The Cardiorenal Connection in Heart Failure

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Heart failure (HF) and renal dysfunction frequently coexist; this combination is commonly referred to as the "cardiorenal syndrome." The intersection of cardiac and renal dysfunction has important therapeutic and prognostic implications in patients with HF. Approximately 60% to 80% of patients hospitalized for HF have at least stage III renal dysfunction; this comorbid renal insufficiency (RI) is associated with significantly increased morbidity and mortality risk. Comorbid RI can result from intrinsic renal disease and inadequate renal perfusion. HF and RI stimulate neurohormonal activation, increasing preload and afterload and reducing cardiac output. Inotropic agents augment this neurohormonal activation. Managing cardiorenal patients requires successful negotiation of the delicate balance between adequate volume reduction and adequate renal function. There is a compelling need for additional studies in this patient population.

Introduction

Heart failure (HF) and renal insufficiency (RI) are increasingly common and frequently coexist in the same patient [1•–3•]. This combination, often called the "cardiorenal syndrome," has important therapeutic and prognostic implications for patients with HF. Much of the challenge of achieving successful HF disease management lies in managing fluid overload while avoiding the worsening of renal function.

The cardiorenal syndrome is receiving significant attention from researchers, government agencies, and the pharmaceutical/device industry [4]. In 2004, the National Heart, Lung, and Blood Institute (NHLBI) convened a working group to "evaluate the current state of knowledge regarding interactions between the cardiovascular system and the kidney, to identify critical gaps in our knowledge, understanding, and application of research tools, and to develop specific recommendations for NHLBI in cardiorenal interactions related to heart failure" [4]. Although intense focus has been placed on the syndrome, a clear definition of cardiorenal syndrome had not been developed. Several definitions have been proposed:

- "A pathophysiological condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organ to lead to astounding morbidity and mortality in this patient group" [5•].
- "Presence or development of renal dysfunction in patients with heart failure" [6].
- "A syndrome in which the heart or the kidney fails to compensate for the functional impairment of the respective other organ, resulting in a vicious cycle that will ultimately result in decompensation of the entire circulatory system" [7].
- "The result of interactions between the kidneys and other circulatory compartments that increase circulating volume and symptoms of heart failure and disease progression are exacerbated. At its extreme, cardio-renal dysregulation leads to what is termed 'cardio-renal syndrome' in which therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function" [4].

Epidemiology of HF with Comorbid RI

Data from several sources demonstrate that approximately 20% to 40% of patients admitted for acute decompensated HF (ADHF) have comorbid RI based on clinical history and serum creatinine levels. In an evaluation of data from 1681 patients ≥ 65 years of age admitted for ADHF at 18 hospitals in Connecticut, 21% of patients had baseline renal failure and 41% had a baseline serum creatinine level ≥ 1.5 mg/dL [8]. Similarly, renal dysfunction complicated HF management in 18% of the 11,327 patients admitted to 115 hospitals in the EuroHeart Failure survey program [9]. Finally, 30% of hospitalized HF patients had a history of chronic RI and 20% had a serum creatinine level greater

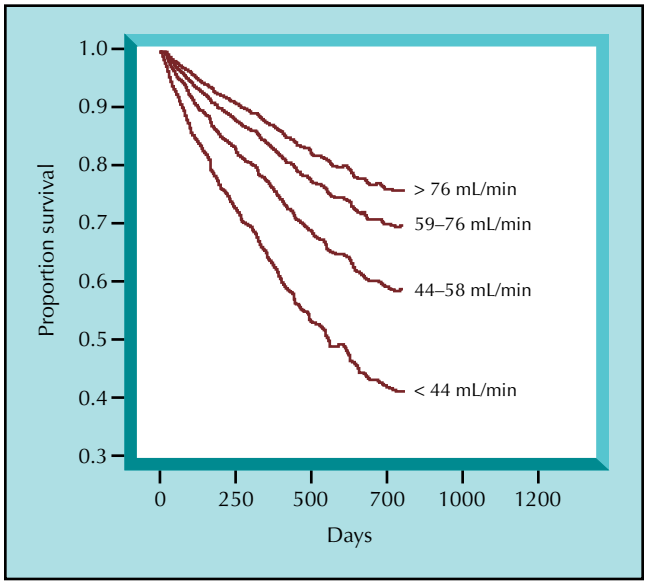

Figure 1. Proportional relationship of glomerular filtration rate with mortality in a Cox-adjusted survival analysis of 1702 patients with moderate-to-severe (New York Heart Association class III/IV) heart failure. (*Adapted from* Dries et al. [16].)

than 2 mg/dL in an evaluation of 105,388 hospitalization episodes at 274 hospitals from ADHERE [10•].

Moreover, these data probably underestimate the true prevalence of RI associated with HF. Creatinine, blood levels of which are used as a surrogate marker for glomerular filtration rate (GFR), is not the most sensitive marker of kidney function. The plot between creatinine and GFR as estimated by inulin clearance is not a straight line because there is a more significant change in GFR at lower values of creatinine. Also creatinine, a byproduct of creatine, depends on muscle mass, which varies with gender, ethnicity, and age, among other things, including muscle wasting as may be seen in HF patients. Patients with ADHF are also typically older adults, with the mean age of patients being 72.4 years in the report from the ADHERE registry [10•]. In the older adults, creatinine production is reduced because of an age-related decline in muscle mass. As a result, serum creatinine concentration alone may not accurately reflect renal function [6,11]. Currently, the National Kidney Foundation recommends that renal function be assessed by estimating the GFR based on predictive equations that take into account not only serum creatinine level but also other factors, such as age, sex, and race [11]. Based on estimated GFR, most patients in the ADHERE registry have at least stage III renal dysfunction as defined by the National Kidney Foundation [11,12].

Additionally, comorbid RI can complicate the management of ADHF, even when it is not present at admission time. Between 27% and 45% of patients hospitalized for ADHF develop an acute worsening of renal function, defined as a ≥ 0.3-mg/dL increase in serum creatinine level, during their hospitalization [8,13,14].

Effect of RI on Prognosis

Several studies have demonstrated that patients with chronic HF who have developed RI have an increased mortality risk. In the PRIME-II, estimated baseline GFR was the most powerful multivariate predictor of mortality risk, exceeding functional status and ejection fraction (Fig. 1) [15]. Similarly, retrospective multivariate analysis of data from the SOLVD prevention and treatment trials found that moderate RI, defined as a baseline creatinine clearance less than 60 mL/min as estimated by the Cockroft-Gault equation, was associated with a 1.41-fold increase ($P = 0.001$) in the risk of all-cause mortality in both trials [16].

Baseline RI has also been shown to be associated with increases in morbidity and mortality risk in patients hospitalized for ADHF [17–22]. In a retrospective analysis of data from 1129 patients, discharge serum creatinine level greater than 2.5 mg/dL was the most powerful independent multivariate predictor of all-cause readmission (hazard ratio [HR], 1.72; 95% CI, 1.35–2.18; $P = 0.0001$) [22]. In a multivariate Cox regression analysis of data from 541 patients, all-cause mortality increased with each quartile of blood urea nitrogen (BUN), with an adjusted mortality relative risk of 2.3 (95% CI, 1.3–4.1; $P = 0.005$) for patients in the highest compared with the lowest quartile [19]. In separate multivariate analyses of data from 906 and 4031 patients, a 5-mg/dL increase in BUN was associated with an increase in the 60-day risk of death or rehospitalization (odds ratio [OR], 1.28; 95% CI, 1.14–1.41; $P = 0.0001$) in the first analysis [20], and a 10-mg/dL increase in BUN was associated with an increased risk of 30-day (OR, 1.55; 95% CI, 1.42–1.71; $P < 0.001$) and 1-year (OR, 1.49; 95% CI, 1.39–1.60; $P < 0.001$) mortality in the second analysis [21]. In an analysis of data from 433 patients in the ESCAPE, baseline serum creatinine (HR, 1.37 per 0.2-mg/dL increase; 95% CI, 1.20–1.56; $P < 0.0001$) and BUN (HR, 1.42 per 20-mg/dL increase; 95% CI, 1.26–1.60; $P < 0.0001$) levels were significant independent 6-month mortality risk factors [17]. Finally, in a classification and regression tree analysis of more than 33,000 ADHF hospitalization episodes in the ADHERE registry assessing more than 40 univariate predictors, admission serum creatinine and BUN levels were two of the three strongest independent risk predictors for in-hospital mortality [18].

Similarly, worsening renal function during hospitalization for ADHF also signifies a significantly poorer prognosis [8,13,14]. Gottlieb et al. [14] evaluated data from 1002 patients who were admitted to academic medical centers for ADHF. Approximately 72% of patients had a serum creatinine increase ≥ 0.1 mg/dL during their hospitalization, and even this small increase was associated with worse outcomes. Increasing the serum creatinine threshold used to define worsening renal function from ≥ 0.1 mg/dL to ≥ 0.5 mg/dL improved specificity but reduced sensitivity, with a level of ≥ 0.3 mg/dL provid-

ing relatively high sensitivity (81%) and useful specificity (62%) for in-hospital mortality. Smith et al. [13] evaluated the mortality risk associated with acute serum creatinine elevation in 412 patients hospitalized for ADHF. Adjusted 6-month mortality HRs were 0.88 (95% CI, 0.49–1.57) for a ≥ 0.1-mg/dL increase, 1.15 (95% CI, 0.67–1.97) for a ≥ 0.2-mg/dL increase, 1.61 (95% CI, 0.94–2.77) for a ≥ 0.3-mg/dL increase, 1.83 (95% CI, 1.05–3.23) for a ≥ 0.4-mg/dL increase, and 2.86 (95% CI, 1.55–5.26) for a ≥ 0.5-mg/dL increase in serum creatinine. A ≥ 25% increase in serum creatinine had high specificity (91%) but lacked sensitivity (14%) and was not statistically significant (adjusted 6-month mortality HR, 1.67; 95% CI, 0.78–3.56).

Pathophysiologic Link Between HF and RI

In HF patients, comorbid RI can result from intrinsic renal disease, hemodynamic abnormalities, or their combination (Table 1) [6]. Atherosclerosis, renal vascular disease, diabetes, and hypertension are significant precursors of renal dysfunction and HF [1•,11]. As a result, intrinsic renal disease frequently coexists with HF.

Diminished renal perfusion is a common consequence of the hemodynamic changes associated with HF and its treatment. Severe pump failure leads to low cardiac output and hypotension (cardiogenic shock). Neurohormonal activation produces fluid retention, increasing central venous pressure, vasoconstriction, and afterload, and diminishing cardiac output. Diuresis can cause hypovolemia, reducing preload [6], and using intravenous vasodilators can lead to hypotension [23]. Also, drugs such as NSAIDs, cyclosporin, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) can decrease renal perfusion. The resultant diminution in renal blood flow/GFR can lead to RI, even in the absence of intrinsic renal disease.

In patients with HF, a correlation between RI and circulating levels of neurohormones exists. Activating the renin-angiotensin-aldosterone system (RAAS) leads to renal hypoxia, vasoconstriction, intraglomerular hypertension, glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria. Similarly, sympathetic nervous system activation causes proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall of intrarenal blood vessels.

High central venous pressure is another cause of renal dysfunction that is often overlooked. Firth et al. [24] used an isolated rat kidney preparation to evaluate the effect of increasing venous pressure on GFR. Normal perfusion pressure was maintained while venous pressure was increased in 6.25-mm Hg steps. In this evaluation, increasing venous pressure above 19 cm of water produced significant reductions in GFR, sodium excretion, and fractional excretion of sodium, which resolved completely when venous pressure was restored to basal levels.

Table 1. Etiologies of comorbid renal dysfunction in patients with heart failure

Intrinsic renal disease
Renal vascular disease
Nephron loss (diabetes, hypertension)
Diuretic resistance
Inadequate renal perfusion
Hypovolemia (inadequate preload)
Inadequate cardiac output (excessive vasoconstriction)
Hypotension
With normal cardiac output (vasodilatory shock)
With low cardiac output (severe pump failure, cardiogenic shock)
Abnormally high central venous pressure
Drug-induced (NSAIDs, cyclosporin, tacrolimus, ACE inhibitors, ARBs)

ACE—angiotensin-converting enzyme; ARBs—angiotensin II receptor blockers; NSAIDs—nonsteroidal anti-inflammatory drugs. (*Adapted from* Heywood [6].)

Angiotensin II–induced vasoconstriction of the efferent glomerular arteriole helps to preserve GFR in patients with HF and RI. Neurohormonal blockade with ACE inhibitors and/or ARBs impedes this vasoconstriction, reducing glomerular capillary pressure and, thus, GFR, leading to an acute, small increase in serum creatinine level. Although initially worrisome, especially given the mortality risk associated with similar acute increases in serum creatinine level in patients with HF [8,13,14], 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 [25,26]. Because patients who are volume-depleted may be especially sensitive to this efferent arteriolar vasodilation [25–27], 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.

In addition to HF's adverse affects on renal function, RI adversely affects cardiac function, producing a vicious cycle in which RI impairs cardiac performance, which then leads to further renal function impairment. As a result, RI is a major determinant of the progression of HF, congestion, and recurrent decompensation and hospitalization [16,22]. Neurohormonal activation is a key component that links not only RI to HF but also HF to RI. HF and RI produce neurohormonal activation. This activation increases the volume and pressure load on the heart, reduces myocardial oxygen supply, promotes deleterious myocardial remodeling, and accelerates atherosclerosis.

RI's etiology in patients with HF is complex, and several factors may be at work in the same patient. Given the increased morbidity and mortality associated with

comorbid RI, recognizing which factors are involved in an individual patient and eliminating these factors whenever possible is an essential component of HF management.

Therapeutic Implications

HF with comorbid RI can be difficult to manage because cardiac and renal function are dependent on circulating volume. In these patients, the overall goals of management should be 1) to normalize volume status while avoiding overdiuresis and attendant renal dysfunction and 2) to implement evidence-based pharmacologic and device therapy to improve patient outcomes.

An initial consideration is to identify potentially reversible factors that may be contributing to cardiorenal dysfunction. In this regard, it is important to evaluate fluid status, cardiac output, and evidence of intrinsic renal disease. The first question that should be answered in the patient with HF and RI is whether he or she is hypovolemic. Diuretics are an integral part of HF therapy. However, their overaggressive use or their use in combination with other factors, such as an intercurrent illness, frequently leads to hypovolemia, reducing cardiac output and GFR [28]. An important clinical pearl in diuresing fluid overloaded patients is gentle fluid removal (< 500 mL/h) so that there is adequate time for vascular refilling. This might allow more fluid removal and, at the same time, might not compromise renal perfusion. However, vascular refilling time and hemodynamic response to fluid removal can vary from patient to patient. If overaggressive diuresis leads to decline in renal function, it should be reversed with appropriate fluid management before further and possibly irreversible renal damage ensues. A rational approach would be to hold the diuresis and observe the patient clinically and by laboratory values. At times, it might be necessary to give fluids back. A careful physical examination and limited echocardiogram with estimation of right and left atrial pressures will usually resolve this question, although invasive assessment of filling pressures will occasionally be necessary [6].

The next item to consider is the adequacy of renal perfusion. Renal perfusion depends on blood pressure and cardiac output. If hypotension is present, pressor and/or inotropic agents should be used to maintain a systolic blood pressure greater than 80 mm Hg and a mean blood pressure greater than 60 mm Hg [2•]. 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 vasodilation [2•]. Renal function may improve as cardiac output and, thus, renal perfusion increase, and low-normal systolic blood pressure (80–90 mm Hg) should be tolerated as long as renal function is improving [6]. Another important consideration is the differential blood supply between the cortex and the medulla of the kidney, with the medulla having very low partial pressure of oxygen values. Because most of the renal blood flow is to the cortex, when renal perfusion is impaired, the medulla is likely to suffer more.

Intrinsic renal disease should be suspected if RI persists after abnormalities in volume status, cardiac output, and systemic vascular resistance have been corrected. Typically, this is due 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 RI [29]. Depending on the degree of renal impairment, these patients may benefit from ultrafiltration or hemodialysis [6,30].

The feasibility of discontinuing drugs that contribute to RI, such as aspirin and other NSAIDs, should be considered. ACE inhibitors and ARBs should be discontinued 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 [6]. However, given their long-term beneficial effects in HF and RI, therapy with an ACE inhibitor or ARB should be continued or reinstituted whenever possible [1•,3•,26,29].

Diuretics

Treating ADHF with comorbid RI often requires the use of diuretics, inotropes, and/or vasodilators. Volume overload is a frequent component of HF and RI and a major cause of clinical symptomatology. Consequently, diuretics play an important role in treating both conditions [1•,2•,26]. Their symptomatic benefit in HF patients has led to almost universal clinical acceptance, even though their efficacy and safety have never been evaluated in large-scale, randomized clinical trials [2•].

HF and RI influence the dose-response curve for diuretics. RI shifts the curve to the right, whereas HF shifts the curve 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 increases as HF progresses. It is also important to remember that diuretics have an S-shaped dose-response curve. Consequently, for any individual patient there is a maximum dose above which toxicity increases without any further improvement in efficacy. Some other important causes of diuretic resistance are increased salt intake, use of NSAIDs, and increased reabsorption of sodium by the distal portions of the nephron. The benefits of compliance with a low-salt diet cannot be overemphasized. If diuretic resistance develops, it is prudent to add a more distally acting diuretic such as metolazone, amiloride, or both. Although HF

and RI frequently require increasing doses of diuretics, it is essential to carefully assess the therapeutic response to these increases to make sure that one remains on the steep part of the dose-response curve.

Using diuretics involves a delicate balance. The dose must be sufficient to effectively relieve fluid overload and its ensuing symptoms without stimulating adverse physiologic effects. Excessive diuresis produces hypovolemia and extracellular fluid contraction, leading to hypotension, reduced cardiac output, diminished GFR, and further impairment of renal function [2•,26]. Also, this impairment in renal function has been correlated directly with the reduction in mean arterial blood pressure. In addition, this extracellular fluid contraction increases the adverse renal effects of therapeutic agents used in treating HF, including ACE inhibitors, ARBs, and natriuretic peptides [26,31], as well as enhancing the risk of radiocontrast agents [32].

Diuretics also stimulate adverse neurohormonal activation [33]. All diuretics induce extracellular volume contraction, which stimulates the secretion of renin while inhibiting the secretion of counterregulatory natriuretic peptides. Also, loop diuretics augment renin secretion through two volume-independent mechanisms. They inhibit sodium chloride uptake into the macula densa cells, a central component of the macula densa–mediated pathway for renin secretion, and stimulate the renal production of prostacyclin, further enhancing the secretion of renin. Data from the SOLVD trial demonstrate that diuretics can induce adverse neurohormonal activation in patients in whom it was not present before diuretic administration [33].

Diuretics (especially high-dose diuretics) have been shown to be associated with increased mortality risk in patients with HF and/or RI [32,34]. In the SOLVD trial, a significant increase in the risk of hospitalization or death due to worsening HF was observed in patients receiving non–potassium-sparing diuretics compared with those not receiving diuretics (risk ratio, 1.31; 95% CI, 1.09–1.57; $P = 0.0004$) [34]. In the PRAISE, use of high-dose diuretics was associated with increased total mortality (HR, 1.37; $P = 0.004$), sudden death (HR, 1.39; $P = 0.042$), and pump failure death (HR, 1.51; $P = 0.034$) [35]. It remains unknown whether requiring higher doses of diuretics is merely a marker of more severe HF or whether higher doses of loop diuretics are contributing to the adverse outcomes observed. Several studies suggest that a continuous infusion of diuretics is more effective than intermittent boluses [36]. When diuretic resistance persists, ultrafiltration should be considered. In patients with moderate-to-severe HF, ultrafiltration has been shown to improve symptoms, hemodynamics, urine output, and diuretic responsiveness [30,37]. Moreover, unlike loop diuretics, ultrafiltration produces less long-term neurohormonal activation [37].

Inotropes

Inotropes augment contractility and are an essential component of the treatment of low-output HF manifested by cardiogenic shock. However, their role in treating other forms of HF is less clearly established. Inotropes primarily target a physiologic parameter (cardiac output) that has not been associated with improved symptoms or outcomes [38]. They improve short-term hemodynamics but increase the risk of adverse events and mortality [38,39•,40]. Patients hospitalized for ADHF who received milrinone or dobutamine had significantly increased in-hospital mortality compared with those who received nitroglycerin or nesiritide after adjusting for differences in baseline covariates and propensity score in an analysis of data from the ADHERE registry [39•]. In the ESCAPE trial, after adjustment for renal function and blood pressure, use of inotropic agents was associated with significant increases in the risk of death (HR, 1.75; 95% CI, 1.05–2.92; $P = 0.032$) and death plus rehospitalization (HR, 2.12; 95% CI, 1.52–2.97; $P < 0.001$) [40]. These adverse effects may, in part, be due to augmentation of the deleterious neurohormonal activation that is already present in patients with ADHF. In a multicenter evaluation of patients with stable HF, treatment with levosimendan or dobutamine was associated with a significant (23% to 43%) increase in plasma renin levels compared with baseline ($P \leq 0.007$) [41]. In a multicenter evaluation of patients admitted for ADHF, dobutamine treatment was associated with a significant (31%) increase in plasma aldosterone levels ($P < 0.001$) [42]. In selected patients with refractory low output syndrome and RI, expeditious placement of a left ventricular assist device may restore clinical stability and reversal of renal dysfunction [43].

Vasodilators

Vasodilators decrease preload and afterload, reducing ventricular work, increasing stroke volume, and augmenting cardiac output [38]. They are indicated in patients with ADHF who have signs of congestion and hypoperfusion with adequate blood pressure [2•].

Nitrates effectively relieve pulmonary congestion, and their use, in combination with a low-dose diuretic, has proven to be more efficacious than high-dose diuretic therapy alone in patients with ADHF [2•]. 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 [2•,35]. Also, tolerance to nitrates develops quickly, especially when they are given intravenously in high doses, generally limiting the duration of effectiveness to 24 to 48 hours and necessitating central hemodynamic monitoring in an intensive care unit setting [2•,35].

Nesiritide is a recombinant form of B-type, natriuretic peptide, a counterregulatory hormone produced by the ventricles in response to pressure and volume load [2•]. In HF patients, nesiritide produces balanced vasodilation, improves cardiac output, and inhibits activity of the RAAS, sympathetic nervous system, and endothelin system [2•,44–46]. Nesiritide's renal effects are variable and may depend on underlying volume status and renal function and the nesiritide dose used. In patients with HF, nesiritide has been reported to decrease [47] or maintain renal blood flow and/or GFR [44,46] and to maintain [44] or increase urinary sodium and/or water excretion [45,46]. In a small evaluation of 13 patients with HF who underwent cardiac catheterization, nesiritide exerted a renal vasodilatory effect, predominantly in large conductance vessels, which maintained renal blood flow despite a significant decrease in renal perfusion pressure [48]. However, this adaptive mechanism may not be adequate if reductions in systemic blood pressure or intravascular volume are excessive. In an analysis of data from pooled nesiritide trials, the risk of acute serum creatinine elevation paralleled the prevalence of symptomatic hypotension [49]. In an analysis of data from the VMAC trial, the risk of acute serum creatinine elevation was significantly increased in nesiritide-treated patients who received high-dose diuretics (Table 2) [31]. It is not yet clear whether the rise of creatinine observed is associated with adverse outcome. In a pooled analysis of five randomized nesiritide trials, increases in serum creatinine (> 0.5 mg/dL), which occurred in patients treated with nesiritide, were not associated with an increased risk of mortality at 30 days [50].

Conclusions

Patients admitted for ADHF frequently have comorbid RI; this insufficiency significantly influences treatments and outcomes. Compared to patients with HF who have normal renal function, patients who have comorbid RI have significantly increased morbidity and mortality. Despite this, evidence-based data to guide management decisions in these patients are lacking. There is a compelling need for additional studies in this patient population to create alternative methods for fluid removal in volume-overloaded patients, to develop better strategies to manage existing RI and to prevent future RI (including the development of renal-protective medications), and to reduce the morbidity and mortality associated with ADHF and comorbid RI.

Clinical Trial Acronyms

ADHERE—Acute Decompensated Heart Failure National Registry; ESCAPE—Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; PRAISE—Prospective Randomized Amlodipine Survival Evaluation; PRIME-II—Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy; SOLVD—Studies in Left Ventricular Dysfunction; VMAC—Vasodilation in the Management of Acute Congestive Heart Failure.

Disclosures

Gregg C. Fonarow is a research consultant and receives honoraria from Scios. No other potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Hunt SA, Abraham WT, Chin MH, et al.: **ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult—summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). 2005.** *Circulation* 2005, **112:**e154–e235.

Succinct overview of US guidelines for diagnosing and managing chronic HF in adults.

2.• Nieminen MS, Böhm M, Cowie MR, et al.: **Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology.** *Eur Heart J* 2005, **26:**384–416.

Concise overview of European guidelines for diagnosing and treating acute HF.

3.• Swedberg K, Cleland J, Dargie H, et al.: **Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology.** *Eur Heart J* 2005, **26:**1115–1140.

Brief overview of European guidelines for diagnosing and treating chronic HF.

4. National Heart, Lung, and Blood Institute: **NHLBI Working Group—Cardio-Renal Connections in Heart Failure and Cardiovascular Disease—August 20, 2004.** Available at http://www.nhlbi.nih.gov/meetings/workshops/cardiorenal-hf-hd.htm. Accessed February 21, 2008.

5.• Bongartz LG, Cramer MJ, Doevendans PA, et al.: **The severe cardiorenal syndrome: "Guyton revisited".** *Eur Heart J* 2005, **26:**11–17.

Discussion of the pathophysiology of the cardiorenal connection and syndrome.

6. Heywood JT: **The cardiorenal syndrome: lessons from the ADHERE database and treatment options.** *Heart Fail Rev* 2004, **9:**195–201.

7. Boerrigter G, Burnett JC, Jr: **Cardiorenal syndrome in decompensated heart failure: prognostic and therapeutic implications.** *Curr Heart Fail Rep* 2004, **1:**113–120.

8. Krumholz HM, Chen YT, Vaccarino V, et al.: **Correlates and impact on outcomes of worsening renal function in patients > or = 65 years of age with heart failure.** *Am J Cardiol* 2000, **85:**1110–1113.

9. Cleland JGF, Swedberg K, Follath F, et al.: **The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis.** *Eur Heart J* 2003, **24:**442–463.

10.• Adams KF, Jr, Fonarow GC, Emerman CL, et al.: **Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Failure National Registry (ADHERE).** *Am Heart J* 2005, **149:**209–216.
Discusses the feasibility and initial implications of the ADHERE database.
11. Levey AS, Coresh J, Balk E, et al.: **National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification.** *Ann Intern Med* 2003, **139:**137–147.
12. Heywood JT, Fonarow GC, Wynne J: **Is heart failure really renal failure? Observations from 88,075 admissions with decompensated heart failure in the ADHERE® Registry [abstract 843-8].** *J Am Coll Cardiol* 2005, **45(3 Suppl A):**173A.
13. Smith GL, Vaccarino V, Kosiborod M, et al.: **Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure?** *J Card Fail* 2003, **9:**13–25.
14. Gottlieb SS, Abraham W, Butler J, et al.: **The prognostic importance of different definitions of worsening renal function in congestive heart failure.** *J Card Fail* 2002, **8:**136–141.
15. Hillege HL, Girbes ARJ, de Kam PJ, et al.: **Renal function, neurohormonal activation, and survival in patients with chronic heart failure.** *Circulation* 2000, **102:**203–210.
16. Dries DL, Exner DV, Domanski MJ, et al.: **The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction.** *J Am Coll Cardiol* 2000, **35:**681–689.
17. Hill JA, Shah MR, Hasselblad V, et al.: **Pulmonary artery catheter use does not change the contribution of renal dysfunction to outcomes in patients with advanced heart failure: findings from ESCAPE [abstract 2964].** *Circulation* 2004, **110(Suppl 3):**III–638.
18. Fonarow GC, Adams KF, Jr, Abraham WT, et al.: **Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis.** *JAMA* 2005, **293:**572–580.
19. Aronson D, Mittleman MA, Burger AJ: **Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure.** *Am J Med* 2004, **116:**466–473.
20. Felker GM, Gattis WA, Leimberger JD, et al.: **Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure.** *Am J Cardiol* 2003, **92:**625–628.
21. Lee DS, Austin PC, Rouleau JL, et al.: **Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model.** *JAMA* 2003, **290:**2581–2587.
22. Krumholz HM, Chen YT, Wang Y, et al.: **Predictors of readmission among elderly survivors of admission with heart failure.** *Am Heart J* 2000, **139:**72–77.
23. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF): **Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial.** *JAMA* 2002, **287:**1531–1540.
24. Firth JD, Raine AE, Ledingham JG: **Raised venous pressure: a direct cause of renal sodium retention in oedema?** *Lancet* 1988, **1:**1033–1035.
25. Bakris GL, Weir MR: **Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern?** *Arch Intern Med* 2000, **160:**685–693.
26. **K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease [no authors listed].** *Am J Kidney Dis* 2004, **43(5 suppl 1):** S1–S290.
27. Ljungman S, Kjekshus J, Swedberg K: **Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] Trial).** *Am J Cardiol* 1992, **70:**479–487.
28. Ikram H, Chan W, Espiner EA, Nicholls MG: **Haemodynamic and hormone responses to acute and chronic furosemide therapy in congestive heart failure.** *Clin Sci* 1980, **59:**443–449.
29. Keane WF: **Proteinuria: its clinical importance and role in progressive renal disease.** *Am J Kidney Dis* 2000, **35:**S97–S105.
30. Marenzi G, Lauri G, Grazi M, et al.: **Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure.** *J Am Coll Cardiol* 2001, **38:**963–968.
31. Chow SL, Peng J, Okamoto MP, Heywood JT: **Longer duration of nesiritide infusion may be associated with worsening renal function [abstract].** *J Card Fail* 2006, **12:**S88.
32. Mehta RL, Pascual MT, Soroko S, Chertow GM: **Diuretics, mortality, and nonrecovery of renal function in acute renal failure.** *JAMA* 2002, **288:**2547–2553.
33. Francis GS, Benedict C, Johnstone DE, et al.: **Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD).** *Circulation* 1990, **82:**1724–1729.
34. Domanski M, Norman J, Pitt B, et al.: **Diuretic use, progressive heart failure, and death in patients in the studies of left ventricular dysfunction (SOLVD).** *J Am Coll Cardiol* 2003, **42:**705–708.
35. Packer M, Lee WH, Kessler PD, et al.: **Prevention and reversal of nitrate tolerance in patients with congestive heart failure.** *N Engl J Med* 1987, **317:**799–804.
36. Salvador DR, Rey NR, Ramos GC, Punzalan FE: **Continuous infusion versus bolus injection of loop diuretics in congestive heart failure.** *Cochrane Database Syst Rev* 2004, **(1):**CD003178.
37. Agostoni PG, Marenzi GC, Pepi M, et al.: **Isolated ultrafiltration in moderate congestive heart failure.** *J Am Coll Cardiol* 1993, **21:**424–431.
38. DiDomenico RJ, Park HY, Southworth MR, et al.: **Guidelines for acute decompensated heart failure treatment.** *Ann Pharmacother* 2004, **38:**649–660.
39.• Abraham WT, Adams KF, Fonarow GC, et al.: **In-hospital mortality in patients with acute decompensated heart failure treated with intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE).** *J Am Coll Cardiol* 2005, **46:**57–64.
Comparision of in-hospital mortality in patients with ADHF treated with four different parenteral agents: nitroglycerin, nesiritide, milrinone, and dobutamine.
40. Elkayam U, Tasissa G, Binanay C, et al.: **Use and impact of inotropes and vasodilator therapy during heart failure hospitalization in the ESCAPE Trial [abstract 2415].** *Circulation* 2004, **110(suppl 3):**III–515.
41. Nieminen MS, Akkila J, Hasenfuss G, et al.: **Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure.** *J Am Coll Cardiol* 2000, **36:**1903–1912.
42. Aronson D, Horton DP, Burger AJ: **The effect of dobutamine on neurohormonal and cytokine profiles in patients with decompensated congestive heart failure [abstract 095].** *J Card Fail* 2001, **7(3 suppl 2):**28.
43. de Vivo F, DeSanto LS, Maiello C, et al.: **Role of the heart surgeon in the emergency treatment of diuretic resistant edema in grades III-IV heart failure.** *Kidney Int Suppl* 1997, **59:**S66–S68.

44. Abraham WT, Lowes BD, Ferguson DA, et al.: **Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure.** *J Card Fail* 1998, **4:**37–44.
45. Colucci WS, Elkayam U, Horton DP, et al.: **Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure.** *N Engl J Med* 2000, **343:**246–253.
46. Marcus LS, Hart D, Packer M, et al.: **Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure. A double-blind, placebo-controlled, randomized crossover trial.** *Circulation* 1996, **94:**3184–3189.
47. Sackner-Bernstein JD, Skopicki HA, Aaronson KD: **Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure.** *Circulation* 2005, **111:**1487–1491.
48. Elkayam U, Singh H, Akhter MW, et al.: **Effects of intravenous nesiritide on renal hemodynamics in patients with congestive heart failure [abstract 256].** *J Card Fail* 2004, **10(suppl 4):**S88.
49. Abraham WT: **Serum creatinine elevations in patients receiving nesiritide are related to starting dose [abstract 248].** *J Card Fail* 2005, **11(Suppl):**S156.
50. Elkayam U: **Nesiritide may diminish the increased acute mortality risk associated with worsening renal function [abstract 3168].** *Circulation* 2005, **112(17 Suppl II):**676.