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The Confounding Issue of Comorbid Renal Insufficiency

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ABSTRACT

The United States is currently beleaguered by twin epidemics, heart failure (HF) and renal insufficiency (RI). HF and RI frequently coexist in the same patient, and this conjunction, often called the "cardiorenal syndrome," has important therapeutic and prognostic implications. Approximately 60% to 80% of patients hospitalized for HF have at least stage III renal dysfunction as defined by the National Kidney Foundation (NKF), and this comorbid RI is associated with significantly increased morbidity and mortality risk. Numerous studies have demonstrated that in patients with HF, indices of renal function are the most powerful independent mortality risk predictors. Comorbid RI can result from both intrinsic renal disease and inadequate renal perfusion. Atherosclerosis, renal vascular disease, diabetes mellitus, and hypertension are significant precursors of both HF and RI. Moreover, diminished renal perfusion is frequently a consequence of the hemodynamic changes associated with HF and its treatment. Both HF and RI stimulate neurohormonal activation, increasing both preload and afterload and reducing cardiac output. Inotropic agents augment this neurohormonal activation. In addition, diuretics can produce hypovolemia and intravenous vasodilators can cause hypotension, further diminishing renal perfusion. Management of these patients requires successfully negotiating the delicate balance between adequate volume reduction and worsening renal function. Despite this, few evidence-based data are available to guide management decisions, indicating a compelling need for additional studies in this patient population.

KEYWORDS: Cardiorenal syndrome; Glomerular filtration rate; Heart failure; Outcomes; Renal insufficiency; Treatment

Twin epidemics, heart failure (HF) and renal insufficiency (RI) currently besiege the United States. It is not surprising that the prevalence of these twin syndromes continues to escalate, given an aging population, rising rates of obesity and diabetes mellitus, and shared risk factors. These issues have important implications for the healthcare system. Not uncommonly, HF and RI coexist in the same patient.[1–3] This conjunction, often called the "cardiorenal syndrome," has important therapeutic and prognostic implications for patients with HF. Much of the challenge of achieving successful HF management lies in navigating between the Scylla of fluid overload and the Charybdis of worsening renal function.

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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 cardio-renal interactions related to heart failure."[4] Although intense focus has been placed on the syndrome, a clear definition of cardiorenal syndrome has not yet been developed. Several definitions have been proposed, including the following:

- "A pathophysiologic 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 [*sic*] 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 HEART FAILURE WITH COMORBID RENAL INSUFFICIENCY

Data from several sources demonstrate that approximately 20% to 40% of patients admitted to a hospital for acute HF syndromes (AHFS) have comorbid RI, based on clinical history and serum creatinine levels. In an evaluation of data from 1,681 patients ≥65 years of age admitted for acute decompensated HF (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 (1 mg/dL = 76.25 μmol/L).[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 patients with HF had a history of chronic RI and 20% had a serum creatinine level >2 mg/dL in an evaluation of 105,388 hospitalization episodes at 274 hospitals from the Acute Decompensated Heart Failure National Registry (ADHERE).[10]

Moreover, these data probably underestimate the true prevalence of RI associated with HF. Patients with AHFS typically are elderly; the mean age of patients in the report from the ADHERE registry was 72.4 years.[10] In the elderly, creatinine production is reduced owing to 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 (NKF) recommends that renal function be assessed by estimating the glomerular filtration rate (GFR) based on predictive equations that take into account not only serum creatinine level but also other factors such as age, sex, race/ethnicity, and body size.[11] Based on estimated GFR, a majority of patients in the ADHERE registry have at least stage III renal dysfunction as defined by the NKF.[11,12]

Additionally, comorbid RI can complicate the management of AHFS, even when it is not present at the time of admission. Between 27% and 45% of patients hospitalized for AHFS develop an acute worsening of renal function, defined as a ≥0.3-mg/dL increase in serum creatinine level, during their hospitalization.[8,13–15]

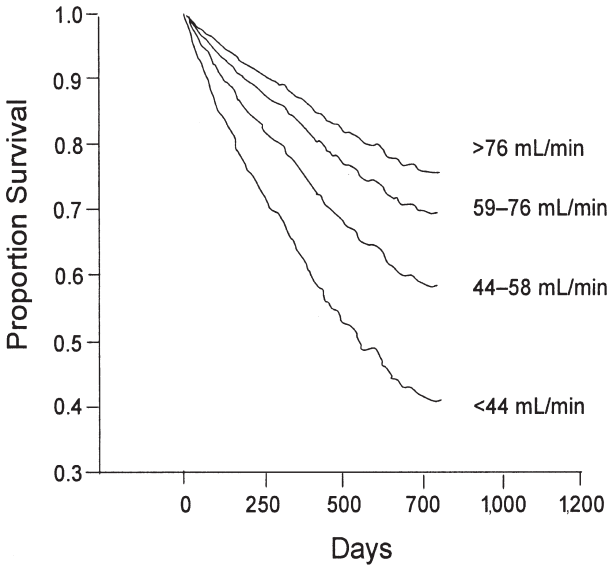

Figure 1 Proportional relation of glomerular filtration rate with mortality in a Cox-adjusted survival analysis of 1,702 patients with moderate-to-severe (i.e., New York Heart Association [NYHA] class III to IV) heart failure. (Adapted with permission from *Circulation*.[16])

EFFECT OF RENAL INSUFFICIENCY ON PROGNOSIS

Several studies have demonstrated that patients with chronic HF who have developed RI have an increased risk of mortality. In the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME-II), estimated baseline GFR was the most powerful multivariate predictor of mortality risk, exceeding both functional status and ejection fraction (**Figure 1**).[16] Similarly, retrospective multivariate analysis of data from the Studies in Left Ventricular Dysfunction (SOLVD) prevention and treatment trials found that moderate RI, defined as a baseline creatinine clearance <60 mL/min as estimated by the Cockroft-Gault equation,[17] was associated with a 1.41-fold increase (P = 0.001) in the risk of all-cause mortality in both trials.[18]

Baseline RI has also been shown to increase both morbidity and mortality risk in patients hospitalized for AHFS.[19–25] In a retrospective analysis of data from 1,129 patients, a discharge serum creatinine level >2.5 mg/dL was the most powerful independent multivariate predictor of all-cause readmission (hazard ratio [HR], 1.72; 95% confidence interval [CI], 1.35 to 2.18; P = 0.0001).[24] In a multivariate Cox regression analysis of data from 541 patients, all-cause mortality increased with each quartile of blood (serum) urea nitrogen (BUN), with an adjusted mortality relative risk of 2.3 (95% CI, 1.3 to 4.1; P = 0.005) for patients in the highest compared with the lowest quartile.[21] In separate multivariate analyses of data from 906 and 4,031 patients, a 5-mg/dL (1 mg/dL = 0.357 mmol/L) 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 to 1.41; P = 0.0001) in the first analysis[22] and a

Table 1 Etiologies of comorbid renal insufficiency in patients with heart failure

- Intrinsic renal disease
  - —Renal vascular disease
  - —Nephron loss (diabetes mellitus, 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, cyclosporine, tacrolimus, ACE inhibitors, ARBs, etc)

ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; NSAIDs = nonsteroidal anti-inflammatory drugs.

Adapted from *Heart Fail Rev*.[6]

10-mg/dL increase in BUN was associated with an increased risk of both 30-day (OR, 1.55; 95% CI, 1.42 to 1.71; $P < 0.001$) and 1-year (OR, 1.49; 95% CI, 1.39 to 1.60; $P < 0.001$) mortality in the second analysis.[23] In an analysis of data from 433 patients in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE), both baseline serum creatinine (HR, 1.37 per 0.2-mg/dL increase; 95% CI, 1.20 to 1.56; $P < 0.0001$) and BUN (HR, 1.42 per 20-mg/dL increase; 95% CI, 1.26 to 1.60; $P < 0.0001$) levels were significant independent 6-month mortality risk factors.[19] Finally, in a classification and regression tree analysis of >33,000 ADHF hospitalization episodes in the ADHERE registry assessing >40 univariate predictors, admission serum creatinine and BUN levels were 2 of the 3 strongest independent risk predictors for inhospital mortality.[20]

Similarly, worsening renal function during hospitalization for AHFS also signifies a significantly poorer prognosis.[8,13–15] Gottlieb and colleagues[14] evaluated data from 1,002 patients 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 providing both relatively high sensitivity (81%) and useful specificity (62%) for inhospital mortality. Smith and colleagues[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 to 1.57) for a ≥0.1-mg/dL increase, 1.15 (95% CI, 0.67 to 1.97) for a ≥0.2-mg/dL increase, 1.61 (95% CI, 0.94 to 2.77) for a ≥0.3-mg/dL increase, 1.83 (95% CI, 1.05 to 3.23) for a ≥0.4-mg/dL increase, and 2.86 (95% CI, 1.55 to 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 to 3.56). In summary, a significant component of the morbidity and mortality associated with HF is predicted by RI.

PATHOPHYSIOLOGIC LINK BETWEEN HEART FAILURE AND RENAL INSUFFICIENCY

In patients with HF, 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 both renal dysfunction and HF.[1,11,26,27] As a result, intrinsic renal disease frequently coexists with HF.[28]

Diminished renal perfusion is frequently a consequence of the hemodynamic changes associated with HF and its treatment. Severe pump failure leads to low cardiac output and hypotension (cardiogenic shock).[29] Neurohormonal activation produces both fluid retention, increasing central venous pressure, and vasoconstriction, increasing afterload and diminishing cardiac output.[29,30] Diuresis can cause hypovolemia, reducing preload,[6] and use of intravenous vasodilators can lead to hypotension.[31,32] In addition, agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) all can decrease renal perfusion.[33–36] The resultant diminution in renal blood flow/GFR can lead to RI even in the absence of intrinsic renal disease.

In patients with HF, there is a correlation between RI and circulating levels of neurohormones. Activation of the renin-angiotensin-aldosterone system (RAAS) leads to renal hypoxia, vasoconstriction, intraglomerular hypertension, glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria.[26,37,38] Similarly, sympathetic nervous system activation causes proliferation of smooth muscle cells and adventitial fibroblasts in the vascular wall of intrarenal blood vessels.[39]

High central venous pressure is another cause of renal dysfunction that is often overlooked. In an elegant study,

Firth and colleagues[40] evaluated the effect of increasing venous pressure on GFR using an isolated rat kidney preparation. 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. Angiotensin II–induced vasoconstriction of the efferent glomerular arteriole helps to preserve GFR in patients with HF and RI.[41,42] Neurohormonal blockade with ACE inhibitors and/or ARBs impedes this vasoconstriction, reducing glomerular capillary pressure and, hence, GFR, leading to an acute, small increase in serum creatinine level.[33,35,43] Although initially worrisome, especially given the mortality risk associated with similar acute increases in serum creatinine level in patients with HF,[8,13–15] 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.[33,44–47] Because patients who are volume-depleted may be especially sensitive to this efferent arteriolar vasodilation,[45,47,48] 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 the adverse affects of HF on renal function, RI adversely affects cardiac function, producing a vicious circle in which RI impairs cardiac performance, which then leads to further impairment of renal function. As a result, RI is a major determinant of the progression of HF, congestion, and recurrent decompensation and hospitalization.[18,24,49] Neurohormonal activation is a key component that links not only RI to HF but also HF to RI (**Figure 2**).[50] Both HF and RI produce neurohormonal activation.[39,50–52] This activation increases the volume and pressure load on the heart, reduces myocardial oxygen supply, promotes deleterious myocardial remodeling, and accelerates atherosclerosis.[30,39]

The etiology of RI 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 both cardiac and renal function are exquisitely dependent on circulating volume.[26] 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.[7]

An initial consideration is the identification of potentially reversible factors that may be contributing to cardiorenal dysfunction. In this regard, it is important to evaluate fluid status, cardiac output, and evidence of intrinsic renal disease. The first question that should be answered in the patient with HF and RI is whether the patient 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 both cardiac output and GFR.[53,54] This hypovolemia should be reversed with fluid before irreversible renal damage ensues. 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 both blood pressure and cardiac output. If hypotension is present, pressors should be used to maintain a systolic blood pressure >80 mm Hg and a mean blood pressure >60 mm Hg.[2,31,55] 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.[56] Renal function may improve as cardiac output and, hence, renal perfusion increase, and low-normal systolic blood pressure (80 to 90 mm Hg) should be tolerated as long as renal function is improving.[6]

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 owing to nephron loss secondary to diabetes, hypertension, or renovascular disease.[30,57,58] The presence of proteinuria usually indicates intrinsic renal disease and is associated with an increased risk for the development of chronic, progressive RI.[59] Depending on the degree of renal impairment, these patients may benefit from ultrafiltration or hemodialysis.[6,60]

Lastly, 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, and these agents may need to be temporarily reduced or discontinued in patients who have excessive vasodilation.[6,33] However, given their long-term beneficial effects in both HF and RI, therapy with an ACE inhibitor or ARB should be continued or reinstituted whenever possible.[1,3,47,59]

Diuretics

Treating AHFS with comorbid RI often requires the use of diuretics, inotropes, and/or vasodilators. Volume overload is a frequent component of both HF and RI and a major cause of clinical symptomatology. Consequently, diuretics play an important role in the treatment of both conditions.[1,2,47] Their symptomatic benefit in patients with HF has led to almost universal clinical acceptance, even though

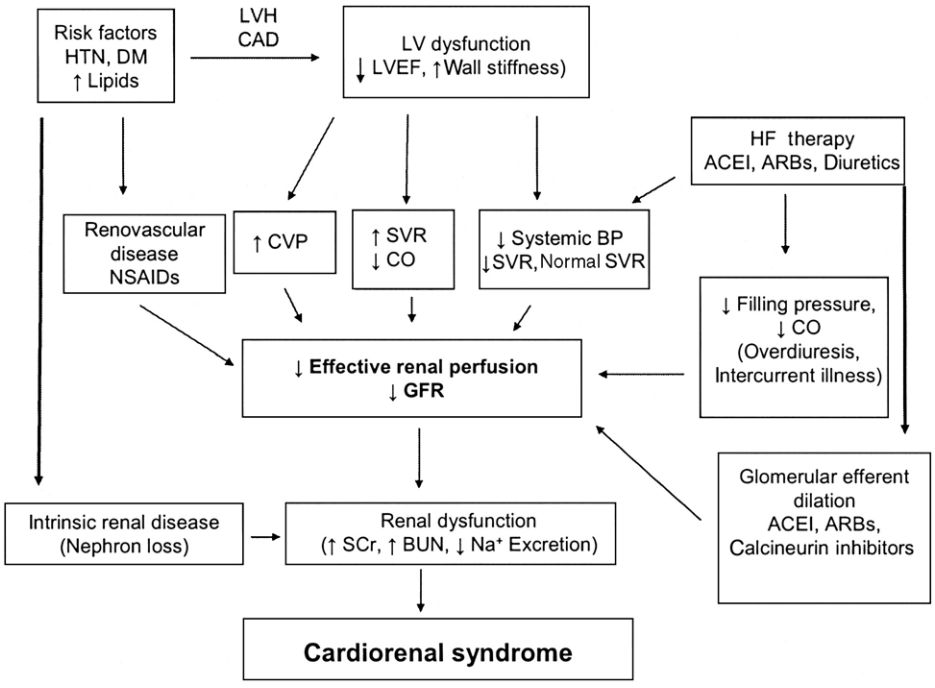

Figure 2 Pathophysiologic link between cardiac and renal failure. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; BUN = blood (serum) urea nitrogen; CAD = coronary artery disease; CO = cardiac output; CVP = central venous pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HF = heart failure; HTN = hypertension; LV = left ventricular; LVEF = LV ejection fraction; LVH = LV hypertrophy; Na^+ = sodium; NSAIDs = nonsteroidal anti-inflammatory drugs; SCr = serum creatinine; SVR = systemic vascular resistance.

their efficacy and safety have never been evaluated in large-scale, randomized clinical trials.[2]

Both HF and RI influence the dose-response curve for diuretics. RI shifts the curve to the right, while HF shifts the curve both downward and to the right.[61] 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.[62] It is also important to remember that diuretics have an S-shaped dose-response curve.[63] Consequently, for any individual patient there is a maximum dose above which nothing is gained by using larger doses.[63] 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.

Use of diuretics involves a delicate balance. The dose must be sufficient to achieve effective relief of fluid overload and its ensuing symptoms without stimulating adverse physiologic effects. Excessive diuresis produces hypovolemia and extracellular fluid contraction, leading to hypotension, reduced cardiac output, diminished GFR, and further impairment of renal function.[2,47,53,64] Furthermore, this impairment in renal function has been correlated directly with the reduction in mean arterial blood pressure.[64] In addition, this extracellular fluid contraction increases the adverse renal effects of therapeutic agents used in the treatment of HF, including ACE inhibitors, ARBs, and natriuretic peptides,[33,45,47,65,66] as well as enhancing the risk of radiocontrast agents.[67]

Diuretics also stimulate adverse neurohormonal activation.[61,68–70] All diuretics induce extracellular volume contraction, which stimulates the secretion of renin while inhibiting the secretion of counterregulatory natriuretic peptides.[61] In addition, loop diuretics augment renin secretion through 2 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 they stimulate the renal production of prostacyclin, further enhancing the secretion of renin.[61] Data from the SOLVD trial demonstrate that diuretics can induce adverse neurohormonal activation in patients in whom it was not present before diuretic administration.[69]

Finally, diuretics, especially high-dose diuretics, have been shown to increase mortality risk in patients with HF and/or RI.[62,67,71] In the SOLVD trial, there was a significant increase in the risk of hospitalization or death due to worsening HF in patients receiving non–potassium-sparing diuretics compared with those not receiving diuretics (risk ratio, 1.31; 95% CI, 1.09 to 1.57; $P = 0.0004$).[71] In the Prospective Randomized Amlodipine Survival Evaluation (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; $P = 0.034$).[62] However, the direct effect of diuretics on long-term HF outcomes cannot be established and must

Table 2 Risk of serum creatinine increase in patients receiving vasodilator: the Vasodilation in the Management of Acute Congestive HF (VMAC) analysis

	SCr Increase >0.5 mg/dL,* n (%)			
Diuretic Dose Category	NES	NTG	NES/NTG RR (95% CI)	*P* value
Low to moderate dose	24/119 (20.2)	17/81 (21.0)	0.96 (0.55–1.66)	0.975
High dose	49/149 (32.9)	28/131 (21.4)	1.50 (1.00–2.25)	0.044

NES = nesiritide; NTG = nitroglycerin; RR = relative risk; SCr = serum creatinine.
*1 mg/dL = 76.25 μmol/L.
Adapted from *J Card Fail.*[66]

be determined prospectively. Several studies suggest that a continuous infusion of diuretics is more effective than are intermittent boluses.[72–79] 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.[60,80–82] Moreover, unlike loop diuretics, ultrafiltration produces less long-term neurohormonal activation.[80,81,83]

Inotropes

Inotropes augment contractility and are an essential component of the treatment of low-output HF manifested by cardiogenic shock. Their role in the treatment of other forms of HF, however, is less clearly established. Inotropes primarily target a physiologic parameter (cardiac output) that has not been associated with either improved symptoms or outcomes.[31,84] They improve short-term hemodynamics but increase the risk of adverse events and mortality.[84–88] Patients hospitalized for ADHF who received milrinone or dobutamine had significantly increased inhospital 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.[85] 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 to 2.92; $P = 0.032$) and death plus rehospitalization (HR, 2.12; 95% CI, 1.52 to 2.97; $P<0.001$).[87] These adverse effects may, in part, be due to augmentation of the deleterious neurohormonal activation that is already present in patients with AHFS. 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 ($P \leq 0.007$),[89] and in a multicenter evaluation of patients admitted for ADHF, dobutamine treatment was associated with a significant, 31% increase in plasma aldosterone levels ($P<0.001$).[90] 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.[91]

Vasodilators

Vasodilators decrease preload and afterload, reducing ventricular work, increasing stroke volume, and augmenting cardiac output.[84] They are indicated in patients with AHFS 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 proved to be more efficacious than high-dose diuretic therapy alone in patients with AHFS.[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.[2,92,93] In addition, 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.[2,93]

Human B-type natriuretic peptide (hBNP) is a counterregulatory hormone produced by the ventricles in response to pressure and volume load.[2,51] In patients with HF, hBNP produces balanced vasodilation, improves cardiac output, and inhibits activity of the RAAS, sympathetic nervous system, and endothelin system.[2,94–98] Renal effects are variable and may depend on underlying volume status and renal function. In patients with HF, hBNP has been reported to either decrease[99] or maintain renal blood flow and/or GFR[94,97,98,100,101] and to either maintain[94,101] or increase urinary sodium and/or water excretion.[96–98]

Nesiritide is a recombinant form of hBNP. In a small evaluation of 13 patients with HF who underwent cardiac catheterization, nesiritide exerted a renal vasodilatory effect, which maintained renal blood flow despite a significant decrease in renal perfusion pressure.[100] In a meta-analysis including supratherapeutic doses of nesiritide, risk of acute serum creatinine elevation paralleled the prevalence of symptomatic hypotension[102]; in an analysis of data from the Vasodilation in the Management of Acute Congestive HF (VMAC) trial, the risk of acute serum creatinine elevation was significantly increased in patients treated with nesiritide who received high-dose diuretics (**Table 2**).[66] It is not yet clear whether the observed increase in creatinine is associ-

ated with adverse outcomes. In a pooled analysis of 5 randomized nesiritide trials, increases in serum creatinine (>0.5 mg/dL) that occurred in patients treated with nesiritide were not associated with an increased risk of mortality at 30 days.[103]

SUMMARY

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

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