CHAPTER 112

Cardiorenal Syndrome Type 2

Ajay Srivastava, Paras Dedhia, and Charuhas V. Thakar

OBJECTIVES

This chapter will:
1. Review the definition and epidemiology of cardiorenal syndrome type 2 (CRS-2).
2. Identify the theoretical pathogenic pathways of CRS-2.
3. Discuss management strategies for CRS-2.
4. Introduce adjunct management assistive devices, such as cardiac resynchronization therapy and implantable pulmonary artery pressure sensors.

Heart failure (HF) is a growing public health problem in the United States, affecting more than 5 million people, with more than 550,000 new cases diagnosed each year.[1,2] Primarily a disease of the elderly, HF is associated with a high prevalence of comorbid conditions, such as hypertension, diabetes, and chronic kidney disease (CKD). Based on an analysis of a 5% Medicare sample between 1994 and 2003, the prevalence of HF in patients over 65 years of age increased from 89 to 121 per 1000 eligible Medicare beneficiaries. This also was accompanied by a significant increase in the prevalence of comorbid conditions: 64% of HF patients suffered from ischemic heart disease, 89% had hypertension, and 35% had diabetes.[3] Acute HF is one of the most common reasons for hospitalization in the United States and accounts for more than 1.1 million admissions annually.[2] It is also evident that, along with other comorbid conditions, approximately 40% of patients hospitalized with HF have abnormal renal function upon hospital admission with a serum creatinine (SCr) value exceeding 1.5 mg/dL.[4] Considering their medical complexity and dual organ involvement, the management of these patients poses an enormous task for healthcare providers, because they have to balance effective implementation of treatment guidelines while minimizing the risk of complications.

The true nature regarding the relationship between the heart and kidney is exemplified when discussing cardiorenal syndromes (CRS), whereby a complex pathophysiologic interplay ensues. Acute or chronic dysfunction of varying severity in one organ leads to the same in the other. A detailed categorization of the five subtypes (i.e., CRS types 1 through 5)[5] has helped elucidate this temporal association regarding the aberrant organ, consequently leading to the subsequent pathophysiologic changes in the other organ. All the subtypes are associated with increased morbidity and mortality and consequently risk factor modification, treatment strategies, and future research depend on our understanding of the precise pathophysiologic mechanisms of each.[6]

CRS type 2 (CRS-2) is defined as the onset or progression of CKD secondary to chronic HF from various causes, including congenital and acquired cardiac disease, stable or progressive HF, or from repeated episodes of acute decompensated HF.[6]

A temporal relationship between the occurrence of chronic HF and a consequent onset or progression of CKD is required to define CRS-2. Given the inherent difficulty in identifying the antecedent causal occurrence in patients that have co-existing chronic HF and chronic kidney disease (CKD), the term CRS "type 2/4" also has been suggested.[7]

This chapter outlines the epidemiology, pathogenesis, diagnosis, and management of CRS-2.

EPIDEMIOLOGY OF CARDIORENAL SYNDROME TYPE 2

Unfortunately, the data regarding the relationship between clinical outcomes and management in subjects with CKD in HF is not very robust because patients with elevated serum creatinine levels are typically excluded from prospective studies in HF.[8] Therefore large observational registries offer insight into the prevalence of CKD in this population of patients. However, these observational studies often report a one-dimensional view based on the presence or absence of a particular comorbidity, such as CKD in HF,[6] making it difficult to distinguish between CRS-2 and CRS-4.[9] Moreover, there appears to be wide variability on prevalence rates: For example, data from the ADHERE registry regarding nearly 120,000 acutely hospitalized HF patients demonstrated that CKD (defined as Modification of Diet in Renal Disease [MDRD] GFR < 60 mL/min/1.73 m^2 of BSA) was present in 64% of patients,[10] while another study indicated it to be as low as 12%.[11]

Another challenge in interpreting the natural history of CRS-2 from observational data is that these studies: (1) typically use acute care admissions as a starting point, which essentially represents CRS-1 superimposed on perhaps an underlying CRS-2 and (2) do not have longitudinal data beyond hospital discharge other than long-term survival. This leaves several gaps between the proposed pathophysiology of CRS-2 and clinical evidence.

PATHOGENESIS

In CRS-1, the decline in renal function occurs in the setting of an acutely decompensated HF with a resulting drop in cardiac output and increased renal venous pressures. In CRS-2, the mechanisms are less acute and not as well understood. A number of intricate mechanisms have been proposed regarding the pathogenesis of CRS-2, which include neurohormonal activation, the imbalance between nitric oxide and reactive oxygen species, renal hypoperfusion, venous congestion, and inflammation.[6]

Neurohormonal Changes in Heart Failure

Neurohormones are formed by specialized neurosecretory cells, which because of their part in the nervous

system structure, can act as a neurotransmitter as well as a hormone. In a pathologic state such as CRS, they play a role in mediating an oxidative stress or injury cascade that includes pervasive inflammation, endothelial dysfunction, and cellular death. Neurohormonal abnormalities represent an imbalance between elevated production of vasoconstrictive mediators such as epinephrine, endothelin, and angiotensin and an altered sensitivity and release of vasodilatory factors such as nitric oxide and natriuretic peptides.[5] Decreased cardiac output and arterial underfilling leads to a persistent activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), which leads to subsequent pathologic volume expansion as well as multi-organ fibrosis including the heart and kidneys.[12] In addition, angiotensin II appears to be especially involved in the development of reactive oxygen species (e.g., superoxide) via activation of NADPH oxidase and NADH oxidase in various cells including cardiac myocytes and renal tubular epithelial cells.[13] Inactivation of nitric oxide by reactive oxygen species may contribute to the endothelial dysfunction seen in vascular smooth muscle as well as the impaired contractile effects on cardiac myocytes in HF.[13]

Role of Congestion and Cardiorenal Hemodynamics

Typically, high renin levels and resultant abnormal angiotensin II production are key mediators in the setting of reduced circulating volume, ultimately leading to pathologic volume overload and consequent downstream effects resulting from microvascular congestion. High venous pressures offer a viable mechanism to the progressive CKD in HF in those with preserved ejection fraction and stable hemodynamics.[14] As such, the ESCAPE (Evaluation Study of Congestive HF and Pulmonary Artery Catheterization Effectiveness) trial evaluated pulmonary artery catheter–guided management of acute decompensated congestive HF in 433 patients and found no correlation between baseline renal function and cardiac index.[15] Furthermore, improvement in the cardiac index did not result in improved renal function nor prevention of rehospitalization or death, suggesting that decreased forward flow and hemodynamics are not the main determinants of progressive renal failure in the HF population.[13]

Consequently, continued RAAS stimulation as a result of venous hypertension rather than hypoperfusion can stimulate continued sodium avidity and persistent resultant pressure and volume overload,[13,16] leading to worsening renal dysfunction including in those with well-preserved left ventricular ejection fraction.[17] An additional facet could be that renal autoregulatory mechanisms are able to preserve intrarenal hemodynamics despite macrophysiologic changes as HF progresses. However, this preservation of glomerular filtration rate (GFR) occurs at the cost of maladaptation, eventually leading to ischemia and glomerulosclerosis.

Inflammation

Although inflammation is associated with HF and CKD, which may be an effect of each disease process rather than the initiating event, it certainly may contribute to the pathologic progression in CRS. Elevated levels of proinflammatory cytokines including TNF-α, IL-1β, and IL-6 are observed in those with CKD and chronic HF. Although the RAAS and sympathetic nervous system do stimulate inflammatory mediators, venous congestion from volume overload also may play a role in promoting the inflammatory process.[18] For example, in the setting of volume overload, endotoxins including lipopolysaccharide may translocate through the gut because of bowel wall edema, which in turn induces proinflammatory cytokines.[19] Cumulatively, these proinflammatory cytokines can have detrimental effects on the heart, kidneys, and vasculature leading to cyclic and progressive organ damage, fibrosis, and dysfunction.[18]

It is not clear whether the inflammatory mediators play a lead role in the causal pathway of CRS regarding the worsening heart and kidney failure or whether they merely represent markers as a consequence of vital organ stress/injury. This latter notion is supported by the fact that several randomized placebo-controlled trials of antiinflammatory therapies (e.g., anti-TNF-α) in chronic HF have not proven to be efficacious in improving clinical outcomes. A host of other reasons why there have not been encouraging results may include the redundancy of the cytokine cascade, differences in inflammatory status for those with varying levels of CHF, as well as those with differing comorbid causes such as diabetes or hypertension.[18]

Link Between Cardiorenal Syndrome Types 1 and 2

A number of hemodynamic and nonhemodynamic factors are involved in the pathogenesis of CRS-2 (Fig. 112.1). By extrapolating the information derived from other clinical settings, it is conceivable that episodes of acute kidney injury (AKI) in the setting of acute HF (CRS-1) either initiate or further facilitate the progression of CRS-2. Inclusive of all of the above mechanisms (RAAS stimulation, inflammation, fibrosis), an episode of AKI consequently can follow a path of progressive loss of renal function initiated by a catastrophic episode of CRS-1 with subsequent partial recovery or nonrecovery. This pathogenic link makes evaluating the epidemiology of this disease more complex. For example, as alluded to earlier, underlying HF and episodic AKI can act as residual confounders when evaluating progressive CKD. However, it is less ambiguous to separate the subgroup of individuals with HF who have a progressive loss of renal function in the setting of worsening systolic function and consequently have a strikingly high risk of morbidity and mortality.

DIAGNOSIS AND BIOMARKERS

The comorbid nature of HF and CKD give rise to notable challenges when attempting to identify their relational occurrence or progression. The use of serum creatinine (SCr) as part of the diagnostic spectrum has many limitations, especially when inferring its clinical utility in management and outcomes. For instance, the variability among those of differing age, gender, race, and muscle mass render diagnostic and management decisions difficult even with regard to the same patient over time. In addition, the use of estimation equations for GFR to account for this variability in SCr is valid only during a steady state. Moreover, the fact that SCr represents a decline in GFR and not necessarily parenchymal disease limits its use in determining the progression of renal decline.[20] Other biomarkers include nonspecific yet classic findings of intrinsic kidney disease such as proteinuria (e.g., >1000 mg daily), active urinary sediment such as hematuria, and renal ultrasound with findings such as smaller kidney sizes, thinning parenchyma, and increased echogenicity.

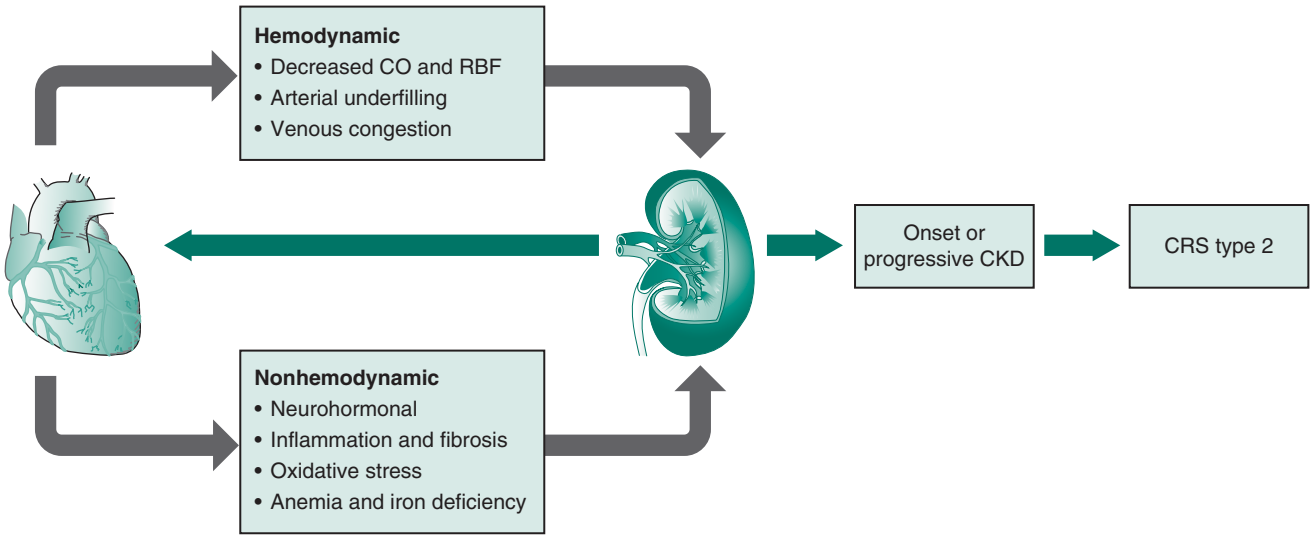

FIGURE 112.1 Hemodynamic and nonhemodynamic effects toward progressive chronic kidney disease (CKD) and cardiorenal syndrome (CRS) type 2 with worsening CKD also imposing negative morbid cardiac effects. *CO,* Cardiac output; *RBF,* renal blood flow.

Biomarkers

The current state of biomarker analysis is focused primarily on the early detection of AKI, and consequently very limited biomarker data are available regarding the early detection of onset and progression of CKD, which would prove invaluable in the evaluation and management of CRS-2. Among the key attributes for potentially viable biomarkers would be their ability to accurately detect kidney damage and/or decline of renal function earlier than what we currently have available. Furthermore, the utility of an endogenous filtration biomarker is related directly to its ability to predict clinical outcome. There are several candidate markers in the inflammatory and fibrotic pathways that have been evaluated in experimental settings but have not yet been validated in CRS-2 patients (Fig. 112.2).

Cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1) have received increased attention and scrutiny in this era of discovering potentially useful biomarkers.

Cystatin C is a low-molecular-weight protein that is believed to be produced by all nucleated cells. It is filtered completely by the glomeruli, and although not reabsorbed, it is metabolized in the tubules and therefore cannot be used to measure clearance directly, but serum levels can be used as a proxy to estimate clearance. Measured GFR appears to be estimated more accurately with the CKD-$EPI_{Cr\text{-}Cys}$ formula.[21]

Produced and secreted by neutrophils in humans, the expression of the NGAL protein is increased significantly in damaged epithelial cells.[20] These increased levels occur earlier in damaged tissue than our classic markers of kidney damage (e.g., SCr) and correlate well with the extent of renal tubular damage cells.[20] Studies continue with regard to its use in the early detection and staging of CKD, the progression of CKD, as well as following the response to treatment.[22] KIM-1 is a transmembrane protein that is not expressed ordinarily in uninjured kidneys but is upregulated by proximal tubular cells after ischemic or nephrotoxic exposure and can be measured in the urine.[20] Given the propensity of CRS-2 subjects to suffer from acute episodes of decompensating heart or kidney failure, it is proposed that markers of acute kidney injury may provide prognostic value in determining the downstream course of kidney disease progression. Such validation studies, however, are seriously lacking.

MANAGEMENT

Many questions arise when considering management optimization with coexisting cardiac and renal dysfunction and specifically CRS-2:

1. How does one weigh the relative contribution of baseline chronic heart dysfunction or the chronic kidney disease to declining renal function?
2. Does the progression of renal dysfunction result from its own inherent disease processes and not necessarily because of the chronic HF affect outcomes to the same degree as if the progression was secondary to the HF?
3. Does a reduction in GFR during HF treatment lead to worsening outcomes (i.e., increased mortality)?
4. What is the optimal end point with regard to co-management of cardiac and renal dysfunction?

Although these questions are being investigated actively, it is clear that striking a proper balance between the optimal therapy for HF and reduced kidney function for the best clinical outcomes is of foremost importance. Although large randomized controlled trials of chronic HF over the last 20 years have not routinely included patients with advanced renal disease,[5] it has been observed that patients with concomitant renal dysfunction have worse outcomes in HF patients. However, observational data using baseline SCr values alone are not enough, as trials have indicated that a relationship between a change in GFR (regardless if it is positive or negative) in those with HF do not necessarily affect outcomes in the same manner, but rather it is the cause of this change that is important. Nonetheless, optimization of cardiac function can actually improve GFR and have a positive impact on those with CRS-2. Consequently, any therapy involving RAAS inhibition and diuretics for CRS-2 patients should include surveillance of renal function and electrolyte balance.

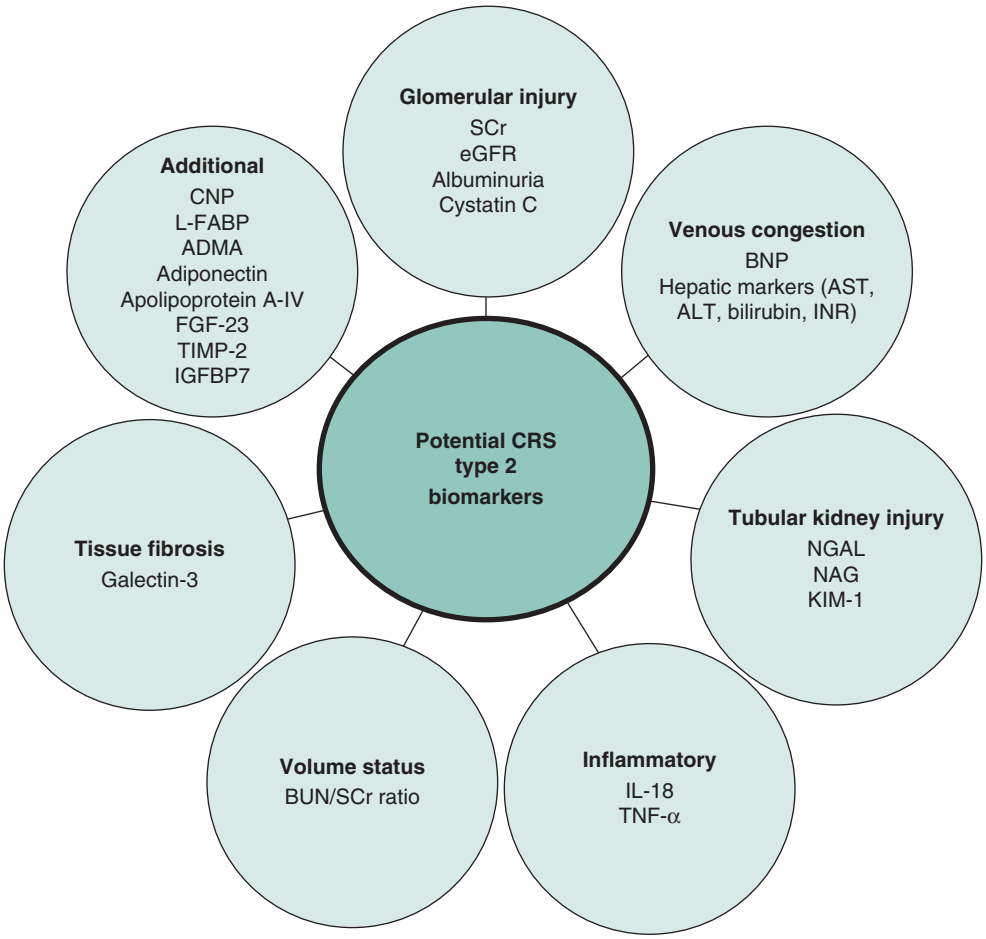

FIGURE 112.2 In search of ideal biomarkers for cardiorenal syndrome type 2. *ADMA,* Asymmetric dimethylarginine; *ALT,* alanine transaminase; *AST,* aspartate transaminase; *BNP,* brain natriuretic peptide; *BUN,* blood urea nitrogen; *CNP,* C-type natriuretic peptide; *eGFR,* estimated glomerular filtration rate; *FGF-23,* fibroblast growth factor-23; *IGFBP7,* insulin-like growth factor binding protein 7; *IL,* interleukin; *INR,* international normalized ratio; *KIM-1,* kidney injury molecule-1; *L-FABP,* liver-type fatty binding protein; *NAG,* N-acetyl-β-D-glucosamine; *NGAL,* neutrophil gelatinase-associated lipocalin; *SCr,* serum creatinine; *TIMP-2,* tissue inhibitor metalloproteinases-2; *TNF,* tumor necrosis factor.

RAAS Blockers

The neurohormonal activation seen in HF makes RAAS blockers a cornerstone therapy in the management of patients with HF and reduced ejection fraction. These include renin inhibitors, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). However, RAAS blockers are underused in those with HF and advanced CKD for fear of worsening renal function and consequently adversely affecting outcomes. Although much of the information gleaned regarding the effect of RAAS blockers on CRS is from posthoc analysis of trials, they offer important insight on renal dysfunction in HF.

An example of the importance placed on the mechanism for worsening renal function in HF patients with regard to its predictability toward adverse outcomes can be observed from the Studies of Left Ventricular Dysfunction (SOLVD) trial, which revealed that although early worsening renal function in the overall population was associated with increased mortality, this was not the case for those treated with an ACE-I (i.e., enalapril) as opposed to the placebo, in which an early worsening of renal function in the presence of an ACE-I was not associated with an adverse prognosis in patients with cardiac dysfunction.[23] Subsequent analysis of this trial indicated proteinuria as an independent predictor of hospitalization for CHF and mortality in patients with diabetes and without diabetes who had left ventricular (LV) dysfunction and that enalapril reduced proteinuria in diabetic patients with LV dysfunction.[24] Similarly, although a higher dose of losartan (150 mg vs. 50 mg) was associated with an increased risk for an acute and chronic reduction in eGFR in the HF end point evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial, there was a decreased risk of hospitalization or death in the former group.[25] Moreover, the Randomized Aldactone Evaluation Study (RALES) trial evaluated patients with severe HF already on an ACEI and loop diuretic and, although the addition of spironolactone was associated with an increased risk of hyperkalemia and decline in renal function versus placebo in those with an already worse baseline renal function, this group benefited the most with regard to all-cause mortality.[26] Given that the efficacious nature of RAAS blockade in HF is well established, the use of multiple RAAS blockers has been surmised but demonstrated to be harmful when combining ACEIs and ARBs,[27,28] including those patients on hemodialysis.[29] The same has been described for the dual use of the renin inhibitor aliskiren

with ACEIs or ARBs in those who are diabetic or have a GFR less than 60 mL/min/1.73 m^2, which has led to an FDA warning.[30]

Conversely, the use of mineralocorticoid receptor antagonists (MRAs), including spironolactone and eplerenone in association with ACEIs or ARBs in those with severe HF, has shown to be more favorable,[31] although these patients should be monitored closely and educated because of an added propensity for hyperkalemia. In addition, this combination of medications also offer added renoprotection with further reduction of proteinuria and blood pressure.[32]

The dose of diuretic and propensity for hypotension in patients with advanced HF strongly predict the risk of rise in SCr values in those taking an ACEI; therefore initiating lower doses of RAAS blocker would be beneficial.[33]

Diuretics

Fluid retention is a fundamental feature in HF,[32] and although it may be overwhelmingly evident in CRS-1, the chronic nature of volume overload in CRS-2 may manifest in differing ways depending on patient characteristics, including the status of renal dysfunction and HF. In addition, although the worsening renal function in HF certainly may be due to prerenal physiology, it can also decline in the setting of volume overload, leading to improved overall outcomes with treatment of the decompensated HF despite a rise in SCr. Although diuretics are the first-line therapy in the management of volume overload in those with HF and typically involve loop diuretics and may include potassium-sparing MRAs and thiazide diuretics, their efficacy and safety has not been evaluated in RCTs, and even their ideal doses are debatable.[20]

Certainly, many factors are involved regarding diuretic effect on GFR in those with HF. Increases in SCr can be attributed to a fall in cardiac output related to a decline in cardiac filling pressures, whereas a decrease in SCr may be attributed to a decline in intraabdominal and renal venous pressures. In some cases, there may be no change in SCr because the patient's cardiac performance may be resting on the flat portion of the Frank-Starling curve.

The classic objective of diuretic-based therapy is to remove the extracellular fluid volume from the intravascular space at a rate that allows for appropriate refilling from the interstitial space, therefore avoiding intravascular depletion and tissue underperfusion.[32] Given the negative effects of venous congestion on CKD progression, uptitration of diuretics has been supported to improve cardiovascular outcomes as well as overall survival,[34,35] although this should not be at the cost of causing hypovolemia, which will lose any protective significance.[20]

The most apparent data with regard to diuretic therapy and outcomes may be found in those with decompensated HF; however, similar strategies can be inferred. For instance, use of multiple diuretic classes (e.g., loop diuretic with long acting thiazide and MRA) with a low sodium diet to offset adaptation and therefore diuretic resistance can enhance diuresis. Caution not to confuse diuretic resistance with poor compliance is warranted.[32] Should patients not respond to maximal multidrug class therapy, then inpatient use of intravenous (IV) diuretic bolusing or continuous drip may be warranted.

The 2013 American College of Cardiology/American Heart Association HF guidelines state that the definitive goal of diuretic therapy is to eliminate clinical evidence of fluid retention,[36] which can be represented by an elevated JVP and peripheral edema. However, such clinical features may not adequately represent the true status of the patient because peripheral edema may have only cosmetic ramifications and not justify aggressive diuresis. Certainly, hypotension and the development of contraction alkalosis can indicate that patients are approaching their target weight.

Cardiorenal Anemia Syndrome

Anemia is common in those with chronic HF[32] as well as CKD when the GFR decreases below 60 mL/min/1.73 m^2. Although the mechanisms behind the anemia seen in CRS may involve other complex mechanisms, it is associated with increased morbidity and mortality in these patient populations. The anemia in CKD is normocytic and normochromic and is largely secondary to decreased renal production of erythropoietin as well as a decline in the survival of red blood cells. Increased cytokine production related to the HF, including tumor necrosis factor-alpha (TNF-α),[37] can antagonize the effect of erythropoietin by directly inhibiting erythroid progenitor cells and also through hepcidin-induced failure of iron absorption and metabolism.[38] In addition, the use of ACEIs can decrease erythropoietin production in a dose-related manner.[39]

Management of anemia in this setting should begin with an evaluation of the possible underlying and reversible causes, including obtaining iron studies, folic acid, and vitamin B_{12} levels as well as thyroid-stimulating hormone.[32]

Although treatment with erythropoietin-stimulating agents (ESAs) has been found to improve the functional cardiac class, exercise tolerance, ejection fraction, and quality of life in this population of patients,[40] the goal hemoglobin (Hgb) level is debatable because higher levels may not improve outcomes and consequently raise safety concerns related to thromboembolic events.[41] In fact, ensuring that iron levels are optimized even with IV iron preparations can improve Hgb levels in CRS patients possibly circumventing an immediate need for ESAs.[42]

OVER THE HORIZON

Cardiac Resynchronization Therapy

Intraventricular conduction delay can be seen in up to 20% to 30% of those with symptomatic HF resulting in dyssynchrony and reduction in pump performance.[43] A survival benefit is seen in those patients with HF and CKD who are responsive to cardiac resynchronization therapy (CRT), as well as preservation and improvement of renal function in some cases.[44]

Implantable Pulmonary Artery Pressure Sensor

CardioMEMS is currently the only FDA-approved miniaturized, wireless monitoring sensor that is implanted in the pulmonary artery to measure PA pressure directly. The information can be submitted electronically to patients' healthcare providers. The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III HF) trial was a randomized, controlled, single-blind trial that evaluated this device (active PA pressure-guided monitoring group) with standard care versus standard care with clinical assessment in 550 NYHA class III HF patients. It showed that incorporation of active monitoring

led to targeted changes with a higher frequency of medication titration and reduced HF hospitalizations.[45]

CONCLUSION

CRS-2 involves a complex interaction between the heart and kidney, resulting in the onset or progression of chronic kidney disease resulting from chronic HF. However, having CKD and HF is not enough to establish CRS-2 but rather a temporal relationship between the occurrence of chronic HF and a consequent onset or progression of CKD is required and proves to be diagnostically challenging. However, biomarkers that could accurately detect the early onset and progression of CKD earlier than what is currently available would yield promising identification, management, and outcome utility. A rise in SCr in the setting of treatment does not necessarily suggest CRS-2 progression or worse outcomes.

Key Points

1. Cardiorenal syndrome type 2 (CRS-2) may be a common but underrecognized clinical entity with novel management considerations.
2. A rise in serum creatinine with regard to treatment with renin-angiotensin-aldosterone system inhibitors or diuretics does not necessarily indicate progression of CRS-2 or worse outcomes.
3. Biomarkers will potentially play an important role in early diagnosis and management of CRS-2.
4. Cardiorenal anemia should be recognized early and managed appropriately.

Key References

5. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52(19):1527-1539.
6. Cruz DN, Schmidt-Ott KM, Vescovo G, et al. Pathophysiology of cardiorenal syndrome type 2 in stable chronic heart failure: Workgroup statements from the eleventh consensus conference of the acute dialysis quality initiative (ADQI). *Contrib Nephrol*. 2013;182:117-136.
9. Ronco C, McCullough P, Anker SD, et al. Cardio-renal syndromes: Report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J*. 2010;31(6):703-711.
16. Ronco C, Di Lullo L. Cardiorenal syndrome. *Heart Fail Clin*. 2014;10(2):251-280.
20. De Vecchis R, Baldi C. Cardiorenal syndrome type 2: From diagnosis to optimal management. *Ther Clin Risk Manag*. 2014;10:949-961.

A complete reference list can be found online at ExpertConsult.com.

References

1. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: 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(12):e154-e235.
2. Bonow RO, Bennett S, Casey DE Jr, et al. ACC/AHA clinical performance measures for adults with chronic heart failure: A report of the american college of cardiology/american heart association task force on performance measures (writing committee to develop heart failure clinical performance measures) endorsed by the heart failure society of america. *J Am Coll Cardiol*. 2005;46(6):1144-1178.
3. Curtis LH, Whellan DJ, Hammill BG, et al. Incidence and prevalence of heart failure in elderly persons, 1994-2003. *Arch Intern Med*. 2008;168(4):418-424.
4. Masoudi FA, Rathore SS, Wang Y, et al. National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. *Circulation*. 2004;110(6):724-731.
5. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52(19):1527-1539.
6. Cruz DN, Schmidt-Ott KM, Vescovo G, et al. Pathophysiology of cardiorenal syndrome type 2 in stable chronic heart failure: Workgroup statements from the eleventh consensus conference of the acute dialysis quality initiative (ADQI). *Contrib Nephrol*. 2013;182:117-136.
7. Bagshaw SM, Cruz DN, Aspromonte N, et al. Epidemiology of cardio-renal syndromes: Workgroup statements from the 7th ADQI consensus conference. *Nephrol Dial Transplant*. 2010;25(5):1406-1416.
8. Masoudi FA, Havranek EP, Wolfe P, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J*. 2003;146(2):250-257.
9. Ronco C, McCullough P, Anker SD, et al. Cardio-renal syndromes: Report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J*. 2010;31(6):703-711.
10. Heywood JT, Fonarow GC, Costanzo MR, et al. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: A report from the ADHERE database. *J Card Fail*. 2007;13(6):422-430.
11. Jose P, Skali H, Anavekar N, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol*. 2006;17(10):2886-2891.
12. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med*. 2001;345(23):1689-1697.
13. Bock JS, Gottlieb SS. Cardiorenal syndrome: New perspectives. *Circulation*. 2010;121(23):2592-2600.
14. Kishimoto T, Maekawa M, Abe Y, et al. Intrarenal distribution of blood flow and renin release during renal venous pressure elevation. *Kidney Int*. 1973;4(4):259-266.
15. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions: Insights from the ESCAPE trial. *J Am Coll Cardiol*. 2008;51(13):1268-1274.
16. Ronco C, Di Lullo L. Cardiorenal syndrome. *Heart Fail Clin*. 2014;10(2):251-280.
17. Damman K, Voors AA, Hillege HL, et al. Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. *Eur J Heart Fail*. 2010;12(9):974-982.
18. Colombo PC, Ganda A, Lin J, et al. Inflammatory activation: Cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome. *Heart Fail Rev*. 2012;17(2):177-190.
19. Anker SD, Egerer KR, Volk HD, et al. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. *Am J Cardiol*. 1997;79(10):1426-1430.
20. De Vecchis R, Baldi C. Cardiorenal syndrome type 2: From diagnosis to optimal management. *Ther Clin Risk Manag*. 2014;10:949-961.
21. Levey AS, Inker LA, Coresh J. GFR estimation: From physiology to public health. *Am J Kidney Dis*. 2014;63(5):820-834.
22. Devarajan P. The use of targeted biomarkers for chronic kidney disease. *Adv Chronic Kidney Dis*. 2010;17(6):469-479.
23. Testani JM, Kimmel SE, Dries DL, et al. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. *Circ Heart Fail*. 2011;4(6):685-691.
24. Capes SE, Gerstein HC, Negassa A, et al. Enalapril prevents clinical proteinuria in diabetic patients with low ejection fraction. *Diabetes Care*. 2000;23(3):377-380.
25. Kiernan MS, Gregory D, Sarnak MJ, et al. Early and late effects of high- versus low-dose angiotensin receptor blockade on renal function and outcomes in patients with chronic heart failure. *JACC Heart Fail*. 2015;3(3):214-223.
26. Vardeny O, Wu DH, Desai A, et al. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: Insights from RALES (randomized aldactone evaluation study). *J Am Coll Cardiol*. 2012;60(20):2082-2089.
27. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372(9638):547-553.
28. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892-1903.
29. Chan KE, Ikizler TA, Gamboa JL, et al. Combined angiotensin-converting enzyme inhibition and receptor blockade associate with increased risk of cardiovascular death in hemodialysis patients. *Kidney Int*. 2011;80(9):978-985.
30. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204-2213.
31. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309-1321.
32. Roubille F, Morena M, Leray-Moragues H, et al. Pharmacologic therapies for chronic and acute decompensated heart failure: Specific insights on cardiorenal syndromes. *Blood Purif*. 2014;37(suppl 2):20-33.
33. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the cooperative north scandinavian enalapril survival study [CONSENSUS] trial). *Am J Cardiol*. 1992;70(4):479-487.
34. Testani JM, Chen J, McCauley BD, et al. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation*. 2010;122(3):265-272.
35. Lucas C, Johnson W, Hamilton MA, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. *Am Heart J*. 2000;140(6):840-847.
36. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-e239.
37. Silverberg DS, Wexler D, Palazzuoli A, et al. The anemia of heart failure. *Acta Haematol*. 2009;122(2-3):109-119.
38. van der Putten K, Braam B, Jie KE, et al. Mechanisms of disease: Erythropoietin resistance in patients with both heart and kidney failure. *Nat Clin Pract Nephrol*. 2008;4(1):47-57.
39. Sica DA, Gehr TW. The pharmacokinetics and pharmacodynamics of angiotensin-receptor blockers in end-stage renal disease. *J Renin Angiotensin Aldosterone Syst*. 2002;3(4):247-254.
40. Ngo K, Kotecha D, Walters JA, et al. Erythropoiesis-stimulating agents for anaemia in chronic heart failure patients. *Cochrane Database Syst Rev*. 2010;(1):CD007613, doi(1):CD007613.
41. Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med*. 2013;368(13):1210-1219.
42. Ben-Assa E, Shacham Y, Shashar M, et al. Target hemoglobin may be achieved with intravenous iron alone in anemic patients with cardiorenal syndrome: An observational study. *Cardiorenal Med*. 2015;5(4):246-253.

43. Janaswamy P, Walters TE, Nazer B, et al. Current treatment strategies for heart failure: Role of device therapy and LV reconstruction. *Curr Treat Options Cardiovasc Med*. 2016;18(9):57.
44. Garg N, Thomas G, Jackson G, et al. Cardiac resynchronization therapy in CKD: A systematic review. *Clin J Am Soc Nephrol*. 2013;8(8):1293-1303.
45. Costanzo MR, Stevenson LW, Adamson PB, et al. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. *JACC Heart Fail*. 2016;4(5):333-344.