Acute decompensated heart failure and the cardiorenal syndrome

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Heart failure is one of the leading causes of hospitalizations in the United States. Concomitant and significant renal dysfunction is common in patients with heart failure. Increasingly, the syndrome of heart failure is one of cardiorenal failure, in which concomitant cardiac and renal dysfunctions exist, with each accelerating the progression of the other. One fourth of patients hospitalized for the treatment of acute decompensated heart failure will experience significant worsening of renal function, which is associated with worse outcomes. It remains unclear whether worsening renal function specifically contributes to poor outcomes or whether it is merely a marker of advanced cardiac and renal dysfunction. Diuretic resistance, with or without worsening renal function, is also common in acute decompensated heart failure, although the definition of diuretic resistance, its prevalence, and prognostic implications are less well defined. The term *cardiorenal syndrome* has been variably associated with cardiorenal failure, worsening renal function, and diuretic resistance but is more comprehensively defined as a state of advanced cardiorenal dysregulation manifest by one or all of these specific features. The pathophysiology of the cardiorenal syndrome is poorly understood and likely involves interrelated hemodynamic and neurohormonal mechanisms. When conventional therapy for acute decompensated heart failure fails, mechanical fluid removal via ultrafiltration, hemofiltration, or hemodialysis may be needed for refractory volume overload. While ultrafiltration can address diuretic resistance, whether ultrafiltration prevents worsening renal function or improves outcomes in patients with cardiorenal syndrome remains unclear. Evidence regarding the potential renal-preserving effects of nesiritide is mixed, and further studies on the efficacy and safety of different doses of nesiritide in heart failure therapy are warranted. Newer therapeutic agents, including vasopressin antagonists and adenosine antagonists, hold promise for the future, and clinical trials of these agents are underway. (Crit Care Med 2008; 36[Suppl.]:S75–S88)

KEY WORDS: cardiorenal syndrome; heart failure; congestive heart failure; renal dysfunction; diuretics; ultrafiltration; vasopressin antagonists; adenosine antagonists; prognosis; therapy

The term *cardiorenal syndrome* has been variably defined but can be considered as a state of advanced cardiorenal dysregulation manifest by one or more of three specific features, including heart failure (HF) with concomitant and significant renal disease (cardiorenal failure), worsening renal function (developing during the treatment of acute decompensated HF (ADHF), and diuretic resistance (DR) (Table 1).

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Cardiorenal Failure

Renal impairment in patients with HF is common and is increasingly recognized as an independent risk factor for morbidity and mortality (1–6). In an analysis of patients enrolled in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study, Hillege et al. (7) showed that the level of renal dysfunction was a potent independent predictor of death or HF admission (Fig. 1). The Acute Decompensated Heart Failure National Registry (ADHERE), a large database of 105,388 patients with HF requiring hospitalization in the United States, reported that 30% had an additional diagnosis consistent with chronic kidney disease (8). Approximately 20% of patients had serum creatinine (Cr) >2.0 mg/dL, 9% had Cr >3.0 mg/dL, and 5% were receiving dialysis therapy. Smith et al. (9) conducted a systematic review and meta-analysis of 16 studies characterizing the association between renal impairment and mortality in 80,098 hospitalized and nonhospitalized HF patients (1945 through May 2005). Renal impairment was defined variably as Cr >1.0 mg/dL, Cr clearance (CrCl) or estimated glomerular filtration rate (eGFR) <90 mL/min, or cystatin-C >1.03 mg/dL. Moderate to severe renal impairment was defined as Cr ≥1.5 mg/dL, CrCl or eGFR <53 mL/min, or cystatin-C ≥1.56 mg/dL. A total of 63% of patients had any renal impairment, and 29% had moderate to severe impairment. Adjusted all-cause mortality was significantly increased for patients with any renal impairment. Mortality worsened incrementally across the range of renal function, with 15% increased risk for every 0.5-mg/dL increase in Cr and 7% increased risk for every 10-mL/min decrease in eGFR (9).

Owan et al. (10) recently reported on secular trends in the severity of renal dysfunction in patients with ADHF in 6,440 consecutive unique patients hospitalized for HF therapy at Mayo Clinic Hospitals, Rochester, MN, from January 1, 1987, to December 31, 2002. Over the 16-yr time period, age and admission Cr increased, eGFR decreased, and hemoglobin decreased (Fig. 2). The more dominant role of renal dysfunction in HF was also stressed in the recent Evaluation Study of Congestive Heart Failure and

Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, where it was emphasized that episodes of HF decompensation were less commonly associated with uncorrected vasoconstriction and more commonly associated with renal dysfunction with requirement of higher diuretic doses at discharge than historically noted (11). Thus, the severity of cardiorenal failure in patients hospitalized for HF is increasing. Importantly, cardiorenal failure is equally prevalent in patients with HF and normal ejection fraction (diastolic HF) or reduced ejection fraction (systolic HF) (9, 10, 12).

Worsening Renal Function

Several studies have established that >70% of patients will experience some increase in Cr during hospitalization for HF, with approximately 20% to 30% of HF patients experiencing an increase of >0.3 mg/dL (10, 12–17). Worsening renal function occurs relatively early in the course of the hospitalization (13) (Fig. 3). Any change in Cr has been shown to be associated with longer length of stay, increased costs, and increased short-term and long-term mortality (10, 12–17). The association of worsening renal function with poorer outcomes is independent of the degree of baseline renal dysfunction and many other pertinent covariables (10, 13, 17, 18). Nonetheless, it remains unclear whether the worsening renal function itself contributes to the increased mortality or whether it merely serves as a marker of more severe cardiac and/or renal dysfunction. Importantly, worsening renal function is as common in diastolic HF as it is in systolic HF (9, 10, 12). While the severity of underlying renal dysfunction in ADHF patients has increased over time, Owan et al. (10) did not find any evidence of increases in the incidence of worsening renal function over time.

Table 1. Features of the cardiorenal syndrome

Cardiorenal failure
Mild: HF + eGFR 30–59 mL/min/1.73 m^2
Moderate: HF + eGFR 15–29 mL/min/1.73 m^2
Severe: HF + eGFR <15 mL/min/1.73 m^2 or dialysis
Worsening renal function during treatment of ADHF
Change in creatinine >0.3 mg/dL or >25% baseline
Diuretic resistance
Persistent congestion despite
>80 mg furosemide/day
>240 mg furosemide/day
Continuous furosemide infusion
Combination diuretic therapy (loop diuretic + thiazide + aldosterone antagonist)

HF, heart failure; eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease equation; ADHF, acute decompensated heart failure.

Diuretic Resistance

In patients with ADHF associated with volume overload, initial therapy focuses on sodium and fluid restriction and diuretics. Diuretic resistance has been defined as persistent pulmonary congestion with or without worsening renal function despite attempts at diuresis (Table 1). The prevalence of DR depends in part on the aggressiveness of the diuretic dosing. While worsening renal function commonly develops in the absence of persistent congestion when diuretic dosing has been too high (termed *overdiuresis*), worsening renal function also often occurs despite persistent pulmonary congestion in patients with DR. Both DR and worsening renal function are more common in patients with underlying renal dysfunction, and the triad of cardiorenal failure, DR, and worsening renal function despite marked persistent volume overload represents the most extreme manifestation of the cardiorenal syndrome.

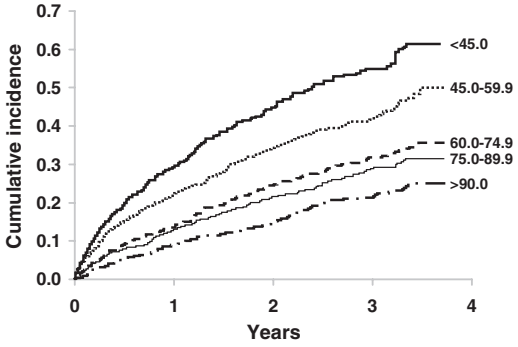

Figure 1. Kaplan-Meier plot of cumulative incidence of cardiovascular death or unplanned admission to hospital for the management of worsening heart failure stratified by approximate quintiles of estimated glomerular filtration rate in mL/min/1.73 m^2 (time in years). Reproduced with permission from Hillege HL, Nitsch D, Pfeffer MA, et al: Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; 113:671–678.

RISK FACTORS FOR CARDIORENAL SYNDROME

The common risk factors of hypertension, diabetes mellitus, and atherosclerosis explain the high prevalence of coexistent cardiac and renal dysfunction (18). Success in preventing death from HF, acute myocardial infarction, stroke, and noncardiovascular disease may result in a longer exposure to risk factors for renal dysfunction contributing to more severe renal dysfunction in HF patients. Importantly, CrCl or eGFR as estimated by the simplified Modification of Diet in Renal Disease formula or Cockcroft-Gault formula is a better estimator of renal function than serum Cr, as serum Cr may overestimate renal function in the HF population, particularly in elderly women. On average, persons developing worsening renal function are older and have a greater prevalence of prior HF, renal dysfunction, diabetes, and hypertension. In an elegant study by Forman et al. (12), the authors used Cox regression analysis in a large (1,004 patients), well-characterized, and regionally diverse HF population to devise a risk score for predicting which patients with ADHF would develop worsening renal function. This analysis yielded a scoring system where 1 point each was assigned to history of HF, history of diabetes, and systolic blood pressure >160 mm Hg at admission; 2 points were assigned to plasma Cr 1.5–2.4 mg/dL; and 3 points were assigned to plasma Cr ≥2.5 mg/dL. Thirty-five percent of the total sample had a score of ≥3 and had a 43% likelihood of developing worsening renal function (12). Risk factors for DR are not as well characterized but are likely similar to those for worsening renal function.

PATHOPHYSIOLOGY OF THE CARDIORENAL SYNDROME

The pathophysiological features contributing to cardiorenal failure, worsen-

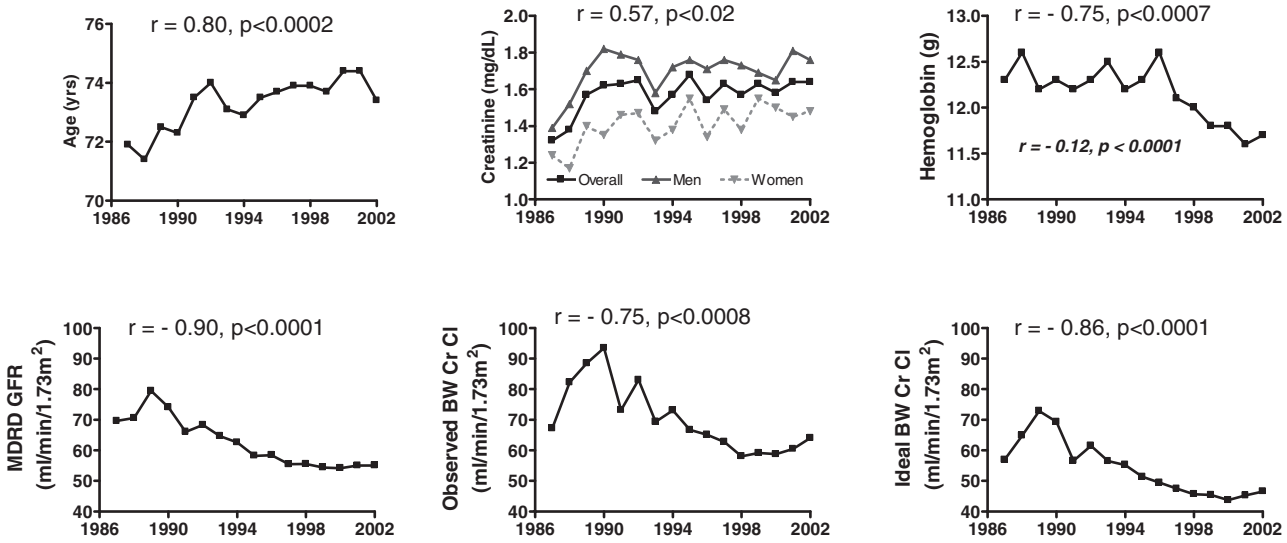

Figure 2. Secular trends in age, renal function, and hemoglobin in patients with acute decompensated heart failure in 6,440 consecutive patients hospitalized for heart failure therapy at Mayo Clinic Hospitals, Rochester, MN, from January 1, 1987, to December 31, 2002. *MDRD*, Modification of Diet in Renal Disease; *GFR*, glomerular filtration rate; *BW*, body weight; *CrCl*, creatinine clearance. Reproduced with permission from Owan TE, Hodge DO, Herges RM, et al: Secular trends in renal dysfunction and outcomes in hospitalized heart failure patients. *J Card Fail* 2006; 12:257–262.

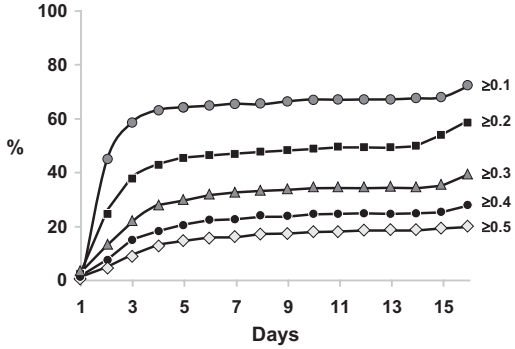

Figure 3. Occurrence of various degrees of worsening renal function (change in creatinine) throughout days of hospitalization. Reproduced with permission from Gottlieb SS, Abraham W, Butler J, et al: The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail* 2002; 8:136–141.

ing renal function, and DR are complex and interrelated.

Pathophysiology of Cardiorenal Failure

In HF, decreases in left ventricular systolic or diastolic function results in a number of hemodynamic derangements, including decreased cardiac output, stroke volume, and arterial underfilling (19). The decrease in effective arterial blood volume is sensed by arterial baroreceptors and causes the release of a cascade of neurohormones that produce compensatory mechanisms aimed at correcting the underfilling and restoration of organ perfusion. Activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, endothelin, and arginine vasopressin promotes volume retention. These sodium-retaining vasoconstrictive systems are balanced by activation of the vasodilatory, natriuretic hormonal or cytokine systems, including the natriuretic peptides, prostaglandins, bradykinin, and nitric oxide (20, 21). Under normal physiologic conditions, these pathways would act in concert to assist in the preservation of volume status and vascular tone and thus optimize cardiac output and organ perfusion. However, in HF, they promote the perpetuation of a vicious cycle of perturbations that ultimately result in chronic renal hypoxia, inflammation, and oxidative stress, which may adversely affect cardiac and renal structure and function independent of changes related to underlying atherosclerosis, hypertension, and diabetes (18, 22, 23). The HF state itself may promote irreversible structural and functional renal disease even in the absence of intrinsic renal disease, as is sometimes noted in younger patients with end-stage HF related to cardiomyopathies in the absence of atherosclerosis, hypertension, or diabetes.

Pathophysiology of Worsening Renal Function During ADHF Treatment

The worsening renal function so often observed during the treatment of ADHF is commonly ascribed to a prerenal state. This classification of acute worsening renal function is characterized by increases in blood urea nitrogen out of proportion to Cr and implies underperfusion of the kidney, which may be related to volume depletion or to decreases in cardiac output despite hypervolemia. As elegantly emphasized by Nohria et al. (16), ascribing worsening renal function during ADHF to existence of a prerenal state "does not clarify the mechanism or the solution" of the worsening renal function. While HF patients may develop worsening renal function associated with low or normal filling pressures with overdiuresis, worsening renal function more commonly occurs early in the treatment of the acute decompensation episode when patients are still markedly volume overloaded (13). Furthermore, extravascular volume redistributes rapidly in markedly volume-overloaded HF patients, protecting against intravascular

volume depletion. Indeed, in patients with less advanced cardiorenal dysregulation, vasodilators and diuretics typically normalize filling pressures without reducing cardiac output (15), and Ljungman et al. (24) showed that renal blood flow is preserved until the cardiac index falls below 1.5 L/m^2. Thus, the simplistic assumption that worsening renal function has developed in response to intravascular volume depletion or relative intravascular volume depletion is likely inaccurate and certainly does not identify a satisfactory therapeutic strategy (volume replacement) for persistently congested HF patients with worsening renal function.

While a single dominant mechanism responsible for worsening renal function in all patients with persistent congestion may never be defined, several contributing factors have been emphasized. In some patients, persistent vasoconstriction may be present, and use of vasodilators may improve cardiac output and renal perfusion. Unfortunately, this mechanism is less common in contemporary patients with long-standing and previously treated HF, as noted previously (16). The adverse effect of congestion and high central (and thus renal) venous pressure must be emphasized. Renal perfusion pressure not only is dependent on arterial pressure but is determined by the transrenal perfusion pressure and thus is equal to mean arterial pressure minus central venous pressure. Pulmonary hypertension, right ventricular dysfunction, and tricuspid regurgitation may contribute to extremely high renal venous pressures and reduce renal perfusion pressure dramatically. Indeed, Firth et al. (25) demonstrated the adverse effects of isolated elevation of central venous pressures on renal hemodynamics and sodium excretion. Improvement of renal perfusion with HF therapy may be due to increases in renal perfusion pressure mediated by reduction in central venous pressure. Inability to reduce central venous pressure may contribute to worsening renal function in some patients.

Adenosine and tubuloglomerular feedback may also play a role in the pathophysiology of cardiorenal syndrome. Adenosine binds to receptors on the afferent arteriole and causes local constriction, thereby reducing renal blood flow. Stimulation of A_1 adenosine receptors also increases sodium resorption in the proximal and distal tubules, leading to sodium and water retention. An acute increase in the delivery of sodium in the distal tubule with diuretic therapy causes an increase in adenosine concentrations via tubuloglomerular feedback (TGF) at the macula densa and afferent arterioles, which subsequently reduces glomerular filtration rate (GFR) (26). While this pathway represents an appealing explanation as it is susceptible to interruption with specific A_1 adenosine receptor antagonists, preliminary studies have reported that worsening renal function is not prevented when volume is removed mechanically without diuretic administration in HF (27), suggesting that distal sodium delivery and TGF are not the sole mechanisms responsible for worsening renal function in ADHF. Patients with new-onset HF will commonly develop minor increases in Cr when angiotensin converting enzyme inhibitors or angiotensin receptor blockers are initiated, as angiotensin II preferentially constricts the efferent renal arterioles, maintaining GFR. However, the typical patient with worsening renal function during an acute episode of decompensation has been treated with these agents for many years, and initiation of angiotensin converting enzyme inhibitors or angiotensin receptor blockers is not commonly the explanation for worsening renal function, as previously established (12, 28).

Unilateral or bilateral renal atherosclerosis is likely underrecognized in HF and may contribute to worsening renal function in many patients with ADHF. Renal artery atherosclerosis may be severe enough to compromise renal blood flow (renal artery stenosis) and it also predisposes to renal atheroembolism, which is particularly common following interventions that instrument the vasculature, including angiography, angioplasty, vascular surgery, and use of an intra-aortic balloon pump. Cholesterol emboli are thought to obstruct smaller renal arteries, which can subsequently lead to ischemic changes, precipitate hypertension, and ultimately cause progression of renal failure due to glomerular and peritubular capillary injury. Cholesterol emboli may also induce acute inflammatory changes (29, 30).

Use of drugs that perturb intrarenal hemodynamics, such as nonsteroidal inflammatory drugs or contrast agents, infection, or obstruction, must always be excluded in HF patients with worsening renal function, but such easily identified insults are not commonly the culprit. The pathophysiology of worsening renal function is likely diverse, with multiple mechanisms contributing in any patient. A comprehensive evaluation to exclude known causes of worsening renal function is mandatory.

Pathophysiology of Diuretic Resistance in HF

In those patients with both renal insufficiency and HF, loop diuretics are the diuretics of choice. This is due to the fact that thiazides have been found to be ineffective in patients with GFR <25–30 mL/min (31). To further understand how patients with HF and renal dysfunction become resistant to loop diuretics, one must understand the pharmacology of the loop diuretic and the physiology of cardiac and renal failure.

Oral absorption of loop diuretics, particularly furosemide, is impaired in the presence of gut hypoperfusion and edema, so intravenous administration is more effective in ADHF. Loop diuretics are avidly bound to protein and must be actively secreted into the proximal tubule. Severe hypoalbuminemia may thus increase the volume of distribution of loop diuretics and impair their delivery to the kidney. Coadministration of albumin with diuretics is advocated in patients with hypoalbuminemia to enhance delivery of diuretics to the kidney, although efficacy of this strategy is not well proven. Loop diuretics are then actively secreted into the tubular lumen and go downstream to the thick ascending limb, where they block the Na/K/2Cl cotransporter (31). Problems arise in patients with chronic renal dysfunction since organic acids are accumulated that act in direct competition with diuretics for secretion at the proximal tubule. In HF there is also reduced renal blood flow, and this further inhibits tubular delivery of the diuretic (19). This sets the background for what is known as the "braking phenomenon," where the response to the diuretic is reduced despite perception of adequate dosing (32, 33). Two important mechanisms contribute to this braking phenomenon. First, an enhanced rebound increase in sodium resorption mediated by poorly defined mechanisms typically occurs after a single daily dose of diuretics. This rebound phenomenon can completely negate the losses in sodium achieved with a single bolus dose of diuretic and may explain the enhanced effectiveness of similar total doses given as a continuous infusion or twice-daily dos-

Table 2. Approach to the patient with cardiorenal syndrome

1. Anticipate
2. Optimize HF therapy
3. Evaluate renal structure and function (ultrasonography accompanied by renal vascular evaluation with Doppler and resistive indices)
4. Optimize diuretic dosing
5. Consider renal-specific therapies
a. Renal-dose dopamine
b. Nesiritide
c. Ultrafiltration and/or hemodialysis
6. Investigational therapies
a. Hypertonic saline + high-dose loop diuretics
b. Vasopressin antagonists
c. Adenosine antagonists

HF, heart failure.

ing. Second, with chronic diuretic therapy, the distal tubular cells develop hypertrophy and enhanced sodium reuptake in response to the constant bombardment of solute delivery caused by the chronic blockade of the Na/K/2Cl transport (31). The effect of enhanced distal tubule sodium reuptake can be blocked by pairing loop diuretics with other diuretics that inhibit distal nephron resorption, such as thiazides.

APPROACH TO THE CARDIORENAL SYNDROME

The development of worsening renal function and/or DR during the treatment of the patient with cardiorenal failure is a common and predictable but difficult clinical problem. There is no consistently effective strategy, and much of the approach is empirical (Table 2).

Recognize the Cardiorenal Syndrome and Anticipate the Development of Worsening Renal Function and/or DR

Patients developing the cardiorenal syndrome in the setting of ADHF and persistent congestion are usually those with long-standing HF who experience an episode of decompensation despite adequate chronic HF therapy and who are already on chronic high-dose diuretic therapy. A progressive increase in Cr over recent years is typically evident and reflects not only the underlying renal disease but the additional effect of the HF state as outlined previously. Patients with severe diastolic dysfunction (regardless of ejection fraction), secondary pulmonary hypertension, right ventricular dysfunction, marked functional tricuspid or mitral regurgitation, previous HF hospitalizations, a history of worsening renal function with previous ADHF episodes, or a history of transient dialysis (often after cardiac surgery or contrast administration) are at the highest risk. In many patients, development of the cardiorenal syndrome is a marker of the transition to stage D HF (Fig. 4). It is helpful to address the potential for worsening renal function with the patient at admission, including the prognostic implications of cardiorenal syndrome and stage D. An assessment of suitability for dialysis and advanced HF therapies, such as cardiac support (left ventricular assist device) or replacement (transplantation), should be made. Unfortunately, the vast majority of patients developing cardiorenal syndrome will not be candidates for advanced HF treatments, such as transplantation or left ventricular assist device, due to age and comorbidities. Anticipation of a very high risk for cardiorenal syndrome may support use of different strategies, such as more gradual volume removal or early use of (potentially) renal-protective strategies (discussed subsequently). However, whether slower volume removal or the variety of strategies available to preserve renal function will affect the development of the cardiorenal syndrome or improve outcomes is unknown.

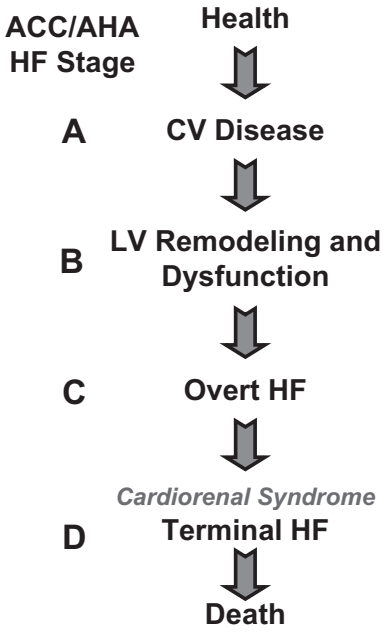

Figure 4. Development of the cardiorenal syndrome as a marker of the transition to stage D heart failure (*HF*). *ACC/AHA*, American College of Cardiology/American Heart Association; *CV*, cardiovascular; *LV*, left ventricular. Reproduced with permission from Hunt SA, Baker DW, Chin MH, et al: ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation* 2001; 104:2996–3007; and reproduced with permission from Hunt SA, Abraham WT, Chin MH, et al: American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society. 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: 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): Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation; endorsed by the Heart Rhythm Society. *Circulation* 2005; 112:e154–235.

Optimize Heart Failure Therapy

While therapy for ADHF often focuses on volume removal, careful review of the patient's HF therapy addressing the adequacy of vasodilator therapy, blood pressure control, or the potential for additional adjuvant therapy (digoxin, nitrates, cardiac resynchronization therapy) is important. Addressing factors that can provide additional symptom relief (paracentesis, thoracentesis) or optimize cardiac function (revascularization, correction of valve disease) should be considered early in the hospitalization. While the ESCAPE trial did not show that early use of hemodynamically guided therapy improved survival in severe HF (11), many centers are still aggressive in the use of pulmonary artery catheters in difficult patients with cardiorenal syndrome to ensure that hemodynamics and standard HF therapies are optimized. In some cases, having such data may reassure the managing cardiologist and the consulting nephrologist that measures to improve cardiac function and renal perfusion have been addressed and may facilitate the decision to offer renal replacement therapy, chronic palliative HF therapy, or hospice care. Importantly, pulmonary artery catheter guided therapy commonly includes administration of an inotropic

agent. Use of inotropic agents is consistently associated with poorer outcomes, whether in randomized trials or retrospective registries, and their ability to improve cardiac status in the hospital must not be equated with improved outcomes (34, 35).

Evaluate Renal Structure and Function

A careful history should identify factors that may be exacerbating disease and HF-related renal dysfunction, such as infection, use of nephrotoxic agents, or risk factors for renal artery stenosis. Urinalysis, including microscopic analysis for urine eosinophils (seen in allergic interstitial nephritis or renal atheroembolism), renal ultrasound with Doppler imaging of renal arteries, and assessment of renal resistive indices, should be performed to assess renal size, renal artery stenosis, or obstruction and to characterize structural renal disease. If suspicion for renal artery stenosis is high, one can consider magnetic resonance imaging with angiography, although this is increasingly difficult in patients with systolic HF due to the presence of devices. Computed tomography angiography to assess for renal artery stenosis is often precluded because of the potentially high risk of contrast nephrotoxicity and renal atheroembolism. The risk-benefit ratio of contrast administration must be weighed carefully as even gadolinium (used with magnetic resonance angiography) carries risk of worsening renal function in HF patients. The role of renal biopsy has not been well defined in this setting, and clearly the risk-benefit ratio must be considered on an individual basis. However, in patients in whom the cause of acute renal failure is unclear even after a thorough history, physical examination, and laboratory and clinical investigations are performed, renal biopsy may provide definitive diagnostic information that is helpful in guiding therapy or prognosis.

Optimize Diuretic Dosing

Continuous infusion of loop diuretics (i.e., furosemide) may provide greater diuresis and better safety profile compared with bolus injection. A meta-analysis of studies comparing continuous infusion vs. bolus injection of loop diuretics in acutely decompensated HF was performed by Salvador et al. (36) and included eight trials involving 254 patients (urine output was greater in patients given continuous infusion with a weighted mean difference of 271 mL/24 hrs, $p < .01$). Electrolyte disturbances (hypokalemia, hypomagnesemia) were not significantly different between the two groups (relative risk [RR] 1.47; 95% confidence interval [CI] 0.52–4.15; $p = .5$). There were fewer adverse effects (tinnitus and hearing loss) after continuous infusion compared with bolus injection (RR 0.06; 95% CI 0.01–0.44; $p = .005$). In addition, one study showed that the hospital duration of stay was significantly shortened (by 3.1 days), one study showed lower cardiac mortality, and two studies showed lower all-cause mortality in patients treated with continuous infusion vs. bolus injection of furosemide. Therefore, most studies suggest a greater diuresis and better safety profile when loop diuretics are given as a continuous infusion. However, since the studies were small, mostly crossover trials and were relatively heterogeneous, evidence is insufficient to definitively recommend one method of administering loop diuretics, and further larger studies are needed.

In addition to the mode of administration of loop diuretics, the addition of thiazide diuretics in combination with loop diuretics has been shown to improve efficacy and diuretic responsiveness in severe refractory HF (37, 38). Dormans and Gerlag (38) found that in 20 patients with New York Heart Association (NYHA) class III and IV HF, edema, and diuretic resistance, addition of hydrochlorothiazide to furosemide resulted in a mean body weight reduction of 6.7 ± 3.3 kg per patient. Mean daily urine volume increased and fractional sodium excretion increased significantly ($p < .001$ for both). Due to potentially dangerous adverse effects, such as hypokalemia, metabolic alkalosis, and dehydration, careful monitoring of the patient is necessary if combination diuretics are used.

Consider Renal-Specific Therapies

Renal Dose Dopamine. The use of low-dose or "renal dose" dopamine, at doses <5 μg/kg/min (usually 2–4 μg/kg/min), has been proposed in the past to prevent or treat acute renal failure and to increase urine output in HF patients refractory to loop diuretics. Physiologically, low-dose dopamine increases renal blood flow and increases urine output by stimulating both dopaminergic (DA-1 and DA-2) and adrenergic (both α and β) receptors. Therefore, low-dose dopamine may affect renal blood flow by direct vasodilation (dopamine receptors), by increasing cardiac output (β receptors), or by increasing perfusion pressure via vasoconstriction (α receptors). At low doses (especially <2 μg/kg/min), dopaminergic receptor effects predominate, resulting in renal vasodilatation and increased renal blood flow. Dopamine also inhibits aldosterone release and inhibits sodium-potassium adenosine triphosphatase at the tubular epithelial cell level, resulting in increased sodium excretion and thereby diuresis (39–43).

Several early studies showed significantly increased natriuresis, diuresis, and improved renal function with use of low-dose dopamine (42, 44–55). Other studies have also suggested a role for dobutamine, ibopamine (a dopamine congener), and fenoldopam in reducing renal vascular resistance, increasing cardiac output, and increasing natriuresis, urine flow, and CrCl (56–60). However, these studies were largely small, underpowered, and nonrandomized.

The overwhelming consensus among studies with more rigorous methodology (e.g., randomized prospective studies with larger sample size) is that there is no convincing scientific evidence of a beneficial effect with low-dose dopamine beyond a possible natriuretic diuresis (39, 40, 56, 61–81). Furthermore, dopamine has significant potential side effects, including digital cyanosis and gangrene (82). Vargo et al. (83) found that dopamine does not enhance furosemide-induced natriuresis in patients with HF, and those investigators had to discontinue the trial after six of eight patients were recruited because of adverse events and lack of natriuretic efficacy after addition of dopamine to furosemide infusion in two of the patients. A large meta-analysis by Kellum and Decker (39) concluded that "the use of low-dose dopamine for the treatment or prevention of acute renal failure cannot be justified on the basis of available evidence and should be eliminated from routine clinical use." Therefore, based on these studies, there is little if any role for renal dose dopamine in heart failure therapy in attempts to preserve renal function.

Nesiritide as Renal Protective Therapy. Nesiritide (synthetic human B-type natriuretic peptide) is a potent vasodilator that has been used to rapidly reduce cardiac filling pressures and improve dys-

pnea in patients with ADHF (84–87). Several early moderately sized controlled trials (87–91) as well as large prospective registries (92) suggested that nesiritide was safe in the short-term management of these patients. However, studies conflict on nesiritide's effects on renal function, natriuresis, and diuresis.

Wang et al. (93) studied 15 patients with NYHA class III or class IV HF (baseline Cr 1.5 ± 0.4 mg/dL, admission Cr 1.8 ± 0.8 mg/dL) with volume overload requiring hospital admission in a double-blind, placebo-controlled, crossover study examining the effects of nesiritide (2 μg/kg bolus followed by an infusion of 0.01 μg/kg/min) vs. placebo given for 24-hr infusion periods. There were no differences in GFR (40.9 ± 25.9 mL/min with placebo vs. 40.9 ± 25.8 mL/min with nesiritide), effective renal plasma flow, urine output (113 ± 51 mL/hr with placebo vs. 110 ± 56 mL/hr with nesiritide), or sodium excretion for any time interval or for the entire 24-hr period between the nesiritide and placebo study days (93).

Sackner-Bernstein et al. (94) performed a meta-analysis of randomized, double-blind, parallel-group controlled trials of nesiritide (vs. placebo or active control) in patients with ADHF to assess the risk of worsening renal function, which suggested that nesiritide may have adverse impacts on renal function. Worsening renal function was defined as an increase in serum Cr >0.5 mg/dL. After rigorous methodological selection criteria, five randomized studies that included 1,269 patients were analyzed. Use of nesiritide at Food and Drug Administration (FDA)-approved doses (≤0.03 μg/kg/min) significantly increased the risk of worsening renal function compared with noninotrope-based control (RR 1.52; 95% CI 1.16–2.00; $p = .003$) or any control therapy, including noninotrope- and inotrope-based therapies (RR 1.54; 95% CI 1.19–1.98; $p = .001$). Even low-dose nesiritide (≤0.015 μg/kg/min) significantly increased risk ($p = .012$ and $p = .006$ compared with noninotrope- and inotrope-based controls, respectively), as did nesiritide at doses up to 0.06 μg/kg/min ($p = .002$ and $p = .001$, respectively). There was no difference in the need for dialysis between therapy groups (94).

Despite these negative studies, subsequent studies and observations have suggested that nesiritide may still hold promise as a renal-protective therapy in advanced HF therapy when used in appropriate doses. Yancy and Singh (95) reported a retrospective substudy of the Follow-Up Serial Infusions of Nesiritide trial (FUSION I) assessing the feasibility of outpatient administration of nesiritide in 138 patients with comorbid advanced HF and renal insufficiency (estimated CrCl <60 mL/min). These patients, deemed high risk for the cardiorenal syndrome, received one of three open-label treatments once weekly for 12 wks: standard care, standard care plus nesiritide 0.005 μg/kg/min, or standard care plus nesiritide 0.010 μg/kg/min. The primary end point was safety, not efficacy. Nesiritide at these two doses was well tolerated with no increase in incidence of worsening renal function. The frequency of all-cause mortality and hospitalization through week 12 was lower in patients receiving nesiritide. These findings suggest that adjunctive therapy with nesiritide on an outpatient basis may be beneficial for patients with advanced HF and renal insufficiency (95).

Riter et al. (96) reported on the safety of nonhypotensive low-dose nesiritide, such as 0.005 μg/kg/min or 0.0025 μg/kg/min without bolus, as opposed to the FDA-approved standard recommended dose, including a bolus of 2 μg/kg followed by an infusion of 0.01 μg/kg/min in ADHF. In this retrospective case-control study, low-dose nesiritide was well tolerated without a significant decrease in systolic blood pressure, whereas there was a significant decrease in systolic blood pressure with standard-dose nesiritide and no nesiritide. The low-dose nesiritide group had improvement in renal function and equivalent diuresis with lower furosemide doses. These findings suggested that the lack of decrease in systolic blood pressure in the low-dose nesiritide group allowed the renal-protective effect of nesiritide. Further prospective randomized controlled trials to test the efficacy of nonhypotensive low-dose nesiritide in patients with ADHF are warranted (96).

Recently, in a preliminary report from Owan et al. (97), use of standard dose nesiritide, despite lowering blood pressure, was associated with improved renal function indices at 24 hrs. This single-center, randomized trial included 72 adult patients with ADHF and renal dysfunction (mean Cr 1.75 ± 0.59 mg/dL and eGFR 34.5 ± 15.7 mL/min/1.73 m^2) who were randomized on admission to receive standard therapy (diuretic dosing algorithm based on renal function) or standard therapy plus adjuvant nesiritide at the standard dose of 2 μg/kg followed by an infusion of 0.01 μg/kg/min for 48 hrs. Diuretic responsiveness, measured by change in weight and/or fluid balance, tended to be less with nesiritide at 24–72 hrs and at discharge, but these trends did not reach statistical significance. The early enhancement of renal function despite bolus diuretic dosing and hypotensive effects of adjunctive nesiritide therapy suggests that further studies to define optimal dose and/or routes of administration for natriuretic peptides as renal protective therapy in ADHF are warranted. Furthermore, preliminary findings from a trial in which nesiritide was administered at a standard dose (0.01 μg/kg/min) without a bolus to patients undergoing cardiac surgery have been reported, and a marked reduction in the incidence of renal dysfunction was noted (98). Thus, the role of nesiritide as a renal-protective and diuresis-promoting therapy in ADHF remains promising but requires further study.

Ultrafiltration. When traditional medical therapies fail or patients become resistant to diuretics, other therapeutic options must be undertaken to relieve volume overload. Ultrafiltration has been recognized as a viable treatment option by the Heart Failure Society of America and the American College of Cardiology/American Heart Association for diuretic-resistant HF (strength of evidence = C) (99).

Ultrafiltration (UF) or slow continuous UF filters plasma water directly across a semipermeable membrane in response to a transmembrane pressure gradient, resulting in an ultrafiltrate that is isoosmotic compared with plasma water (100, 101). In contrast, hemodialysis involves the passage of solutes and water from the blood across a semipermeable membrane down a concentration gradient between the blood and dialysate via diffusion, allowing for changes in electrolytes and small solutes. Hemofiltration uses membranes (polyacrylonitrile or polycarbonate) with greatly increased hydraulic permeability, so that solute is removed by bulk flow (101, 102). In continuous venovenous hemofiltration, fluid and medium-sized solutes are removed by bulk flow and solvent drag at large volumes per hour, with replacement fluids administered to the patient simultaneously. This allows for clearance of potentially toxic solutes, while maintaining stable hemodynamics. Continuous venovenous hemodiafiltration is essentially continuous venovenous hemofiltration with the addition of dialysate on the other

side of the semipermeable membrane, allowing diffusion of small solutes to occur simultaneously with continuous venovenous hemofiltration.

Extracorporeal UF for fluid removal dates from the advent of dialysis therapy, and its technique was proposed by Silverstein et al. (103) in 1974 as a modification of the standard hemodialysis circuit (100, 103, 104). Since then, it has been studied extensively and proven to be an effective treatment for patients with HF who are fluid overloaded and diuretic resistant, with fewer adverse effects than hemodialysis and peritoneal dialysis. UF promotes the resorption of systemic extravascular water and can effectively treat pulmonary edema in patients with HF.

Agostoni et al. (105) performed UF in outpatients with moderate HF without volume overload and showed dramatic physiologic responses to a single UF treatment to reduce right atrial pressure by 50%. Clinical and functional improvement was dramatic and lasted up to 6 months. The radiographic score of lung water, exercise tolerance (peak oxygen consumption), dynamic lung compliance, ventilation, tidal volume, and deadspace/tidal volume ratio at peak exercise improved significantly (105). In addition, there were improvements in neurohumoral responses (106). In contrast, furosemide infusion at a dosage that achieved equivalent fluid removal produced clearing of the lungs, but this benefit was not sustained, and the dramatic improvements in lung function, exercise performance, and neurohumoral function observed with the UF treatment were not observed with diuretic administration titrated to produce a similar reduction in right atrial pressure (106, 107). These remarkable observations suggest that this form of therapy may have unique benefits, but these elegant studies have not been repeated in patients with ADHF and marked volume overload.

Multiple retrospective case cohort studies have been performed studying the efficacy of traditional UF in severe diuretic refractory HF, with variable results (108–120). Some studies showed sustained symptomatic improvement, some restoration of diuretic responsiveness, and no deterioration in renal function following UF (108–113, 115, 116, 118–120), whereas others found only transient improvement (109, 113–116, 118–120). In aggregate, these studies showed a highly variable clinical response to UF in severe refractory, diuretic resistant HF. Indeed, the morbidity and mortality of this patient population remained high despite UF, even when it was used successfully in these cohorts. Therefore, the role of UF to improve renal function, avoid the need for chronic renal replacement therapy, or modify outcomes in severe HF remains unclear.

Recently, a peripherally inserted UF device manufactured by HF Solutions (Aquadex, System 100) was approved by the FDA for therapy in HF. This device allows UF to be performed at very low flows (40 mL/min) using only a peripheral intravenous catheter and a midline catheter in an antecubital vein, with only 33–40 mL of extracorporeal blood at any given time. This simple machine is designed for use by nonnephrologists and nurses, avoiding the need for intensive care or dialysis units.

Jaski et al. (121) performed the first prospective observational study to verify the safety and function of this device for rapid reversal of volume overload states in patients with symptoms and signs of fluid congestion. These investigators concluded that rapid removal of fluid could be safely achieved in volume overload states via peripherally inserted UF without the need for central venous catheter placement.

Bart et al. (122) conducted a multicenter randomized controlled trial (RAPID-CHF) with the System 100 device and compared a single 8-hr session of UF to usual care in patients admitted with ADHF with volume overload. UF was successful in 18 of the 20 patients, but the primary end point, weight loss after 24 hrs, was 2.5 kg in the UF group vs. 1.86 kg in the usual care group ($p = .24$). This study was limited by the small number of patients, short follow-up, variable use of diuretics in the UF group, lack of reporting of incidence of worsening renal function, and lack of data concerning variability in results (122).

Costanzo et al. (123) also studied this device in a prospective observational study to assess if early UF before use of intravenous diuretics could reestablish euvolemia and diuretic responsiveness (EUPHORIA trial). Twenty patients with volume overload and diuretic resistance received UF within 4.7 ± 3.5 hrs of hospitalization. This study did not include a control group, did not report incidence of worsening renal function or daily changes in Cr during hospitalization, but did demonstrate that fluid could be removed with UF in this HF population (123).

Dahle et al. (124) also reported successful use of the peripherally inserted UF device in a cohort of nine hospitalized patients with decompensated HF refractory to standard inpatient medical therapy. In this study, UF was performed for much longer durations (mean length of time of UF therapy was 33.3 ± 20.0 hrs with a mean volume removal of 7.0 ± 4.9 L). There was no statistically significant change in renal function based on pre- and post-UF Cr, although this patient population was relatively young with less severe renal dysfunction. Whether these patients were resistant to aggressive diuretic dosing was unclear.

Liang et al. (125) described the initial experience with the peripherally inserted UF device in a subset of 11 severe HF patients with DR despite aggressive HF and diuretic therapy. Baseline Cr was 2.2 ± 0.8 mg/dL and CrCl was 35 ± 17 mL/min. Nine patients had documented right ventricular dysfunction, six with severe tricuspid regurgitation. Of the total UF runs, 13 (41%) removed >3500 mL, 11 (34%) removed 2500–3500 mL, and eight (25%) removed <2500 mL. Five patients experienced an increase in Cr of ≥0.3 mg/dL. In these patients with severe cardiorenal syndrome, despite successful removal of fluid via the UF device, 50% ultimately required dialysis, and length of stay, costs, and mortality rates were high (125).

Recently, Costanzo et al. reported on Ultrafiltration vs. IV Diuretics for Patients Hospitalized for Acute Decompensated HF (UNLOAD), a larger randomized controlled trial using the System 100 UF device (126). Patients were randomized within 24 hrs to UF vs. intravenous diuretics. UF was performed at flows up to 500 mL/hr. Weight loss at 48 hrs and fluid loss was greater in the UF group than the standard care group ($p = .001$ for both), but change in dyspnea score was not statistically significant. Rate of rehospitalization (18% in UF vs. 32% in standard care) and days of hospitalization (123 days vs. 330 days in standard care) were significantly lower in the UF group compared with the standard care group. Further analyses of the data from the recent UNLOAD trial showed that while there were no greater increases in serum Cr or in the percent of patients with increases in serum Cr >0.3 mg/dL between those treated with UF and those given intravenous diuretics at all time intervals

(24 hrs, 48 hrs, and discharge), there was also no protective effect of UF (vs. diuretics) on renal function and there were trends toward greater increases in creatinine with UF (albeit in the setting of greater volume removal). There was also no correlation between net fluid removed and changes in serum Cr in either the UF group or the intravenous diuretics group. These findings suggest that other mechanisms besides volume depletion cause worsening renal function in HF patients during volume overload treatment (27). Importantly, UF was shown to remove more sodium and less potassium than diuretics for an equivalent amount of volume reduction (127). This critical difference may promote more sustained volume reduction and offer the potential for improved long-term outcomes with UF compared with diuretics. However, the expense and complexity of treatment limit the potential use of UF as a first-line strategy in all patients with ADHF. Whether rescue therapy with UF in patients with established cardiorenal syndrome will prove superior to standard care remains to be established.

Investigational Therapies for Cardiorenal Syndrome

Hypertonic Saline Plus Furosemide. Paterna et al. (128) described success in treating patients with refractory HF with the combination of high-dose furosemide and small-volume hypertonic saline solution. A total of 94 patients with refractory HF with ejection fraction <35%, serum Cr <2 mg/dL, blood urea nitrogen <60 mg/dL, urine output <500 mL/day, and urine sodium excretion <60 mEq/day were randomized to receive either high-dose intravenous furosemide (500–1000 mg) plus hypertonic saline solution twice a day in 30 mins or intravenous bolus furosemide (500–1000 mg) twice a day, for 4–6 days. Significant increases in daily diuresis and natriuresis, as well as improvements in B-type natriuretic peptide and bioelectrical impedance measurements, were observed in the furosemide plus hypertonic saline solution group. The hypertonic saline solution group also showed a significant reduction in hospitalization time and readmission rate.

Potential mechanisms of increased sodium load in the therapy of HF may relate to an acute osmotic effect of hypertonic saline to increase mobilization of extravascular fluid into the central circulation and renal circulation. Increases in renal blood flow may facilitate diuretic responsiveness. In addition, direct intratubular effects of sodium flooding may overwhelm the rebound sodium retention seen in diuretic therapy, thus reducing the "braking phenomenon" discussed previously. Furthermore, neurohormone levels may have been suppressed by hypertonic saline. The increased intravascular volume and greater distal tubule sodium delivery may inhibit the renin-angiotensin-aldosterone system, causing reductions in aldosterone, angiotensin II, and vasopressin (or antidiuretic hormone) release despite a temporary increase in serum osmolarity. There may also be a small contribution of increased intravascular volume causing inhibition of antidiuretic hormone release via volume/baroreceptors, leading to reduced free water resorption via aquaporin channels in the collecting tubules of the kidney (129). This novel strategy has yet to be tested by other groups.

Vasopressin Antagonists in Heart Failure Therapy. Vasopressin antagonists represent another promising class of therapeutics that may improve aquaresis and hyponatremia in patients with chronic HF. Vasopressin, also known as arginine vasopressin or antidiuretic hormone, is a cyclic hexapeptide produced in the hypothalamus and released from secretory granules in the posterior pituitary lobe in response to hyperosmolality, volume depletion, angiotensin II, and sympathetic stimulation. Vasopressin causes vasoconstriction and renal water resorption via the vasopressin receptor subtypes V1a (vascular), V2 (renal), and V3 (pituitary) receptors (130, 131). V1a receptors, found in vascular smooth muscle cells and the kidney, mediate vasoconstriction and prostaglandin production at supraphysiologic concentrations of vasopressin (132). V2 receptors, found in the renal collecting tubules (principal cells), mediate renal water resorption via insertion of aquaporin 2 channels into the luminal membranes and also release of von Willebrand factor and factor VIII from the vascular endothelium. V3 receptors, found in the pituitary gland, are responsible for stimulating adrenocorticotropic hormone secretion by pituitary corticotropes.

In HF, vasopressin levels are elevated due to signaling of the carotid sinus baroreceptors functioning as volume receptors in the setting of decreased effective arterial blood volume from low cardiac output. When systemic blood pressure drops sufficiently, as in advanced HF, antidiuretic hormone secretion markedly increases to levels that far exceed those induced by changes in plasma osmolality. In addition, the volume depletion can prevent the inhibition of antidiuretic hormone release normally induced by a decrease in plasma osmolality, which contributes to the development of hyponatremia in HF.

Antagonism of the V1a and V2 receptors may be beneficial in HF patients (132–135). Antagonism of V1a receptors increases cardiac output, reduces total peripheral vascular resistance, reduces mean arterial blood pressure, and inhibits vasopressin-mediated cardiomyocyte hypertrophy (132). Antagonism of V2 receptors results in aquaresis, causing increased serum sodium concentration and reduced cardiac preload (132). In HF, two vasopressin antagonists have shown promise in early clinical trials: 1) conivaptan (YM-087), an oral or intravenous V1a/V2-receptor antagonist; and 2) tolvaptan (OPC-41061), an oral specific V2-receptor antagonist.

The acute efficacy of intravenous conivaptan was evaluated in 142 patients with symptomatic HF (NYHA class III and IV) in a randomized double-blind, short-term study (136). Conivaptan reduced preload and increased urine output and serum sodium levels. The ADVANCE trial is a double-blind, placebo-controlled study of the safety and efficacy of 12 wks of chronic oral conivaptan therapy in three doses compared with placebo on chronic HF symptoms in 345 patients with NYHA class II–IV symptoms. This trial will assess functional capacity during treadmill exercise and the symptoms of heart failure (137). While a role for oral conivaptan therapy in HF is being tested in this clinical trial, currently only the intravenous formulation of conivaptan has been developed and approved in the United States, and it is only approved for treatment of patients with euvolemic hyponatremia.

Tolvaptan, an oral V2-receptor antagonist, has been shown to induce aquaresis in animals and humans (138–140). In a randomized double-blind trial, 254 patients with NYHA class I–III heart failure were randomly assigned to administration of tolvaptan at variable doses in combination with standard furosemide therapy for 25 days (141). Tolvaptan significantly decreased body weight, increased urine volume, increased net fluid loss, decreased urine osmolality, increased mean

total 24-hr urinary sodium excretion, increased serum sodium, and improved edema. Its effect was observed primarily on the first day. In the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist (ACTIV) in HF study (142), 319 patients admitted for decompensated HF were randomized to placebo vs. tolvaptan at variable doses plus routine therapy, including diuretics for up to 60 days. After 24 hrs, patients treated with tolvaptan had a significant reduction in body weight compared with those administered placebo; this effect was not dose dependent. There was also an increase in mean urine output at 24 hrs and a slight increase in mean serum sodium levels from baseline in patients treated with tolvaptan. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial is an ongoing international, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the long-term efficacy and safety of oral once-daily tolvaptan in patients hospitalized with worsening HF (143).

The results of these ongoing trials will add further insight into the potential therapeutic usefulness of vasopressin antagonists in the treatment of advanced HF and define their impact on the cardiorenal syndrome.

Adenosine Antagonists in Heart Failure Therapy. Another promising new class of therapeutic agents is the A1 adenosine receptor antagonists. Plasma adenosine levels are elevated in patients with HF, with increasing levels as the severity of disease increases (144). As noted previously, TGF promotes release of adenosine, and adenosine binding to A1 receptors causes vasoconstriction of the afferent arteriole, decreased renal blood flow and GFR, and enhanced sodium resorption by the proximal tubule. Antagonism of A1 adenosine receptors has the potential to improve renal function and overcome DR in patients with HF by disrupting the TGF loop (26, 145).

BG9719 (or CVT-124) is a selective A1 adenosine receptor antagonist that has been shown to cause a potassium-neutral diuresis while maintaining renal function in animal studies (146) as well as human studies (26, 147). In a pilot study of 12 patients with NYHA class III or IV HF, the renal effects of placebo, CVT-124, and furosemide were compared (147). Administration of CVT-124 increased sodium excretion without decreasing GFR; in contrast, furosemide decreased GFR significantly.

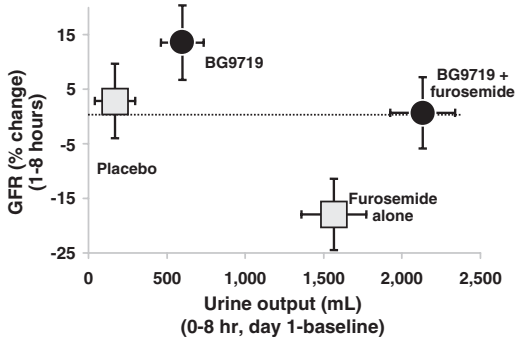

Figure 5. The relationship between change in urine volume and change in creatinine clearance for patients receiving the 0.75-μg/mL concentration of the A1 adenosine receptor antagonist BG9719 (CVT-124). BG9719 increased urine output when given with or without furosemide. The decrease in glomerular filtration rate (*GFR*) with furosemide alone was not seen when BG9719 was given. Reproduced with permissions from Gottlieb SS, Brater DC, Thomas I, et al: BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. *Circulation* 2002; 105:1348–1353.

Gottlieb et al. (26) subsequently studied 63 edematous patients with symptomatic NYHA class II–IV HF with ejection fraction ≤40% in a randomized, double-blind, ascending-dose, crossover study evaluating three doses of BG9719 (given as a loading dose followed by a 7-hr infusion) and placebo, in combination with 80 mg of intravenous furosemide. Both BG9719 alone and furosemide alone caused a large diuresis, but the addition of BG9719 to furosemide increased diuresis. BG9719 alone improved GFR, while furosemide alone caused a decline in GFR. When BG9719 was added to furosemide, it prevented the furosemide-mediated decline in GFR (Fig. 5). Therefore, A1 adenosine receptor antagonism may preserve renal function while simultaneously promoting enhanced response to loop diuretics during treatment for heart failure.

Similar findings have been reported in small, early studies with the A1 adenosine receptor antagonist KW-3902 (148, 149). A large phase III multicenter study of KW-3902 (PROTECT-1) in ADHF is currently underway (150). The results of larger randomized studies such as this one are needed to determine whether A1 adenosine receptor antagonists will prevent worsening renal function and avoid DR in patients with HF at risk for cardiorenal syndrome. In addition, adenosine may exert negative inotropic and chronotropic effects via A1 receptors in the heart. Thus, A1-receptor antagonists could potentially have positive inotropic effects, and if used clinically, their cardiac safety will need to be proven (145).

CONCLUSION

The cardiorenal syndrome is a complex and diverse pathophysiologic state manifest by concomitant heart and kidney failure (cardiorenal failure), worsening renal function during ADHF treatment, and diuretic resistance in the setting of persistent congestion. The cardiorenal syndrome often heralds the transition to end-stage, preterminal (stage D) HF. The challenge is to recognize the syndrome, reverse it when possible, and deal with its consequences for ADHF management. An incomplete understanding of the pathophysiology and the limited treatment options enhance the difficulty of defining satisfactory approaches in individual patients. The diversity in HF patients in terms of age, type of HF, and underlying disease and the variation in the relative role of each of the features of the cardiorenal syndrome (cardiorenal failure, worsening renal function, and diuretic resistance) preclude the use of a single approach. Emerging therapies bring hope for better outcomes in these challenging patients, but currently available strategies are largely unproven.

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