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Acute decompensated heart failure: The cardiorenal syndrome

■ ABSTRACT

The cardiorenal syndrome is not well understood, and a uniform definition is lacking. Worsening renal function as determined by a decline in creatinine clearance in patients with decompensated heart failure is an identifier of patients with this syndrome. Treatment is a challenge. Diuretic therapy is valuable in treating congestion but may worsen renal function. Patients with decompensated heart failure are often refractory to diuretics, in which case higher doses must be used or alternate methods explored to reduce salt and water.

■ KEY POINTS

Worsening renal function is common in acute heart failure and increases mortality and hospital resource utilization.

A decrease in creatinine clearance or glomerular filtration rate can identify patients with cardiorenal syndrome.

Loop diuretics remain the mainstay of therapy but may worsen renal function, and patients may become refractory to them.

Fluid removal by ultrafiltration may be useful in the setting of chronic volume overload when renal function is declining with the use of loop diuretics.

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A CONSENSUS DEFINITION of the cardiorenal syndrome has not been established. Many believe that it is the final manifestation of deteriorating renal function in the presence of heart failure.

Not much is understood about the pathophysiology of the cardiorenal syndrome. An imbalance in interactions between the failing heart, neurohormonal systems, and host inflammatory responses has been implicated, leading to structural and functional damage to the heart and kidneys. Worsening renal function is common in decompensated heart failure and is associated with greater hospital resource utilization and mortality.

Because the process is complex, treatment can be a challenge. The worsening renal function in patients with this syndrome can also lead to resistance to many standard therapies and exacerbation of symptoms.

This article will explain the relationship between changes in creatinine clearance and prognosis in patients with acute heart failure exacerbations, the challenges in managing this syndrome (including diuretic resistance), and several alternate approaches to diuretic therapy to reduce salt and water retention.

■ CREATININE CLEARANCE PREDICTS PROGNOSIS

A rise in serum creatinine or diminishment in creatinine clearance in patients with acute decompensated heart failure is associated with a worsened prognosis.¹ The prognosis is even poorer if the increase in serum creatinine or the decrease in creatinine clearance is accompanied by oliguria (≤ 50 mL/hr), edema, hyponatremia, or refractoriness to diuretics.

Any detectable decrease in renal function in patients with heart failure is associated with increases in mortality and length of hospital

Diuretic-based clinical strategies are not effective in reducing edema

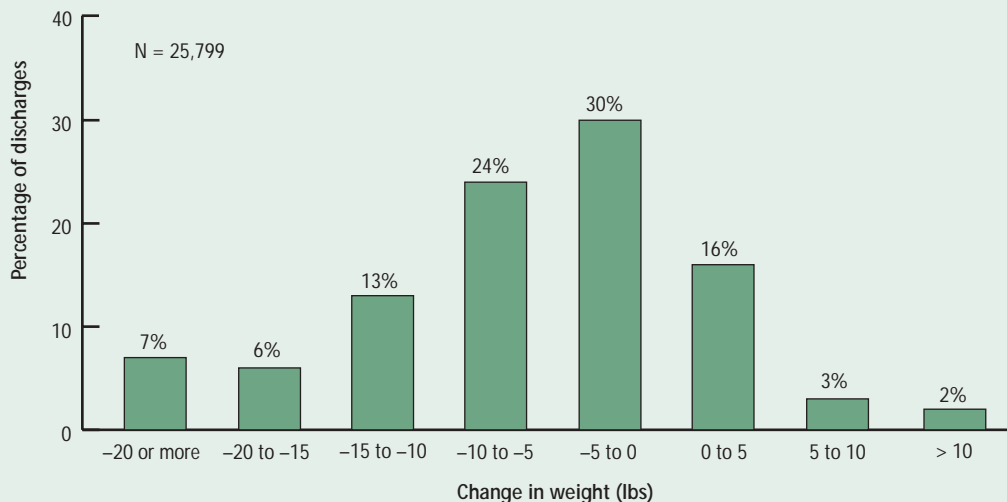


FIGURE 1. Nearly one fourth of patients with acute decompensated heart failure failed to lose weight from admission to discharge despite treatment with intravenous (IV) diuretics. Data are from the Acute Decompensated Heart Failure National Registry (ADHERE),² in which 90% of the patients received IV diuretic therapy.

stay, and although a rapidly rising creatinine level is more specific for these outcomes, smaller changes in creatinine are encountered more often in practice. Traditionally, loop diuretics or inadequate blood flow to the kidney have been blamed for these changes in renal function, but the actual cause is likely to be more complex.

Although the terms creatinine clearance and glomerular filtration rate (GFR) are often used interchangeably, creatinine clearance is a clinical laboratory test that requires 24-hour urine collection and a blood sample, whereas GFR is largely a research tool performed in general clinical research units. Calculation of GFR requires inulin or iothalamate infusion. Creatinine clearance tends to overestimate the GFR, which is the gold standard for measuring kidney function. GFR can be estimated by the Modification of Diet in Renal Disease (MDRD) equation, which can be found on many handheld computers.

Renal insufficiency is common

The Acute Decompensated Heart Failure National Registry (ADHERE) of 100,000 patients admitted with acute decompensated heart failure reveals that moderate and severe renal insufficiency, and even renal failure, are common in this population, and that normal

renal function is rare. Most institutions use large doses of loop diuretics in an attempt to rescue these patients. Intravenous medications used less frequently are dobutamine, dopamine, milrinone, nitroglycerin, and nesiritide.

Diuretic therapy falls short

Unfortunately, diuretic-based strategies are not always effective in reducing edema. In ADHERE, 21% of patients admitted for decompensated heart failure were discharged without weight loss or with a gain in weight (Figure 1).² In my experience, patients who do not manifest weight loss in the hospital tend to have a poor prognosis.

IDENTIFYING CARDIORENAL SYNDROME

Disconnect between serum creatinine and GFR
Commonly, a lower creatinine clearance or GFR, and not always an increase in serum creatinine, identifies patients with the cardio-renal syndrome. Relative to a decline in ejection fraction, a fall in GFR is more important to prognosis in patients with heart failure.³ Measuring serum creatinine alone is probably misleading. Approximately two thirds of patients admitted to the Cleveland Clinic for acute heart failure have an inadequate GFR or

Any detectable decrease in renal function is associated with increases in mortality and hospital stay

Mortality and creatinine clearance in heart failure patients: Cleveland Clinic experience

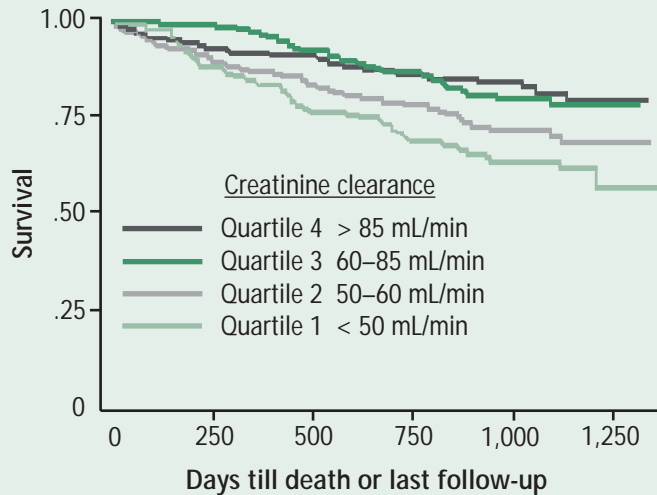


FIGURE 2. Among 585 ambulatory patients with chronic congestive heart failure, estimated creatinine clearance predicted all-cause mortality with follow-up of more than 3 years. Mortality increased with decreasing quartile of estimated creatinine clearance. Reprinted from reference 5, copyright 2002, with permission from the American College of Cardiology.

a reduced creatinine clearance, despite many of them having relatively preserved levels of serum creatinine.⁴ Remarkably reduced rates of clearance are possible with levels of serum creatinine that are only slightly elevated. In a series of 585 patients with congestive heart failure at our institution, those with the lowest levels of creatinine clearance had the highest mortality when followed for more than 3 years (Figure 2).⁵

Cardiac output is not a reliable indicator

The presence of low filling pressures, a low cardiac index, or even reduced renal perfusion is not necessary to identify cardiorenal syndrome, as often believed. More often than not, in fact, cardiac output will be normal. Modest increases in serum creatinine and blood urea nitrogen rarely indicate reduced cardiac output or left ventricular filling pressure (ie, overdiuresis), but more often reflect a low creatinine clearance at baseline.

PROBLEMS WITH LOOP DIURETICS

Furosemide is the most commonly used loop diuretic for the treatment of patients hospitalized for an acute exacerbation of conges-

tive heart failure. Although furosemide promotes diuresis, it does so at the cost of a further reduction in GFR (Figure 3).⁶

Hemodynamic response

In the 1980s it was recognized that transient hemodynamic abnormalities occurred with high-dose furosemide administration in patients with heart failure, and that these abnormalities subsided with adequate diuresis. A mechanism was proposed for this phenomenon, in which stimulation of the renin-angiotensin system and sympathetic nervous system by loop diuretic therapy was responsible for vasoconstriction, an increase in levels of arginine vasopressin (AVP), and an increase in afterload and preload, resulting in adverse hemodynamic effects.⁷

The hemodynamic response after administration of large doses of furosemide consists of an increase in heart rate, a slight increase in mean arterial pressure, a slight reduction in stroke volume, an increase in systemic vascular resistance, and a transient increase in filling pressure and right atrial pressure.⁷ Levels of plasma norepinephrine and AVP increase, as does plasma renin activity, mimicking the changes in hemodynamics. Soon after administration, cardiac function is depressed, but as diuresis occurs, filling pressures fall and stroke volume increases. So although loop diuretics remain the mainstay of treatment for patients in a volume-overloaded state and achieve effective diuresis, they may be contributing to the worsening hemodynamics and progressive renal dysfunction in patients with heart failure.

Chronic diuretic therapy may also worsen renal function

This same deleterious effect on neurohormones occurs with chronic diuretic treatment. Bayliss and colleagues found that 4 weeks of furosemide and amiloride treatment resulted in an increase in plasma renin and aldosterone activity.⁸

Inadequate renal perfusion is not the entire explanation behind worsening renal function in acute heart failure. Deterioration in renal function occurs in patients with decompensated heart failure, increased right atrial pressure, and peripheral tissue congestion, even

though cardiac systolic function is preserved.⁹ This decline in renal function despite presumed preserved blood flow to the kidney suggests that some mechanism in heart failure that is associated with a rise in atrial pressure and peripheral congestion is a major contributor to the cardiorenal syndrome.

■ MANAGING CARDIORENAL SYNDROME

Body weight is probably the single most important measurement in managing the cardiorenal syndrome. Hemodynamic monitoring is often required, especially if there is low blood pressure and uncertain filling pressure.

Free water restriction, although difficult, is advised if the patient is hyponatremic. In my practice, I restrict free water to less than 1,000 mL per 24 hours. In a few cases, volume expansion is required, especially if the patient has documented low filling pressure and hypotension.

In patients with oliguria and rising creatinine levels, a nephrology consultation is desirable.

Before starting loop diuretics, patients are often primed with 250 or 500 mg of intravenous chlorothiazide. It is difficult to obtain, however; hospital pharmacies may not carry it because it is used so infrequently. Furosemide drips, 5 to 10 mg per hour, may be useful. If the patient can take medications orally, 5 to 10 mg of metolazone may enhance the response to the loop diuretic.

Treating diuretic resistance

Overcoming diuretic refractoriness is part of the management of the cardiorenal syndrome. The braking phenomenon (short-term tolerance) is said to occur when the response to a diuretic is reduced after the first dose has been administered.¹⁰ In this instance, we use a continuous infusion of furosemide, starting at 5 to 10 mg per hour, following an intravenous thiazide diuretic.

Other methods to reduce salt and water

Nesiritide. Although some choose to use nesiritide to treat patients with cardiorenal syndrome, the data are not supportive of this practice. Wang et al¹¹ found that urine flow, sodium excretion, GFR, and effective renal plasma flow were no different when comparing placebo and nesiritide infusions in patients with chronic heart failure and wors-

Furosemide monotherapy may cause significant decline in glomerular filtration rate

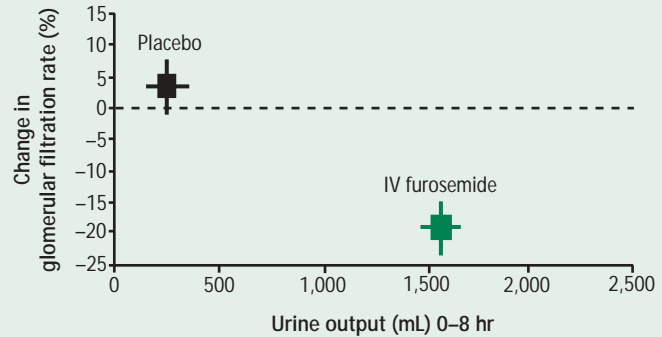


FIGURE 3. In a study of 63 patients with congestive heart failure, treatment with intravenous furosemide caused a decline in glomerular filtration rate compared with placebo. Adapted, with permission, from reference 6.

ening serum creatinine. In a meta-analysis of five randomized studies, Sackner-Bernstein et al¹² reported that nesiritide significantly increased the risk of worsening renal function compared with controls not receiving inotrope-based therapy.

Ultrafiltration has been used in patients with therapy-resistant chronic volume overload.¹³⁻²⁶ Conventional ultrafiltration requiring central venous access is most often used, particularly if the patient is extremely edematous.

Generally, the hemodynamic changes produced by ultrafiltration are fairly modest.¹⁹ The reduction in water with ultrafiltration is accompanied by decreases in right atrial pressure and wedge pressure. Cardiac output and stroke volume are unchanged or increase slightly. Importantly, the weight loss is sustained relative to furosemide treatment.¹⁵

The typical volume of water removed per ultrafiltration session is 3,000 to 4,000 mL. In a randomized study of 40 patients with decompensated heart failure, Bart et al²⁴ found that fluid removal after 24 hours was 4,650 mL in patients assigned to ultrafiltration and 2,838 mL in those assigned to usual care ($P = .001$).

A newer ultrafiltration method in which peripheral venous blood is removed was recently compared with standard intravenous diuretic therapy in 200 patients with acute decompensated heart failure.²⁷ Weight loss and net fluid loss at 48 hours were signifi-

Body weight may be the most important measure in managing the cardiorenal syndrome

cantly greater in the patients undergoing peripheral ultrafiltration. Moreover, the rehospitalization rate, the number of rehospitalization days, and the number of unscheduled office or emergency department visits at 90 days were also significantly lower in patients managed with ultrafiltration. There was no significant deterioration in renal function, but dyspnea was not improved.

AVP receptor inhibitors, which will be discussed in detail later in this supplement, tend to be aquaretic and may have a possible therapeutic role in volume-overloaded patients who are hyponatremic.

Targeted renal delivery of drugs has been proposed to increase local drug concentration in the hopes of enhancing renal effects or providing a previously unattainable effect. Direct intrarenal delivery will lead to renal first-pass elimination, resulting in less systemic exposure and reduction or elimination of serious adverse effects. Intrarenal delivery of fenoldopam was associated with a lower

incidence of hypotension than intravenous fenoldopam,^{28,29} which is also true of intrarenal vs intravenous administration of nesiritide (unpublished data). Given its potential advantages, intrarenal drug delivery is worthy of further study.

■ SUMMARY

Management of the patient with cardiorenal syndrome is fraught with difficulty given the absence of a consensus definition. The pathophysiology is not well understood but seems only loosely coupled to central hemodynamics, ejection fraction, and GFR. Creatinine clearance is more valuable than serum creatinine level in identifying patients with this syndrome, and creatinine clearance is tied to prognosis.

Treatment is challenging, as the syndrome can be aggravated by diuretics and is not predictably responsive to inotropic agents or nesiritide. Ultrafiltration and selective renal artery infusion of drugs require further study.

■ REFERENCES

1. 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.
2. ADHERE™ (Acute Decompensated Heart Failure National Registry). Third quarter 2004 National Benchmark Report. Available at: www.adhereregistry.com/nat.html. Accessed April 26, 2006.
3. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000; 102:203-210.
4. Mezu UL, Philip K, Francis GS, Starling RC, Taylor DO, Tang WHW. The impact of baseline glomerular filtration rate on the incidence of worsening renal failure in patients admitted for acute decompensated heart failure. *J Am Coll Cardiol* 2005; 45(Suppl 3A). Abstract 1133-178.
5. Mahon NG, Blackstone EH, Francis GS, Starling RC 3rd, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. *J Am Coll Cardiol* 2002; 40:1106-1113.
6. Gottlieb SS, Brater DC, Thomas I, et al. BG9717 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. *Circulation* 2002; 105:1348-1353.
7. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985; 103:1-6.
8. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart*

- J* 1987; 57:17-22.
9. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC, ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006; 47:76-84.
10. Brater DC. Diuretic therapy. *N Engl J Med* 1998; 339:387-395.
11. Wang DJ, Dowling TC, Meadows D, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. *Circulation* 2004; 110:1620-1625.
12. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; 111:1487-1491.
13. Fauchald P, Forfang K, Amlie J. An evaluation of ultrafiltration as treatment of therapy-resistant cardiac edema. *Acta Med Scand* 1986; 219:47-52.
14. Rimondini A, Cipolla CM, Della Bella P, et al. Hemofiltration as short-term treatment for refractory congestive heart failure. *Am J Med* 1987; 83:43-48.
15. Agostoni PG, Marenzi GC, Pepi M, et al. Isolated ultrafiltration in moderate congestive heart failure. *J Am Coll Cardiol* 1993; 21:424-431.
16. Pepi M, Marenzi GC, Agostoni PG, et al. Sustained cardiac diastolic changes elicited by ultrafiltration in patients with moderate congestive heart failure: pathophysiological correlates. *Br Heart J* 1993; 70:135-140.
17. Agostoni P, Marenzi G, Lauri G, et al. Sustained improvement in functional capacity after removal of

The typical volume of water removed per ultrafiltration session is 3,000 to 4,000 mL



- body fluid with isolated ultrafiltration in chronic cardiac insufficiency: failure of furosemide to provide the same result. *Am J Med* 1994; 96:191-199.
18. **Canaud B, Leblanc M, Leray-Moragues H, Delmas S, Klouche K, Beraud J-J.** Slow continuous and daily ultrafiltration for refractory congestive heart failure. *Nephrol Dial Transplant* 1998; 13(Suppl 4):51-55.
 19. **Marenzi G, Lauri G, Grazi M, Assanelli E, Campodonico J, Agostoni P.** Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. *J Am Coll Cardiol* 2001; 38:963-968.
 20. **Jaski BE, Miller D.** Ultrafiltration in decompensated heart failure. *Curr Heart Fail Rep* 2005; 2:148-154.
 21. **Raman JS, Hata M, Bellomo R, Kohchi K, Cheung HL, Buxton BF.** Hemofiltration during cardiopulmonary bypass for high risk adult cardiac surgery. *Int J Artif Organs* 2003; 26:753-757.
 22. **Saltzberg MT.** Beneficial effects of early initiation of vasoactive agents in patients with acute decompensated heart failure. *Rev Cardiovasc Med* 2004; 5(Suppl 4):S17-S27.
 23. **Sheppard R, Panyon J, Pohwani AL, et al.** Intermittent outpatient ultrafiltration for the treatment of severe refractory congestive heart failure. *J Card Fail* 2004; 10:380-383.
 24. **Bart BA, Boyle A, Bank AJ, et al.** Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J Am Coll Cardiol* 2005; 46:2043-2046.
 25. **Costanzo MR, Saltzberg M, O'Sullivan J, Sobotka P.** Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. *J Am Coll Cardiol* 2005; 46:2047-2051.
 26. **McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW.** Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; 109:1004-1009.
 27. **Costanza MR.** Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. Presented at the 55th Annual Scientific Session of the American College of Cardiology; March 13, 2006; Atlanta, GA.
 28. **Grube E, Teirstein P, Baim D, Mueller R, Schmid T, Burkhoff D.** Intrarenal fenoldopam increases renal artery flow velocity and causes fewer effects on blood pressure lowering than intravenous fenoldopam. *Am J Cardiol* 2004; 94(Suppl 6A):176E.
 29. **Madyoon H, Teirstein P, Baim D, Croushore L, Anderson E, Mathur V.** Differential effects between intravenous and local renal delivery of fenoldopam on renal function and blood pressure: a randomized, controlled trial. *Am J Cardiol* 2004; 94(Suppl 6A): 22E-23E.
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