a clinical course that typically fluctuates with the patient's clinical status and treatment. Despite growing recognition of the frequent presentation of combined cardiac and renal dysfunction, or "cardiorenal syndrome," its underlying pathophysiology is not well understood, and no consensus as to its appropriate management has been achieved. Because patients with heart failure are surviving longer and dying less frequently from primary arrhythmia, we expect that the cardiorenal syndrome will become more common. Against this background, the article by Wang and colleagues¹ in the present issue of *Circulation* is particularly significant because it is the first prospective, controlled therapeutic trial in patients with this condition. To place the findings and implications of this study in context, we first briefly review what is currently known about the cardiorenal syndrome and its treatment options.

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Characteristics and Outcomes of Patients With Cardiorenal Dysfunction

In ambulatory heart failure patients, the presence of concomitant renal dysfunction consistently has been one of the strongest risk factors for mortality.²⁻⁴ This risk becomes evident even at serum creatinine clearance levels >1.3 mg/dL and estimated creatinine clearance values ≤ 60 to 70 mL/min. Furthermore, renal function is at least as powerful an adverse prognostic factor as most clinical variables, including ejection fraction and New York Heart Association function class. Although renal dysfunction predicts all-cause mortality, it is most predictive of death from progressive heart failure, which suggests that it is a manifestation of and/or exacerbating factor for left ventricular dysfunction.²

In the setting of hospitalization for decompensated heart failure, worsening renal function is even more important than baseline renal function for predicting adverse outcomes.⁵⁻⁸ Although any increase in creatinine is associated with poorer

survival rates, longer hospitalization, and more frequent readmission, several studies have used a threshold of a 0.3-mg/dL (26.5-mmol/L) rise in serum creatinine over baseline to define this phenomenon. Changes of this magnitude generally occur in 25% to 45% of patients admitted for heart failure (dependent primarily on whether the cutpoint is defined as >0.3 versus ≥ 0.3).⁴⁻⁷ Such patients are more likely to require management in an intensive care unit and aggressive treatment with intravenous vasodilators or positive inotropic agents. Patients with this syndrome experience high rates of morbidity and mortality, and clinicians frequently become frustrated by their inability to improve the patient's clinical status. In one multicenter cohort study, a creatinine increase of ≥ 0.3 mg/dL had a sensitivity of 65% and specificity of 81% for predicting in-hospital mortality.⁷ Other studies have reported this degree of worsening renal function to be associated with a 2.3-day longer length of stay,⁵ a 67% increased risk of death within 6 months after discharge, and a 33% increased risk for hospital readmission.⁸

Among heart failure patients, several clinical features are more common in those who develop worsening renal function: On average, they are older and have a greater prevalence of prior heart failure, renal dysfunction, diabetes, and hypertension. Somewhat surprisingly, they are not more likely to have systolic dysfunction; in fact, 37% to 55% have left ventricular ejection fractions $\geq 40\%$. In addition, worsening renal function does not appear to be characterized by a "low-output state" because a greater proportion of these patients present with elevated blood pressure (39% with systolic pressure ≥ 160 mm Hg versus 30% without worsening renal function)⁶ and fewer complained of fatigue (21% versus 28%).⁶ In contrast, the findings that accompany worsening renal function have been those of fluid retention (tachypnea, rales, and elevated jugular venous pressure).^{6,7}

Treatment of Patients With Cardiorenal Dysfunction

Unfortunately, we have no evidence from clinical heart failure trials on which to base our therapy for patients with significant renal dysfunction,⁹ largely because these studies predominantly recruited populations with relatively preserved renal function. As a result, treatment is largely empirical. Inhibitors of the renin-angiotensin-aldosterone system are the cornerstone of our 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. Unfortunately, in the presence of underlying renal disease, use of angiotensin-converting enzyme (ACE) inhibitors and other renin-angiotensin-aldosterone inhibitors may be associated with elevations in creatinine, thereby creating a therapeutic dilemma. Although physicians frequently avoid or discontinue these medications

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for fear of exacerbating renal function,¹⁰ the rise in creatinine levels after the initiation of an ACE inhibitor actually may identify a subgroup of patients who will achieve the greatest benefit from their use.¹¹ Furthermore, discontinuation of ACE inhibitors because of renal dysfunction identified a patient group with a high mortality risk (57% over an 8.5-month period in one study).¹² Therefore, a sensible approach is to continue these agents despite a rise in creatinine, as long as renal dysfunction does not steadily deteriorate and severe hyperkalemia does not develop. Consider the diagnosis of renal artery stenosis in patients who are extremely intolerant to ACE inhibitors.

A considerable controversy in the management of the cardiorenal syndrome relates to the role of diuretics. Numerous studies have found that aggressive diuresis can be associated with worsening renal function, especially in the presence of ACE inhibitors.^{13,14} High diuretic doses have been associated with increased mortality rates,^{15–17} leading some clinicians to conclude that the diuretics are causally related to increased mortality risk. A more likely explanation is that diuretic resistance and concomitant worsening renal dysfunction necessitate high doses of diuretics, which are a marker rather than a mechanism for poor outcomes. In any case, ongoing volume overload is poorly tolerated and a frequent cause of hospital admission in patients with heart failure. The absence of a controlled survival trial for diuretics has been cited as reason for concern about their safety; however, this absence of evidence is not an appropriate justification for inadequate treatment of volume-overloaded patients.

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.¹⁸ In some cases, achieving effective diuresis with aggressive measures (eg, continuous infusions of loop diuretics or combinations of loop diuretics and thiazides) actually will improve renal function. More often, positive inotropic agents (including dobutamine, phosphodiesterase inhibitors, and where available, levosimendan) are used in this setting to facilitate a diuresis with preservation or improvement in renal function. Although dopamine also is used because of its presumed ability to improve renal blood flow, this effect is severely limited in advanced heart failure.¹⁹ Intravenous vasodilators can improve hemodynamics, but they are less likely to improve renal function.

Is Nesiritide Effective in Patients With Cardiorenal Dysfunction?

In the absence of an effective therapy for patients with cardiorenal dysfunction, recent attention has focused on treatment with natriuretic peptides because they appear to play a beneficial role in mediating the interactions between the heart and the kidney in chronic heart failure, at least in some models and clinical settings. In patients with heart failure, nesiritide induces vasodilatation, with resultant reductions in blood pressure and cardiac filling pressures and increases in cardiac output. These hemodynamic effects are accompanied by natriuresis and diuresis, although the latter

responses may be quantitatively smaller than in normal subjects and appear to be blunted in patients with more severe heart failure.^{20,21} Moreover, creatinine clearance was not improved by nesiritide, even in patients who exhibited natriuresis and diuresis.²⁰

Several larger nesiritide clinical trials confirmed the earlier hemodynamic results and also showed evidence of symptomatic improvement. In a 6-hour, randomized, double-blind, placebo-controlled trial in which diuretics and other intravenous therapies were withheld, nesiritide produced hemodynamic and symptomatic improvement and significantly higher urinary output.²² When nesiritide was compared with physician-selected intravenous inotropic or vasodilator therapy, comparable improvement in symptoms and urinary output was observed, although there was somewhat less diuretic use in the nesiritide-treated patients.²² In the pivotal Vasodilator in the Management of Acute CHF (VMAC) trial, nesiritide was compared with intravenous nitroglycerin, with comparable clinical improvement over a 24-hour infusion period but with less diuretic use observed in the nesiritide group (85% versus 94% of patients).²³ A subsequent analysis of the nesiritide-treated patients in VMAC compared 60 patients with a baseline serum creatinine ≥ 2.0 with 209 patients with lower creatinine values and suggested that the improvements in hemodynamics and symptoms were comparable.²⁴ However, that trial did not evaluate renal hemodynamics or excretory function, so it did not shed light on the renal effects of nesiritide.

Thus, the study by Wang et al¹ is the first to address renal effects of nesiritide in patients with demonstrated cardiorenal dysfunction. The authors tested the hypothesis that nesiritide has beneficial effects on glomerular filtration rate and renal plasma flow by standard techniques as well as by urine output and sodium excretion in heart failure patients hospitalized with worsened renal function. They designed and implemented a crossover clinical trial in which 15 participants received a 24-hour infusion of nesiritide according to the recommended bolus and infusion regimen and a 24-hour infusion of placebo on consecutive days, but in random order. Renal function parameters were monitored throughout the 48-hour study period, and diuretic dose was held constant unless a change was required clinically. The primary finding of this trial was that, compared with the placebo infusion, nesiritide had no effect on glomerular filtration rate, renal plasma flow, urine output, and sodium excretion.

How do the negative findings of this study by Wang and colleagues inform us about the clinical role of nesiritide in heart failure patients with worsened renal function? The first possibility to consider is that the negative finding of this study could be a type II error, so that the study may have failed to detect a difference between nesiritide and placebo because of its small sample size and the wide variability of its outcome measures. However, the similarity of mean values of each renal measurement during nesiritide and placebo infusion makes this explanation relatively unlikely. Another possibility is that nesiritide's hemodynamic and clinical effects are blunted in the presence of worsening renal function, perhaps as a result of their decreased renal perfusion or extreme sodium avidity and resistance to diuretics. Argu-

ing against this conclusion is the previously discussed subgroup analysis from the VMAC trial that found nesiritide to have similar efficacy compared with placebo among participants with and without renal dysfunction.²⁴ Alternatively, nesiritide might lead to symptom improvement in heart failure patients with worsened renal function but have no effect on renal function. This explanation is consistent with the previous study in which no effect was observed on creatinine clearance,²⁰ but the lack of difference in urine volume in the study by Wang et al¹ despite the identical use of diuretics differs from the earlier observations in which either urine output was higher than on placebo or diuretic doses were lower.^{22,23}

In any case, the findings in the Wang et al¹ study do not support the hypothesis that nesiritide improves or protects renal function in patients with the cardiorenal syndrome, but they also do not exclude a role for this agent in treating heart failure symptoms or improving clinical outcomes in this population. Indeed, an ongoing randomized, placebo-controlled trial of nesiritide, administered as once- or twice-weekly 4-hour infusions (Follow-Up Serial Infusions of Nesiritide-II [FUSION-II]) is underway that is evaluating the effect of this treatment approach in high-risk patients, including many with cardiorenal dysfunction, on the risk of death and repeat hospitalization. Notably, this trial incorporates serial measurements of renal function.

Future Directions in the Study and Treatment of Cardiorenal Dysfunction

As this brief review clearly demonstrates, the cardiorenal syndrome represents an ominous and frequent development in the natural history of chronic heart failure. Our understanding of the underlying mechanisms remains rudimentary, and we lack effective therapies. However, this problem has gained the attention of investigators, industry, and authorities responsible for setting research priorities, as indicated by the convening of a Working Group on Cardio-Renal Connections in Heart Failure by the National Heart, Lung and Blood Institute in August 2004. Potentially promising pharmacological approaches include selective adenosine A₁ receptor blockers, which have a variety of effects on intrarenal hemodynamics and tubular function,²⁵ and vasopressin antagonists.²⁶ 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. These are drastic interventions, but currently few other options are available. The clinical challenges of the cardiorenal syndrome likely will worsen before they get better; as a byproduct of our success in improving survival in heart failure, growing numbers of patients will survive to reach the true end stage of heart failure—cardiorenal dysfunction. It is hoped that new and effective therapies will be identified for the treatment and prevention of this challenging syndrome.

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KEY WORDS: Editorials ■ heart failure ■ kidney ■ natriuretic peptides ■ vasodilation