Cardiorenal syndrome: A literature review

Narayan Pokhrel MD, Najindra Maharjan MD, Bismita Dhakal PharmD, Rohit R Arora MD FACC FAHA FACP FSCAI

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The incidence of cardiorenal syndrome is increasing; however, its pathophysiology and effective management are still not well understood. For many years, diuretics have been the mainstay of treatment for cardiorenal syndrome, although a significant proportion of patients develop resistance to diuretics and even deteriorate while on diuretics. Trials on different ways to counteract diuretic resistance and newer treatment modalities, such as nesiritide, arginine vasopressin receptor antagonists, adenosine receptor antagonists and ultrafiltration, have shown promising results.

Key Words: *Cardiorenal syndrome; Diuretic resistance; Diuretics; Nesiritide; Tolvaptan; Ultrafiltration*

CASE PRESENTATION

A 71-year-old man presented to the emergency department (ED) with complaints of severe shortness of breath and chest pain. His past medical history was significant for hypertension, chronic heart failure (CHF)-New York Heart Association (NYHA) class IV and chronic kidney disease, with temporary dialysis performed three times for acute-on-chronic renal failure. Bilateral crackles in the chest and pedal edema were found on clinical examination. Chest radiography showed cardiomegaly with a small right pleural effusion and pulmonary vascular congestion. Echocardiography showed marked left ventricular hypertrophy (LVH) with diastolic dysfunction, ejection fraction (EF) of 40%, and pulmonary artery systolic pressure of 45 mmHg to 50 mmHg. His blood urea nitrogen level was 22 mmol/L and serum creatinine was 2.23 mg/dL (197.04 µmol/L). The patient was admitted with a diagnosis of CHF exacerbation and was treated with furosemide. During the course of treatment, he developed acute-on-chronic renal failure with serum creatinine level rising to 4.7 mg/dL (415.29 µmol/L), necessitating hemodialysis. The case was further complicated by the development of respiratory failure and pericardial effusion. After treatment with milrinone, dopamine, dobutamine and furosemide, as well as therapeutic thoracocentesis and pericardiocentesis, the patient improved.

INTRODUCTION

Over recent years, the field of medicine has been challenged by the twin epidemic of heart failure and renal insufficiency. Concomitant renal insufficiency is being recognized as one of the most common and most confounding comorbidities, not only in CHF but also in acute decompensated heart failure (ADHF). Moreover, the coexistence of the two problems in the same patient, referred to as 'cardiorenal syndrome' (CRS), has an extremely poor prognosis (1,2). Studies (3) have shown that more than 30% of the overall ADHF patients develop renal dysfunction. Even a slightly decreased kidney function is associated with a substantial increase in mortality in such patients. This important association of renal function with in-hospital mortality in ADHF has been demonstrated in a study by Fonarow et al (4). They found that death rate increased to double the overall in-hospital mortality rate (9.4%) in patients with a serum creatinine level of 3.0 mg/dL (265.08 µmol/L) or more. Inversely, cardiovascular disease is common in chronic renal failure, with 43.6% of all deaths in patients with end-stage renal disease (ESRD) due to cardiac causes (5). Patients with chronic renal failure are found to be 10 to 20 times more likely to die from cardiac causes than their matched segments of the general population (5).

DEFINITION OF CRS

Because many details about CRS still need to be revealed, there is no single definition that appropriately describes it. The term CRS has generally been reserved for declining renal function in the setting of advanced CHF. It is now a well-accepted fact that there is a correlation between cardiovascular morbidity and mortality and decreased renal function; this relationship exists regardless of whether the initial event is a cardiac disease or a renal parenchymal disease. Some authors have proposed the term 'renocardiac syndrome' for the condition in which cardiovascular morbidity and mortality is increased in a patient with chronic kidney disease (6). Other authors have even proposed the modification of the definition of CRS to stress the bidirectional nature of the heart-kidney interaction. This proposed definition divides CRS into five subtypes: type I, acute CRS; type II, chronic CRS; type III, acute renocardiac syndrome; type IV, chronic renocardiac syndrome; and type V, secondary CRS, meaning systemic diseases such as diabetes, sepsis and amyloidosis causing simultaneous cardiac and renal dysfunction (7,8).

PATHOPHYSIOLOGY

To date, little is known regarding the pathophysiology of CRS. A reduced cardiac output (CO) in CHF resulting in decreased

Department of Medicine, Rosalind Franklin University/Chicago Medical School, Chicago, Illinois, USA
Correspondence: Dr Rohit R Arora, Rosalind Franklin University/Chicago Medical School, 3333 Green Bay Road, North Chicago, Illinois 60064, USA. Telephone 224-610-4503, fax 224-610-3878, e-mail rohit.arora@rosalindfranklin.edu
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renal perfusion could be an easy explanation for the worsening renal function. Interestingly, worsening renal function has been demonstrated in patients with ADHF even though left ventricular EF is preserved (9,10). This decline in renal function, despite a presumed preservation of blood flow to the kidneys, has led to the search for other mechanisms of CRS, including the role of the renin-angiotensin-aldosterone system (RAAS), various chemicals (nitric oxide [NO], prostaglandins, natriuretic peptides, endothelins, etc), oxidative stress and sympathetic overactivity.

RAAS effects

When the heart fails, both CO and mean arterial blood pressure decrease. This leads to decreased renal perfusion and, in turn, activation of the RAAS. Reversely, when the kidney fails, this also leads to both neurohormonal and sympathetic nervous system (SNS) maladaptation, resulting in the inappropriate activation of the RAAS. Besides vasoconstriction and sodium retention leading to increased preload and afterload, one of the most deleterious actions of the RAAS in CRS is the activation of NADPH-oxidase by angiotensin II, resulting in the formation of reactive oxygen species (ROS) (11). Increased NADPH-oxidase activity has been found in the hearts of patients with end-stage heart failure (12). Finally, a vicious cycle sets in, causing structural and functional damage to the heart and the kidneys.

Endothelin effects

The release of endothelin has some adverse effects because it causes vasoconstriction and induces hypertrophy of cardiac myocytes. Moreover, it stimulates and potentiates noradrenaline, angiotensin II and aldosterone (13).

Arginine vasopressin effects

Arginine vasopressin (AVP), too, has adverse effects on CRS progression by fluid retention and potentiation of angiotensin II and noradrenaline actions. It also stimulates myocardial hypertrophy (14).

B-type natriuretic peptide effects

B-type natriuretic peptide (BNP) provides some beneficial effects by counteracting many of the negative adaptations. It inhibits the RAAS, endothelin-1 and other vasoconstrictors. As its name suggests, BNP promotes diuresis, enhances sodium excretion and may even increase glomerular filtration rate (GFR).

NO and ROS imbalance

In CRS, the balance between NO and ROS is skewed toward the latter by increased production of ROS, a low antioxidant status and lower availability of NO. Oxidative stress is a major initiator of an inflammatory response, with the production (and activation) of proinflammatory cytokines, in particular interleukin-1, interleukin-6, C-reactive protein and tumour necrosis factor-alpha. These cytokines play a crucial role in the pathophysiology of atherosclerosis, have negative inotropic effects, assist in cardiac remodelling and even cause thrombotic complications (5).

SNS overactivity

The SNS is initially activated in heart failure by the baroreflex to provide inotropic support and preserve CO. However, excessive sympathetic activity can induce cardiomyocyte apoptosis, hypertrophy and focal myocardial necrosis. Cardiac hypertrophy is partly due to the direct actions of catecholamines, because several studies (5) have shown that noradrenaline induces hypertrophy of cultured cardiomyocytes.

Other contributors

Some drugs may have harmful effects in the progression of CRS. Inotropic drugs augment neurohormonal activation. High-dose diuretics produce hypovolemia, and intravenous vasodilators cause hypotension. Both drugs further diminish renal perfusion (15).

DIAGNOSIS OF CRS

While making a diagnosis of CRS, it should be kept in mind that there is no correlation between serum creatinine and GFR. Relative to a decline in EF, a fall in GFR is more important regarding the prognosis in heart failure patients (16). In addition, measurements of serum creatinine alone could also be misleading in terms of prognosis. Approximately two-thirds of patients admitted for acute exacerbations of CHF have decreased GFR or creatinine clearance, despite many of them having relatively normal levels of serum creatinine (16).

The estimation of GFR should be a part of the initial evaluation because GFR provides a general sense of prognosis. Moreover, GFR is helpful in the evaluation for planning a management strategy (use of ACE inhibitors, angiotensin receptor antagonists and radiocontrasts for diagnostic tests, etc). Because serum creatinine level is a relatively insensitive indicator of CRS, true GFR is calculated, although cumbersome, using the Cockcroft-Gault formula (by calculating creatinine clearance) or the Modification of Diet in Renal Disease equation.

The CO is also not a reliable indicator to assess the severity of CRS. More often, CO will be normal in cases of CRS. Nevertheless, the presence of low filling pressures, a low cardiac index or even reduced renal perfusion is not necessary to identify CRS (16).

MANAGEMENT

The heterogeneous and complex pathophysiology of CRS makes patient management an intricate clinical challenge. To date, there is no single success-guaranteed treatment for CRS because each patient has his or her own unique medical history, risk profile and combination of comorbidities. With the development of resistance to many standard therapies, such as diuretics and inotropes, there is an increasing concern toward novel therapies (eg, use of AVP antagonists, adenosine A_1 receptor antagonists and ultrafiltration).

Body weight of the patient is the single most important indicator while managing CRS (16). The patient needs continuous hemodynamic monitoring, especially if his or her blood pressure is low and the filling pressure is uncertain. It is better to restrict the intake of free water to less than 1000 mL per 24 h if the patient is hyponatremic. A few cases with low filling pressure and low blood pressure may need volume expansion.

Diuretics

Despite limited clinical trial data suggesting a beneficial role, diuretics have long been considered to be an initial and essential part of the management of CRS patients. The importance

of diuretics is illustrated by data from the Acute Decompensated Heart Failure National Registry (ADHFNR), which revealed that 80.8% of patients enrolled in this registry were on chronic diuretic therapy at the time of presentation, and 88% were treated acutely with an intravenous diuretic during their admission for ADHF (17).

Loop, thiazide and potassium-sparing diuretics provide diuresis and natriuresis in as quickly as 20 min after administration. Moreover, they provide effective short-term symptomatic relief. However, the use of diuretics is not free from drawbacks, such as long-term deleterious cardiovascular effects. Diuretic use exacerbates neurohormonal activity, increases systemic vascular resistance and worsens left ventricular function, thus increasing the risk of mortality. It also increases renal dysfunction as measured by an increase in serum creatinine and declining GFR (18,19).

Diuretic resistance: In the management of ADHF, the lack of a clinical response to diuretic therapy is commonly observed. Because diuretic therapy can worsen renal function, and worsening renal function is associated with poorer outcomes, diuretic resistance can be considered to be another indicator of poor prognosis in patients with CHF. However, in the absence of definitive data, patients with volume overload should not be restricted from receiving loop or thiazide diuretics as necessary to alleviate symptoms (3).

Etiology of diuretic resistance: Many factors ranging from delayed intestinal absorption of oral drugs, decreased renal perfusion and decreased diuretic excretion into the urine are responsible for diuretic resistance. The concomitant use of nonsteroidal anti-inflammatory drugs may also play a role in diuretic resistance by inhibiting the synthesis of vasodilator and natriuretic prostaglandins. Inadequate drug dosing and dietary noncompliance such as excess salt intake may produce a false clinical picture similar to diuretic resistance.

Treating diuretic refractoriness: Because the lack of response to diuretic therapy is a common scenario, overcoming this problem is an important part of CRS management. The braking phenomenon or short-term tolerance means that the response to a diuretic is reduced after the first dose has been administered. This effect is managed by a continuous infusion of furosemide, rather than bolus doses, starting at 5 mg/h to 10 mg/h, following an intravenous thiazide diuretic (often primed with 250 mg or 500 mg of intravenous chlorothiazide). If the patient can take 5 mg to 10 mg of metolazone orally, this treatment may enhance the response to loop diuretic, but it requires careful monitoring for excessive sodium and potassium losses (16).

While deciding on the optimum dose of diuretics in a case of refractory edema, we have to consider several factors. First, a single effective dose should be determined. It is important to remember that diuretics do not have a smooth dose-response curve; hence, no natriuresis occurs until a threshold rate of drug excretion is attained. Thus, a patient who does not respond to 20 mg of furosemide may not be exceeding this threshold, and the dose should be increased to 40 mg rather than giving the same dose twice a day. Second, the patient should be encouraged to cut down his or her daily sodium intake, because high sodium can prevent net fluid loss even though adequate diuresis is being achieved. Third, the patient may initially need intravenous diuretic therapy to avoid the poor oral bioavailability due to decreased intestinal perfusion, reduced intestinal mobility and intestinal mucosal edema. Finally, to avoid the risk of ototoxicity, high-dose intravenous diuretics should be given slowly over 30 min to 60 min (3).

A Cochrane review (20) examined eight trials comparing continuous infusion of a loop diuretic with bolus injections in 254 patients with CHF. The urine output (as measured in mL/24 h) was noted to be greater in patients given continuous infusion with weighted mean difference of 271 mL/24 h (95% CI 93.1 to 449; P<0.01). The duration of hospital stay was significantly shortened by 3.1 days using continuous infusion (weighed mean difference –3.1, 95% CI –4.06 to –2.20; P<0.0001), while cardiac mortality was significantly different in the two treatment groups (RR 0.47, 95% CI 0.33 to 0.69; P<0.0001).

If the patient is resistant to furosemide, he or she is not likely to respond to a similar dose of another loop diuretic such as bumetanide or torsemide, particularly with intravenous therapy. This problem can be overcome by increasing the dose of furosemide, or by switching to oral bumetanide or torsemide, which are much more completely absorbed from the intestinal mucosa than oral furosemide (3). Another approach to enhance the efficacy of intravenous furosemide is to add salt-poor albumin to the regimen because patients respond poorly to diuretics at low serum albumin level. When salt-poor albumin is added to the infusion, the resulting furosemide-albumin complex is believed to deliver more diuretic to the kidney, primarily by staying in the vascular space. Studies have shown that adding salt-poor albumin substantially increased sodium excretion (21).

Low-dose dopamine

In clinical practice, low (renal) doses of dopamine are commonly used in conjunction with diuretic therapy, although available data do not clearly support favourable effects on kidney function. Rather than improving renal function, dopamine has been shown to impair renal oxygen kinetics, inhibit feedback systems that protect the kidney from ischemia, and possibly worsen tubular injury (22). A prospective, double-blind, randomized, controlled study to investigate the effect of 'low-dose' dopamine on renal resistance indexes concluded that low-dose dopamine can worsen renal perfusion in patients with acute renal failure, which adds to the rationale for abandoning the routine use of low-dose dopamine in critically ill patients (23).

Inotropes

If renal dysfunction in CRS is primarily due to low CO, a trial of inotropic therapy using dopamine or milrinone may be considered. Systematic review of the use of inotropes in acute and chronic heart failure suggests a negative impact on survival, except in a very limited number of patients presenting with severe 'low output failure' – candidates for bridging to more definitive therapy (assist device or transplantation).

Ultrafiltration (aquapheresis)

This treatment modality is useful as a palliative measure in cases of chronic CRS when renal function is declining despite the use of loop diuretics, and when the patient is extremely edematous (24). The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial (25) randomly assigned 200 patients, either ultrafiltration or intravenous diuretics. They showed that at 48 h, ultrafiltration safely produced

greater weight loss (5.0±3.1 kg versus 3.1±3.5 kg; P=0.001) and net fluid loss (4.6 L versus 3.3 L; P=0.001) than intravenous diuretics. Moreover, at 90 days, the ultrafiltration group had fewer patients rehospitalized for heart failure (16 of 89 [18%] versus 28 of 87 [32%] patients; P=0.037), heart failure rehospitalizations (0.22±0.54 versus 0.46±0.76; P=0.022), rehospitalization days (1.4±4.2 versus 3.8±8.5 days; P=0.022) per patient and unscheduled visits (14 of 65 [21%] versus 29 of 66 [44%] visits; P=0.009).

However, ultrafiltration does not provide a long-term solution to the chronic cases of CRS. These patients often continue to retain fluid. If the dose of diuretics is increased in such a case, it may further worsen the already compromised renal function. A randomized, controlled trial by Rogers et al (26) on the renal effects of ultrafiltration in patients with ADHF showed that during a 48 h period, ultrafiltration did not cause any significant differences in renal homodynamics (as measured by urine output, GFR and renal plasma flow) compared with the standard treatment of intravenous diuretics.

Nesiritide (BNP)

Recent studies regarding the risks associated with the use of nesiritide in ADHF have produced inconclusive results. A pooled analysis of randomized controlled trials by Sackner-Bernstein et al (27) showed that the death rate within 30 days of therapy tended to occur more often among the patients randomly assigned to nesiritide therapy than control therapy (35 of 485 [7.2%] versus 15 of 377 patients [4.0%], respectively). It shows a concern of possible short-term (within 30 days) risk of death after nesiritide use for ADHF. However, a multicentre, randomized, double-blind, placebo-controlled pilot study by Peacock et al (28) on 237 ED or observation unit patients with ADHF showed that nesiritide is safe when used in the ED, observation units or similar settings. Compared with the standard care plus placebo (SCP) group, patients using nesiritide had 11% fewer inpatient hospital admissions at the index ED visit (55% SCP and 49% nesiritide; P=0.436), and 57% fewer inpatient hospitalizations within 30 days after discharge from the index hospitalization (23% SCP, 10% nesiritide; P=0.058). The duration of rehospitalization was shorter for nesiritide patients (median length of stay 2.5 days versus 6.5 days; P=0.032).

A meta-analysis by Arora et al (29) based on seven large randomized controlled trials on nesiritide showed that the relative risks for adjusted 30-day and 180-day mortality revealed no significant differences between the nesiritide arm (RR 1.243, 95% CI 0.798 to 1.935) and the control arm (RR 1.002, 95% CI 0.798 to 1.259). Hence, more large-scale randomized controlled trials are still required to conclusively address these findings.

ACE inhibitors

ACE inhibitors should be used cautiously in patients with renal insufficiency. To reduce the incidence of renal dysfunction, ACE inhibitors should be started at a lower dose while monitoring the patient's hydration status. The concomitant use of nonsteroidal anti-inflammatory drugs should be avoided. Many trials that confirmed the benefits of ACE inhibitors in CHF have considered creatinine level before administering ACE inhibitors. Studies of Left Ventricular Dysfunction (SOLVD) (30) excluded patients with serum creatinine level greater than 2.0 mg/dL (176.72 µmol/L), while Cooperative North Scandinavian Enalapril Survival (CONSENSUS) study excluded patients with greater than 3.4 mg/dL (300.42 µmol/L) (3). CONSENSUS (31) also showed that patients having the most severe CHF had a substantial increase in creatinine (greater than 30%) when an ACE inhibitor was added to their regimen, independent of their baseline renal function.

Cardiac transplantation or left ventricular assist devices

These treatment modalities have very low clinical applicability due to their high surgical risks and poor prognosis. Patients with a substantial reduction in exercise capacity (peak exercise O_2 consumption less than 14 mL/min/kg) with an EF less than 25% and no contraindications, such as irreversible renal insufficiency, are the candidates for cardiac transplantation. The criteria for left ventricular assist devices are even stricter; only patients who are dependant on inotropes are considered.

PROMISING FUTURE APPROACHES

AVP receptor antagonists

In CHF, secretion of AVP is increased because of low blood pressure and diminished arterial volume. Excess AVP can also lead to hyponatremia. V_2 receptor antagonists known as vaptans, such as conivaptan and tolvaptan, can produce diuresis and retention of electrolytes. Some studies (32) have reported a powerful aquaretic effect without renal impairment in patients with ADHF treated with tolvaptan.

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) was a randomized, double-blind, placebo-controlled study (33,34) conducted at 359 sites in North and South America and Europe between October 2003 and February 2006. This outcome trial comprised 4133 patients within two short-term trials, who were hospitalized with heart failure and then followed up during long-term treatment. Both of the short-term trials showed more patients receiving tolvaptan to have significant reduction in mean body weight and improvement in dyspnea. Significant edema reduction was found in only one trial, and neither of them showed significant improvement in the global clinical status (33). However, tolvaptan initiated for the acute treatment of patients hospitalized with heart failure had no effect on long-term mortality or heart failure-related morbidity (34).

Adenosine A_1 receptor antagonists

Adenosine lowers cortical blood flow and has antinatriuretic responses. The elevated plasma adenosine levels observed in CHF can contribute to renal dysfunction. A_1 adenosine receptor antagonists cause diuresis and natriuresis, and are emerging as a therapeutic option. Gottlieb et al (35) reported that the A_1 adenosine antagonist BG9719, when administered with furosemide, increases urinary output while protecting renal function.

Use of hypertonic saline with diuretics

Optimizing diuresis via the simultaneous use of hypertonic saline with diuretics has been studied and found successful at relieving signs and symptoms of congestion. When treated only with diuretics, different compensatory pathophysiological mechanisms come into play in heart failure to maintain vascular resistance leading to diuretic refractoriness. The use of hypertonic saline, along with a high dose of loop diuretics, produces a reduction or inhibition of the activated neurohormonal systems in heart failure patients (36). In a study by Licata et al (37), NYHA class IV patients in group 1

(20 women and 33 men) received an intravenous infusion of furosemide (500 mg to 1000 mg) plus hypertonic saline (150 mL of 1.4% to 4.6% NaCl) twice a day over 30 min. Patients in group 2 (19 women and 35 men) received an intravenous bolus of furosemide (500 mg to 1000 mg) twice a day, without hypertonic saline, during a period lasting for six to 12 days. A significant increase in daily diuresis and natriuresis was observed in both groups, but it was more significant in the group receiving hypertonic saline ($P<0.05$). In the follow-up period (31±14 months), 25 patients from group 1 were readmitted to the hospital for heart failure. In group 2, 43 patients were readmitted to the hospital at a higher NYHA class than at discharge. Twenty-four patients in group 1 died during follow-up, versus 47 patients in group 2 ($P<0.001$).

Targeted renal delivery of drugs

The benephit infusion system (38), a simple bifurcated catheter, enables the direct administration of drugs to both renal arteries simultaneously. This method of drug administration increases local drug concentration, enhancing renal effects. On the other hand, it leads to renal first-pass elimination, minimizing systemic serious adverse effects. Intrarenal delivery of fenoldopam (dopamine D_1 agonist, moderate affinity to α_2-adrenoceptors, and no significant affinity for D_2 receptors, α_1 and β adrenoceptors) was associated with a lower incidence of hypotension than intravenous fenoldopam (39), which is also true of intrarenal versus intravenous administration of nesiritide because BNP has high first-pass renal metabolism.

PROGNOSIS OF CRS

Considering the unclear pathophysiology and treatment modality of CRS, these patients have poor prognosis. A rise in serum creatinine or decrease in creatinine clearance in patients with ADHF is associated with a worsened prognosis. The prognosis is even poorer if the increase in serum creatinine or the decrease in creatinine clearance is accompanied by oliguria (less than 50 mL/h), edema, hyponatremia or refractoriness to diuretics (40). Moreover, two of the three noninvasive measures found to predict in-hospital mortality drawn from an ADHFNR (4) analysis were reflections of kidney function: baseline blood urea nitrogen levels, systolic blood pressure and serum creatinine concentrations. As renal dysfunction radically worsens the prognosis of patients with heart failure, heart failure conversely worsens the prognosis of patients receiving dialysis, decreasing the probability of survival by as much as 50% (41,42).

CONCLUSION

The CRS has a unique and complex pathophysiology. Any degree of combination of renal insufficiency with heart failure makes patient management a great challenge and is associated with a poor prognosis. Most of the current therapies in use can have detrimental effects on renal function; hence, good clinical judgement is essential for proper patient management. Further large-scale studies are still necessary to understand the exact pathophysiology of CRS and to determine an effective means of therapy.

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