Getting to the Heart of the Matter: Review of Treatment of Cardiorenal Syndrome

Kausik Umanath and Sitaramesh Emani

Acute decompensated heart failure is a common cause of hospitalization with worsening kidney function or acute kidney injury often complicating the admission, which can result in further dysfunction of both systems in the form of a cardiorenal syndrome. Therapy in this arena has been largely empiric as rigorous clinical trial data to inform therapeutic choices are lacking. Here we review and discuss the available clinical evidence for common approaches to the management of this condition. A multidisciplinary approach to the care of patients with cardiorenal syndrome that relies on the experience of nephrologists and cardiologists to individualize treatment is critical given the paucity of rigorous clinical trial data.

Key Words: Acute Decompensated Heart Failure, Acute Kidney Injury, Cardiorenal, Hospitalization, Diuretics, Vasodilators, Ultrafiltration

INTRODUCTION

A large proportion of patients admitted to the hospital have some degree of dysfunction of either the kidneys or the heart.[1] These 2 organ systems interact with one another such that primary disease of one often results in secondary dysfunction of the other.[2] Recognition of this complex interaction along with the need to better codify these pathophysiological processes led to the formalization and classification of the cardiorenal syndrome (CRS) and its 5 categories.[3,4] Acute decompensated heart failure (ADHF) is a common cause of hospitalization with worsening kidney function or acute kidney injury (AKI) complicating nearly 1 in 5 admissions.[5] These patients were noted to have an increased risk of mortality compared with ADHF patients without AKI. AKI during an admission for heart failure is also associated with repeat ADHF admissions.[6] Thus, the evolution and management of CRS is a common clinical problem, which significantly affects and individual patient's health and the health care system as a whole.

The classification and pathophysiological underpinnings of CRS and its 5 categories have been reviewed in detail elsewhere[2-4] (Table 1). Therapeutic approaches to manage congestion and fluid overload in patients with ADHF while mitigating renal harm have centered on the use of diuretics, vasodilators, and extracorporeal approaches, namely ultrafiltration (UF). Therapy in this arena has been largely empiric as conclusive clinical trial data to inform therapeutic choices are lacking. Our aim in this article is to review and discuss the available clinical evidence for common approaches to the management of this condition.

DIURETICS

Diuretic therapy has been the mainstay of treatment for ADHF as it assists with the relief of symptoms (shortness of breath, lower extremity edema, etc.). Although these agents reduce congestive symptoms, this improvement may come at the cost of inciting a vicious cycle of neurohormonal activation, AKI, and resultant diuretic resistance. Diuretics can also cause adverse perturbations in electrolyte balance and acid-base homeostasis. The goal of diuretic therapy should reduce the extracellular fluid volume at a rate commensurate with the rate of refilling from the interstitium to the intravascular compartment (plasma refill rate). Typically, a loop diuretic is used over other agents like thiazides, which have limited efficacy in states of reduced kidney function.[8]

Optimal diuretic strategies including dose, frequency, and route of administration have not shown superiority of any one approach over others. Salvador and colleagues attempted to synthesize the available data via a Cochrane meta-analysis in 2005 comparing bolus intravenous administration of loop diuretics vs continuous infusion in ADHF.[9] The analysis covered 8 trials totaling 254 subjects and found greater urine output, less ototoxicity (tinnitus and hearing loss), and a similar frequency of electrolyte disturbances in subjects given continuous infusion compared with intermittent therapy. Unfortunately, the authors were unable to compare effects on survival or kidney outcomes because of heterogeneity and lack of sample size.

Subsequently, Allen and colleagues[10] conducted a single-center pilot study of 41 patients comparing bolus vs continuous dosing of furosemide for ADHF. In this small study, no difference was noted in serum creatinine change, total urine output, or length of stay. This lead to the NIH-sponsored Diuretic Optimization Strategies Evaluation (DOSE) trial.[11] This study was a prospective, placebo-controlled trial in which 308 subjects were randomized to receive intravenous furosemide either by continuous infusion or bolus infusion every 12 hours. The trial used a 2 × 2 factorial design in which subjects either received a low or high dose of furosemide (the equivalent of 1 or 2.5 times the previous oral dose, respectively). The co-primary end points were subjects' global assessment of symptoms, as quantified by area under the curve of the score on a visual analogue scale over the course of 72 hours

From Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI; and Division of Cardiology, The Ohio State University Wexner Medical Center, Columbus, OH.

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Address correspondence to Kausik Umanath, MD, MS, Division of Nephrology and Hypertension, Clara Ford Pavilion 5, Henry Ford Hospital, Detroit, MI 48202. E-mail: kumanat1@hfhs.org

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Table 1. Classification of Cardiorenal Syndromes

Type	Name	Description
1	Acute cardiorenal syndrome	Acute worsening of cardiac function leading to decreased kidney function
2	Chronic cardiorenal syndrome	Long-term abnormalities in cardiac function leading to decreased kidney function
3	Acute renocardiac syndrome	Acute worsening of kidney function causing cardiac dysfunction
4	Chronic renocardiac syndrome	Long-term abnormalities in kidney function leading to cardiac disease
5	Secondary cardiorenal syndrome	Systemic conditions causing simultaneous dysfunction of the heart and kidney

Adapted from House et al.[7]

and change in serum creatinine from baseline to 72 hours. Among several secondary end points were two kidney-specific outcomes: worsening kidney function (defined as an increase in serum creatinine >0.3 mg/dL at any time from randomization to 72 hours) and changes in serum creatinine or cystatin C at baseline, 72 hours, and 60 days.

In the comparison of bolus vs continuous infusion, no difference was noted in the primary efficacy end point of patient-reported global assessment of symptoms. The difference in serum creatinine at 72 hours compared with baseline was also not statistically significant (0.05 ± 0.3 mg/dL bolus group and 0.07 ± 0.3 mg/dL continuous infusion group, $P = 0.45$).[11] The authors also found no differences across all the secondary end points. Additionally, they noted no interaction between the factorial groups for the co-primary end points. With regard to high-dose vs low-dose strategies, a non-statistically significant trend toward greater improvement in symptom score was noted in the high-dose group. The difference in serum creatinine at 72 hours compared with baseline was not statistically significant (0.04 ± 0.3 mg/dL low-dose group and 0.08 ± 0.3 mg/dL high-dose group, $P = 0.21$). Among the secondary end points, the high-dose group was noted to have statistically significant greater changes in weight loss, net fluid loss, and relief from dyspnea. These improved symptoms did not seem to come at the expense of kidney function loss. Although there was a statistically significant increase in the event of worsening kidney function (23% in high-dose group, 14% in low-dose group, $P = 0.04$), there were no differences noted in the primary end point (change in serum creatinine at 72 hours) as noted earlier or changes in serum creatinine or cystatin C levels at 60 days.

In summary, the available clinical evidence supports the use of loop diuretics with equivalent safety and efficacy using either a bolus or continuous infusion dosing approach. A high-dose strategy also appears to provide a trend toward improved symptom relief and some other favorable outcomes. Although there were increased worsening kidney failure events with a high-dose strategy, this must be taken in the context of no changes in serum creatinine by 72 hours and over 60 days. Based on the available data, a reasonable approach for ADHF would be the use of high-dose diuretics via either bolus or continuous infusion.

CLINICAL SUMMARY

- Disturbances in kidney and cardiac homeostasis result in challenges when managing patients with underlying processes of either organ system.
- Current treatments of cardiorenal syndromes focus on the use of diuretics, vasodilators, and ultrafiltration.
- The best clinical evidence exists for the use of diuretics, whereas evidence for the use of vasodilators and ultrafiltration is inconclusive.
- Novel therapeutic agents that may play role in the treatment of cardiorenal syndromes are in development.

VASODILATOR THERAPIES

When examining mechanisms of worsening CRS, a major correlation between kidney function and central venous pressure (CVP) has been shown. In an analysis by Mullens and colleagues,[12] an increased CVP during ADHF was more predictive of worsening kidney function than other indices of cardiac performance including cardiac index or pulmonary capillary wedge pressure. This association is driven by the net filtration pressure across the glomerulus, which is a function of the pressure gradient between afferent and efferent vessels within the kidney. When CVP rises, the net filtration pressure drops as a result of a reduced pressure gradient.[13]

One strategy for treating CRS in ADHF is to improve kidney perfusion pressure by reducing CVP through the use of vasodilating agents. The long-standing standard of care for vasodilation in ADHF has been nitroglycerin, which is recommended for relief of dyspnea when used with diuretic therapy.[14] Acceptance of nitroglycerin within this context has led to its use as a comparator for other agents aimed at treating ADHF and CRS.[15-17] Despite the theoretical benefit of nitroglycerin to decrease CVP through its venodilating properties, thereby improving renal perfusion, minimal data exist looking at its efficacy in improving outcomes in CRS. The same lack of evidence exists for nitroprusside, which is another commonly used agent to treat ADHF.[15]

NESIRITIDE

Natriuretic peptides are naturally occurring amino acid rings that are involved in cardiorenal homeostasis through vasodilation and induction of natriuresis and diuresis.[18-21] A review of various natriuretic peptides, both analogues of natural forms and synthetically designed forms, can be