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# Addressing the challenges of cardiorenal syndrome

## ■ ABSTRACT

In heart failure, as the heart gets worse, often so do the kidneys, complicating the treatment of heart failure and worsening the prognosis. This article addresses challenges in the use of diuretics, angiotensin-converting enzyme (ACE) inhibitors, and other therapies in the cardiorenal syndrome, as well as novel therapies that hold promise, such as arginine vasopressin antagonists, adenosine A<sub>1</sub> receptor antagonists, and ultrafiltration.

## ■ KEY POINTS

In clinical studies, up to 30% of patients with heart failure had worsening renal function, which was associated with longer hospital stays, higher hospital costs, higher in-hospital mortality rates, and more readmissions.

Use of ACE inhibitors among patients with renal insufficiency should be approached cautiously. Patients should be started on the lowest dose while they are volume-replete, and they should avoid nonsteroidal anti-inflammatory drugs.

If a patient has an inadequate response to a loop diuretic, one should establish the single effective dose that exceeds the threshold rate of drug excretion. Some patients with severe heart failure may initially require intravenous diuretic therapy.

**C**ARDIORENAL SYNDROME—the spiral of worsening heart failure and kidney failure that leads to diuretic resistance, volume overload, and further worsening of heart failure—is only beginning to receive the attention it deserves. We still have no answers to basic questions such as:

- What is the true incidence? Lacking a standard definition, we can only say it is common.
- What causes it? Reduced cardiac output—the intuitive answer—does not in fact explain the worsening renal failure.
- How should it be managed? Treatment is largely empiric. Diuretic therapy relieves symptoms of fluid overload but may be associated with worse outcomes.
- What determines prognosis? Although renal function may remain stable at a diminished level in heart failure patients, in many it eventually leads to worsening end-organ damage, resistance to standard therapy, frequent hospitalizations, exacerbation of symptoms, inability to maintain a good quality of life, and, eventually, death.

In this review, we describe the prevalence, prognostic factors, pathophysiology, and treatment of cardiorenal syndrome. We outline suggestions for clinicians on how to use existing therapies, including angiotensin-converting enzyme (ACE) inhibitors and diuretics, and we address the controversial role of nesiritide. We also discuss exciting new data on novel therapies including arginine vasopressin receptor antagonists (the “vaptans”), adenosine A<sub>1</sub> receptor antagonists, and ultrafiltration.

## ■ TRUE PREVALENCE UNKNOWN

Thanks to improved treatment, patients with heart failure are living longer and with a better

quality of life. As they live longer, however, they are more likely to experience long-term effects of prolonged cardiac dysfunction, such as progressive renal insufficiency.

The term “cardiorenal syndrome” implies concomitant cardiac and renal failure with volume overload in which patients become resistant to diuretic therapy, but there is no uniform definition, so we cannot extrapolate its true prevalence from the literature.

That said, approximately one third to one half of patients with heart failure develop renal insufficiency,<sup>1</sup> defined by the National Kidney Foundation<sup>2</sup> as a glomerular filtration rate (GFR) of less than 60 mL/minute/1.73 m<sup>2</sup>.

Patients with cardiorenal syndrome were excluded from most studies of heart failure treatment. However, many studies in patients with advanced heart failure with New York Heart Association class III or IV symptoms did provide data about worsening renal function.

The Evaluation of Losartan in the Elderly (ELITE) study<sup>3</sup> compared the effects of captopril (an ACE inhibitor) vs losartan (an angiotensin-receptor blocker) in older patients with heart failure. Worsening renal function (defined as a rise in serum creatinine of 0.3 mg/dL or more) occurred in 29.7% of captopril recipients and in 26.1% of losartan recipients.

Similarly, Forman et al<sup>4</sup> found that renal function worsened in 27% of patients hospitalized for heart failure.

#### ■ PREDICTORS OF RENAL FAILURE

Several studies identified risk factors for renal impairment in patients with advanced heart failure.

In the Studies of Left Ventricular Dysfunction (SOLVD),<sup>5</sup> factors that correlated with worsening renal function (defined as a rise in serum creatinine of 0.3 mg/dL) were:

- Old age
- Low ejection fraction
- Elevated baseline creatinine level
- Low systolic blood pressure
- Diabetes mellitus
- Hypertension
- Use of antiplatelet therapy, diuretics, or beta-blockers.

Some intriguing data suggest that calcium

channel blockers and loop diuretics, but not ACE inhibitors, are associated with a higher risk of worsening renal function in patients with heart failure.<sup>5</sup>

#### ■ THE PATHOPHYSIOLOGY IS NOT WELL UNDERSTOOD

Little is understood about the pathophysiology of the cardiorenal syndrome.

Interestingly, worsening renal function had no correlation with ejection fraction in some studies.<sup>4,6,7</sup> This finding runs counter to the intuitive notion that a low ejection fraction (and in turn, possibly lower cardiac output) would contribute to renal hypoperfusion and subsequently exacerbate renal dysfunction. Similarly, the degree of diuresis and the change in weight were not related to the development of worsening renal function among hospitalized heart failure patients.<sup>6</sup>

These observations suggest that the pathophysiology of renal dysfunction is much more complex than simply reduced cardiac output. Vascular factors such as nitric oxide, prostaglandin, natriuretic peptides, and endothelin may mediate renal perfusion independently of cardiac hemodynamics.<sup>4</sup>

The heart, kidneys, renin-angiotensin system, sympathetic nervous system, endothelium, and immune system often interact through intricate feedback loops. An imbalance in this complex system will often cause deterioration in both cardiac and renal function.<sup>8</sup> If cardiac output and mean arterial pressure fall, so does renal blood flow, activating the renin-angiotensin system, reducing nitric oxide in the endothelium, activating the sympathetic nervous system, and inducing inflammatory mediators, all of which, in a vicious circle, cause structural and functional damage to the kidneys and heart.

Recently, researchers have been focusing on the role of inflammatory markers as links between cardiovascular and kidney disease. C-reactive protein (CRP), an acute-phase reactant that is believed to play a crucial role in the pathophysiology of atherosclerosis, is found in high levels during end-stage renal failure.<sup>9</sup> It is likely that CRP and many other inflammatory mediators play a synergistic role in progression of both renal and cardiovascular disease.

**1/3 to 1/2 of patients with heart failure develop renal insufficiency**



Other nontraditional factors, such as hyperhomocysteinemia, oxidant stress, and dyslipidemia, are associated with atherosclerosis and may be important mediators in the development of cardiac and renal disease.<sup>10</sup>

Although these theories and models are plausible mechanisms for the cardiorenal syndrome, the exact mechanism for its development is not fully understood.

### ■ RENAL DISEASE PREDICTS POOR OUTCOMES

Renal insufficiency significantly increases the risk of death and thus is an important prognostic indicator in heart failure patients.<sup>6</sup>

Forman et al<sup>4</sup> found that patients whose renal function worsened while in the hospital had longer stays, incurred higher hospital costs, were more likely to die in the hospital, and, if they survived the hospitalization, were more likely to be readmitted.

In SOLVD, patients with a GFR lower than 60 mL/minute/1.73 m<sup>2</sup> had a 40% higher risk of death.<sup>11</sup>

Hillege et al<sup>12</sup> reported in the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME-2) that patients with GFRs in the lowest quartile (< 44 mL/minute) had almost a three times higher risk of mortality than those in the highest quartile (GFR > 76; relative risk 2.85, *P* < .0001). Impaired renal function was a stronger predictor of death in these patients with heart failure than a low ejection fraction.

In the Prospective Randomized Amlodipine Survival Evaluation (PRAISE),<sup>13</sup> patients with diuretic resistance and cardiorenal syndrome had an increased risk of death, sudden death, and pump failure (adjusted hazard ratios 1.37 [*P* = .004], 1.39 [*P* = .042], and 1.51 [*P* = .034], respectively). Compared with patients with no renal insufficiency or heart failure, those with either have a twofold higher risk of death at 2 years, which quadruples if both are present.

#### Estimate the GFR at baseline

We believe that physicians should estimate the GFR as part of the initial evaluation to establish a baseline value, both to get a gener-

al sense of prognosis and to help in medical planning (eg, for planning the doses of ACE inhibitors and aldosterone antagonists and for estimating the risk of contrast exposure during radiographic procedures). Thereafter, the GFR can be estimated whenever there has been a consistent, clinically meaningful worsening in serum creatinine levels.

Since measuring the true GFR is cumbersome and the serum creatinine level is relatively insensitive, the GFR is commonly estimated using either the Cockcroft-Gault equation or the Modified Diet in Renal Disease (MDRD) equation. (Calculators for both equations can be found at [www.nephron.com](http://www.nephron.com).)

The National Kidney Foundation<sup>2</sup> classifies renal insufficiency as follows:

- Mild—GFR 60 to 89 mL/minute/1.73 m<sup>2</sup>
- Moderate—30 to 59
- Severe—15 to 29
- End-stage renal failure—less than 15.

### ■ TREATMENT REMAINS A CHALLENGE

Medical management of patients with concomitant heart failure and renal failure remains a tremendous challenge. The burden is exacerbated because most of the evidence for treating heart failure comes from clinical trials that excluded patients with significant renal impairment.<sup>1</sup>

#### ACE inhibitors should be used, but cautiously

ACE inhibitors are known to increase the survival rate in patients with heart failure. However, these drugs should be used cautiously in patients with renal insufficiency. Many trials that confirmed the benefits of ACE inhibitors, such as SOLVD,<sup>14</sup> excluded patients with serum creatinine concentrations greater than 2.0 mg/dL.

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),<sup>15</sup> in patients with severe heart failure, included patients with renal impairment, but only if their serum creatinine concentrations were no higher than 3.4 mg/dL. Although only a minority of patients in CONSENSUS had creatinine levels greater than 2.0 mg/dL, this subgroup showed evidence of improved outcomes when treated with an ACE inhibitor.

**The cause of renal failure in heart failure is more complex than just reduced cardiac output**

CONSENSUS also showed that patients with the most severe heart failure had a substantial increase in creatinine (> 30%) when an ACE inhibitor was added to their regimen, independent of their baseline renal function, although few patients needed to stop therapy. In most of the patients in whom the ACE inhibitor was stopped, the creatinine level returned to baseline.

To reduce the incidence of renal dysfunction, patients should be started on the lowest dose of an ACE inhibitor when the patient is judged not to be dehydrated. Nonsteroidal anti-inflammatory drugs should be avoided.<sup>1</sup>

However, ACE inhibitor therapy in patients with baseline renal insufficiency is associated with significant long-term benefits,<sup>16</sup> and unless contraindicated, should be routinely used.

Most patients who are already on an ACE inhibitor who develop renal insufficiency during hospitalization for heart failure decompensation should not have their ACE inhibitor stopped. ACE inhibitors are not associated with worsening renal function in these patients in general.<sup>6</sup> However, clinical judgment needs to be exercised for extreme clinical situations, eg, patients in cardiogenic shock or acute renal failure.

#### Diuretic therapy is controversial

The role of diuretic therapy in cardiorenal syndrome is controversial. Several studies found that higher doses of diuretics were independently associated with death, sudden death, and pump failure.<sup>6,13</sup> Although this relationship persists after controlling for other confounding variables, whether it is related to diuretic use per se or to higher diuretic doses being used in sicker patients is still difficult to judge.

Because diuretic therapy can worsen renal function, and worsening renal function is associated with poorer outcomes,<sup>17</sup> diuretic resistance can be considered another indicator of poor prognosis in patients with chronic heart failure. However, in the absence of definitive data, patients in a volume-overloaded state should not be restricted from receiving loop or thiazide diuretics as necessary to alleviate symptoms.

#### Treatment of diuretic resistance

Persistent fluid retention in patients with heart failure is problematic.

Multiple factors may account for diuretic resistance, including inadequate diuretic dose, excess sodium intake, delayed intestinal absorption of oral drugs, decreased diuretic excretion into the urine, and increased sodium reabsorption at sites in the nephron that are not sensitive to diuretics.<sup>18–22</sup> Nonsteroidal anti-inflammatory drugs are another culprit, since diminished synthesis of vasodilator and natriuretic prostaglandins can impair diuretic responsiveness.<sup>21</sup>

When deciding the diuretic dose in patients with refractory edema, one should consider several factors:

- The single effective dose should be determined. Diuretics do not have a smooth dose-response curve: no natriuresis occurs until a threshold rate of drug excretion is attained. Thus, a patient who does not respond to 20 mg of furosemide may not be exceeding this threshold, and the dose should be increased to 40 mg rather than giving the same dose twice a day.
- A high sodium intake can prevent net fluid loss even though adequate diuresis is being achieved.
- Some patients with severe heart failure may initially need intravenous diuretic therapy because decreased intestinal perfusion, reduced intestinal motility, and perhaps mucosal edema may substantially slow the rate of drug absorption and therefore the rate of drug delivery to the nephron.<sup>22</sup> Also, decreased renal perfusion and competitive inhibition of tubular secretion in renal failure may contribute to diuretic unresponsiveness.
- Impaired efficiency of secretion is treated by raising the plasma diuretic level, and therefore the rate of urinary excretion, by increasing the diuretic dose to the maximum effective dose—the dose at which transport of sodium chloride in the loop of Henle is presumably completely inhibited. High-dose intravenous therapy should be given slowly, over 30 to 60 minutes, to minimize the risk of ototoxicity.<sup>23–26</sup>

Inadequate response to oral diuretics is often reversible once the acute volume overload is resolved, and many patients can return to oral therapy.

### The role of diuretic therapy in cardiorenal syndrome is controversial



### **Raise the oral furosemide dose, or switch to bumetanide or torsemide**

In general, a patient who is resistant to oral furosemide is not likely to respond to a similar dose of another loop diuretic. However, these drugs do have differences in bioavailability. Only about 50% of oral furosemide is absorbed in edematous states, and some patients absorb much less. In this setting, apparent resistance to seemingly adequate doses of oral furosemide may be overcome by increasing the dose or by switching to oral bumetanide or torsemide, agents that are much more completely absorbed.

### **Add salt-poor albumin to intravenous furosemide?**

Some patients with low serum albumin levels may be resistant to diuretic therapy. Data suggest that these patients might respond to furosemide if salt-poor albumin is added to the infusion. The resulting furosemide-albumin complex is believed to deliver more diuretic to the kidney, primarily by staying in the vascular space.

In one study,<sup>27</sup> adding salt-poor albumin substantially increased sodium excretion. However, another study,<sup>28</sup> in patients with nephrotic syndrome, found that combination therapy resulted in only a modest increase in sodium excretion compared with furosemide alone. This increase in excretion was approximately the same as the amount of sodium contained in the colloid solution, and therefore volume expansion may have actually resulted in the enhanced natriuresis.

### **Bolus diuretic injections or constant infusion?**

An alternative to giving bolus injections of loop diuretics in diuretic-refractory patients is to give them by continuous intravenous infusion. A constant infusion maintains an optimal rate of drug delivery to the renal tubules and in turn inhibits sodium reabsorption more consistently.

A Cochrane review<sup>29</sup> looked at eight trials comparing continuous infusion of a loop diuretic with bolus injections in 254 patients with heart failure. Urine output was modestly higher (271 mL/24 hours) and the incidence of ototoxicity was less with continuous infu-

sions. The overall data, however, were insufficient to confidently recommend one approach as superior to the other.

### **Thiazide plus loop diuretic**

Another option is to inhibit sodium reabsorption at multiple sites within the nephron by concurrently giving a thiazide diuretic to block distal reabsorption. Combination therapy requires careful monitoring, as it may lead to excessive sodium and potassium losses.<sup>30</sup>

### **Low-dose dopamine: Data are sparse**

The common clinical wisdom is to give dopamine in low (“renal”) doses by infusion. Though this therapy is commonly used in conjunction with diuretic therapy, efficacy data are sparse, with most studies showing no benefit.<sup>31</sup>

### **Inotropes: For short-term therapy in low-output states**

If the worsening renal function is thought to be related primarily to low cardiac output and decreased renal perfusion, a trial of inotropic therapy with dobutamine or milrinone may be considered. However, these agents should be given only for low cardiac output states for a short term in monitored settings, as they may exacerbate the risk of arrhythmias.

### **Nesiritide’s role must be further defined**

B-type natriuretic peptide (BNP) is synthesized in the ventricular myocardium in response to stretching and overloading. BNP dilates arteries and veins, enhances sodium excretion, and suppresses the renin-angiotensin system. Nesiritide, a synthetic BNP, has been used in heart failure to reduce preload and afterload, to cause natriuresis and diuresis, and to suppress norepinephrine, endothelin-1, and aldosterone.

The Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial<sup>32</sup> assessed the impact of early nesiritide infusion on symptoms and pulmonary pressures in patients with decompensated heart failure. A total of 489 patients with renal insufficiency received either nesiritide or nitroglycerin. At 24 hours, 83% of the patients with renal insufficiency and 91% of patients without renal insufficiency who were

**Give high intravenous doses of diuretic slowly to minimize ototoxicity**



treated with nesiritide reported improvements in dyspnea.<sup>33</sup>

Although nesiritide was effective in patients with renal insufficiency in this analysis, some recent data suggest that it might actually increase the risk of renal insufficiency in heart failure patients. To further understand its role and its safety, especially in the outpatient setting, further studies are being conducted with intermittent nesiritide infusion to investigate its effects on mortality, hospitalizations, and renal function in heart failure patients.<sup>34</sup>

#### ■ TRANSPLANTATION, LVADs USUALLY NOT OPTIONS

Patients with cardiorenal syndrome are usually not candidates for advanced heart failure therapies such as cardiac transplantation or implantation of a left ventricular assist device (LVAD), owing to their high surgical risks and poor prognosis. Current criteria for transplantation include a substantial reduction in exercise capacity (peak exercise oxygen consumption < 14 mL/minute/kg) combined with an ejection fraction lower than 25% and no contraindications such as irreversible renal insufficiency. The criteria for LVAD placement are even stricter, and require that patients be dependent on inotropes.

#### ■ PROMISING FUTURE APPROACHES

##### Arginine vasopressin receptor antagonists

Arginine vasopressin (AVP) is secreted from the pituitary gland, and its effects are mediated by three types of receptors: V<sub>1A</sub>, V<sub>1B</sub>, and V<sub>2</sub>. V<sub>2</sub> receptors are located in the renal distal tubules and the collecting duct.<sup>35</sup> When AVP binds to the V<sub>2</sub> receptors, intracellular levels of cyclic adenosine monophosphate increase; this molecule acts as a second messenger in the translocation of vesicles containing the water channel aquaporin-2 and in increasing the transcription of aquaporin-2. AVP-regulated aquaporin-2 activity determines the water permeability of the collecting duct and is associated with decreased diuresis.<sup>36</sup>

In heart failure, secretion of AVP may be increased because of low blood pressure or diminished arterial volume. Excess AVP can also lead to hyponatremia.

V<sub>2</sub> receptor antagonists (“vaptans,” eg, conivaptan and tolvaptan) result in diuresis and retention of electrolytes. These agents are currently under investigation.

##### Adenosine A<sub>1</sub> receptor antagonists

The elevated plasma adenosine levels observed in patients with heart failure can contribute to renal dysfunction. A<sub>1</sub> adenosine receptor antagonists are therefore emerging as a therapeutic option. Adenosine can lower cortical blood flow, resulting in antinatriuretic responses.<sup>18</sup> A<sub>1</sub> receptor antagonists have been shown to cause diuresis and natriuresis while minimally affecting potassium excretion or glomerular filtration. These agents are currently under investigation.

##### Ultrafiltration

Another potential therapy in patients with diuretic resistance is to use ultrafiltration to alleviate volume overload.

Renal replacement therapy (ultrafiltration or dialysis) improves renal responsiveness and cardiac hemodynamics, but is usually used palliative in the end stages of cardiorenal syndrome and does not provide a long-term solution.<sup>37</sup> These patients often continue to retain fluid, and giving them larger doses of diuretics poses the clinical dilemma of potentially improving symptoms at the cost of further worsening the already compromised renal function. Ultrafiltration may, however, be more beneficial if used earlier.

In one study,<sup>38</sup> 21 patients in a volume-overloaded state had peripheral catheters placed with a disposable circuit, which allowed the removal of 1 L of fluid during an 8-hour treatment. The incidence rates of orthopnea, rales, and peripheral edema were decreased after the treatment.

The Ultrafiltration Versus IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial compared the use of intravenous diuretics and ultrafiltration in 200 patients hospitalized for decompensated heart failure. Preliminary data were presented at the 2005 American College of Cardiology meeting, March 11–14, Atlanta GA, and indicated that patients randomly assigned to receive ultrafiltration lost more weight and, at 90 days, had a lower rate of rehospitalization.

**Under investigation: vaptans, adenosine A<sub>1</sub> receptor antagonists, ultrafiltration**



Although the long-term impact and feasibility of ultrafiltration in a clinical setting is still uncertain, it offers an exciting possibility for the management of patients with heart failure and renal insufficiency.

### Giving hypertonic saline with diuretics

Optimizing diuresis with the simultaneous use of hypertonic saline with diuretics has been studied and found successful at relieving signs and symptoms of congestion.<sup>39–40</sup>

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