

Cardiorenal syndrome

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ABSTRACT

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease. Heart failure may lead to acute kidney injury and vice versa. Chronic kidney disease may affect the clinical outcomes in patients with cardiovascular disorders. Renal impairment with any degree of albuminuria has been increasingly recognized as an independent risk factor for cardiovascular events and heart failure hospitalizations, while chronic heart failure may cause chronic kidney disease. The bidirectional nature of these disorders contributes to the complexity and the composite definitions of cardiorenal syndromes. However, the most important clinical trials in heart failure tend to exclude patients with significant renal dysfunction. The mechanisms whereby renal insufficiency worsens the outcome in heart failure are not known, and several pathways could contribute to the "vicious heart/kidney circle." Traditionally, renal impairment has been attributed to the renal hypoperfusion due to reduced cardiac output and decreased systemic pressure. The hypovolemia leads to sympathetic activity, increased renin-angiotensin-aldosterone pathway, and arginine-vasopressin release. These mechanisms cause fluid and sodium retention, peripheral vasoconstriction, and volume overload. Therapy to improve renal dysfunction, reduce neurohormonal activation and ameliorate renal blood flow could lead to a reduction in mortality and hospitalization in patients with cardiorenal syndrome.

Key words: Cardiorenal syndrome, heart failure, acute kidney injury, chronic kidney disease, biomarkers, morbidity

The case below illustrates a common clinical problem in patients with both acute and chronic cardiac diseases, namely the development of renal dysfunction. This clinical presentation has been called a cardiorenal syndrome; this construct should lead to a better understanding of the interactions between cardiac and renal disorders and the effect of this interaction on management and outcomes. We have reviewed this topic by discussing the definitions, prevalence, pathophysiology, and treatment of cardiorenal syndromes.

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CASE

A 68-year-old man with ischemic heart disease, type 2 diabetes mellitus, hypertension, and hyperlipidemia had been admitted with a ST segment elevation myocardial infarction three months previously. At this follow up visit he presented with gradually increasing shortness of breath, generalized swelling, and some abdominal distension. The patient was admitted to the coronary care unit. On admission, his blood pressure was 110/62 mmHg, and he had bibasilar rales and bipedal pitting edema. The patient had oliguria with a urine output of 10 ml/hour during the first day. The patient's baseline creatinine was 1.2 mg/dl; on admission his creatinine was 2.6 mg/dl and his blood

urea nitrogen was 54 mg/dl. A renal ultrasound was unremarkable. An echocardiogram showed an ejection fraction of 32% with a dilated left ventricle. What has happened to this patient?

DISCUSSION

DEFINITIONS AND TYPES OF CARDIORENAL SYNDROMES

Cardiorenal syndrome (CRS) is a complex pathophysiological disorder of the heart and kidneys in which acute or chronic dysfunction in one organ causes acute or chronic dysfunction in the other organ.¹⁻² CRS is classified into five subtypes that recognize the potential underlying pathophysiological mechanisms (Table 1).² Patients can move from one subtype to another depending on the clinical course. Since the current literature provides more information on CRS type 1, our discussion emphasizes this syndrome.

PREVALENCE OF CARDIORENAL SYNDROME

Many patients (20-67%) with heart failure have moderate to severe reductions in glomerular filtration

rate (GFR) (less than 60 mL/min/1.73m²); this renal dysfunction is associated with age, female gender, baseline chronic kidney disease, Caucasian American ethnicity, systolic and diastolic heart failure, diabetes, and hypertension.³⁻⁷ In a systematic review of 16 studies of more than 80,000 hospitalized and nonhospitalized patients with heart failure, moderate to severe kidney impairment (defined as an estimated GFR less than 53 ml/minute, a serum creatinine of 1.5 mg/dl or higher, or a serum cystatin C of 1.56 mg/dl or higher) was present in 29 percent.⁸ The Acute Decompensated Heart Failure National Registry (ADHERE) database reported data on over 100,000 patients with heart failure requiring hospitalization. Approximately 30 % had a diagnosis of chronic kidney disease (defined as a serum creatinine greater than 2.0 mg/dL). The mean estimated GFR was 55 mL/min/m², and only 9 % had a normal estimated GFR (defined as greater than 90 mL/min/1.73m²).⁹ These studies demonstrate that renal insufficiency occurs very frequently in patients with cardiac diseases, especially in patients with heart failure.

Table 1 Cardiorenal syndrome classification

Type	Definition
CRS type I (acute cardiorenal syndrome)	Abrupt worsening of cardiac function (e.g. acute cardiogenic shock, acute decompensation of chronic heart failure or acute coronary syndrome) leading to acute kidney injury.
CRS type II (chronic cardiorenal syndrome)	Chronic abnormalities in cardiac function (e.g. chronic heart failure) causing progressive chronic kidney disease.
CRS type III (acute renocardiac syndrome)	Abrupt worsening of renal function (e.g. acute kidney failure due to volume depletion or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, pulmonary edema).
CRS type IV (chronic renocardiac syndrome)	Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and / or increased risk of adverse cardiovascular events.
CRS type V (secondary cardiorenal syndrome)	Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction.

PATHOPHYSIOLOGY

The term cardiorenal syndrome is an umbrella term for a worse outcome when these two organs fail simultaneously. However, the pathophysiology of kidney disease in heart failure is quite different from the pathophysiology of cardiovascular complications in chronic kidney disease.¹⁰ When renal parenchymal disease leads to cardiovascular complications, it is reasonable to call this presentation the renocardiac syndrome.¹¹ CRS types 1 and 2 are frequently encountered in patients with heart disease, especially heart failure. Both acute heart failure leading to acute kidney injury and chronic heart failure leading to progressive renal insufficiency and chronic kidney disease represent conditions that may seem interchangeable. In some cases it difficult to distinguish between the two entities without the necessary time based information in the clinical history of the patient. The pathophysiology of CRS type 1, renal dysfunction in patients with decompensated heart failure, is complex. Reduced cardiac output and low mean arterial pressures cause renal hypoperfusion and passive congestion of the kidney, and this activates the renin-angiotensin system, reduces nitric oxide in the endothelium, activates the sympathetic nervous system, and induces inflammatory mediators. Deterioration of renal function can also occur in patients with acute decompensated heart with preserved left ventricular ejection fraction.¹² Vascular factors, such as nitric oxide, prostaglandin, natriuretic peptides, and endothelin, may modulate renal perfusion independently of cardiac hemodynamics.¹³ The heart, kidneys, renin-angiotensin system, sympathetic nervous system, immune system, and endothelium interact through intricate feedback loops (Figure). Any imbalance in this complex system may cause deterioration in both cardiac and renal function.¹⁴ Cardiac biomarkers in CRS type 1 include troponin, CK-MB, BNP, NT-proBNP, myeloperoxidase, and ischemia modified albumin; renal biomarkers include serum cystatin C, creatinine, and neutrophil gelatinase-associated lipocalin, and urinary kidney injury molecule-1, IL-18, neutrophil gelatinase-associated lipocalin, and N-acetyl-D-glucosaminidase. These markers reflect activation of hormonal, immunologic, inflammatory, and oxidative processes and are associated with an

increased risk deterioration in renal function.^{15,16} These biomarkers have the potential to identify cardiorenal syndromes and predict outcomes and need more study. Patients with chronic heart failure can develop chronic renal failure (CRS type2) through a similar pathophysiology. Of course, adverse medication effects can contribute to the progression of renal disease.

The development of acute kidney injury as a primary event leading to cardiac dysfunction (CRS type 3) occurs frequently in critically ill patients but has not been systematically studied as much as CRS type 1. Acute kidney injury can affect the heart through several pathways. Fluid overload contributes to the development of pulmonary edema and atrial dilation leading to arrhythmias. Hyperkalemia can contribute to arrhythmias and may cause cardiac arrest. Untreated uremia affects myocardial contractility through the accumulation of myocardial depressant factors and can cause pericarditis.¹⁷ Partially corrected or uncorrected acidemia produces pulmonary vasoconstriction, which in some patients contributes to right-sided heart failure. Acidemia appears to have a negative inotropic effect and may, together with electrolyte imbalances, contribute to an increased risk of arrhythmias.¹⁸⁻²⁰ Cardiac myocyte apoptosis and neutrophil infiltration are two of the most important contributors to the pathophysiology of myocardial infarction during acute kidney injury (renocardiac syndrome type 3), and transgenic models have shown that even apoptosis alone can lead to lethal heart failure.²¹

CRS type 4 recognizes the extreme burden of cardiovascular disease risk in patients with chronic kidney disease. The risk factors for cardiovascular disease (smoking, hypertension, dyslipidemia, age, and diabetes) also contribute to the progression of renal disease.²² Nontraditional risk factors for cardiac disease, including biomarkers such as troponin, asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, natriuretic peptides, C-reactive protein, serum amyloid A protein, and ischemia-modified albumin, progressively increase as GFR decreases.^{23,24} Many of these have an inde-

pendent associations with subsequent vascular disease in chronic kidney disease. For example, B-type natriuretic peptide and the related N-terminal pro-B-type natriuretic peptide are increased significantly in chronic kidney disease patients; these reflect the contribution of myocardial wall stress from hypertension and volume overload, ventricular hypertrophy, subclinical ischemia, cardiac remodeling, and fibrosis

Cardiorenal syndrome type 5 is defined as dysfunction of the heart and kidney secondary to systemic disease; it can occur simultaneously in acute conditions, such as sepsis, systemic lupus, toxin exposure (arsenic, snake bite, and scorpion bite), and Wegener’s granulomatosis, or sequentially in chronic diseases, such as diabetes mellitus, hypertension, systemic amyloidosis, and chronic lead toxicity.

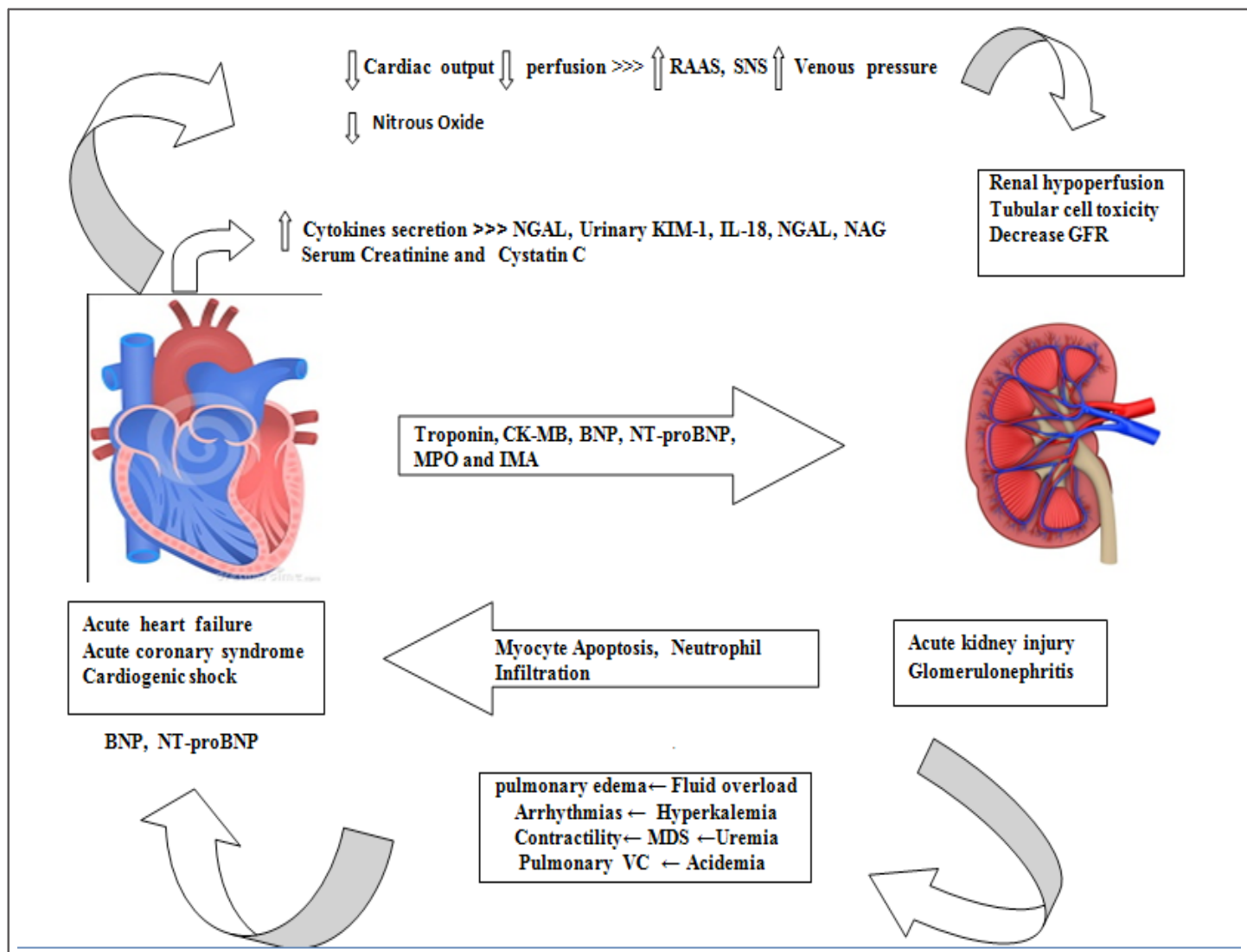


Figure 1. Pathophysiology of cardiorenal syndrome.

Human neutrophil gelatinase-associated lipocalin (NGAL), Kidney injury molecule-1 (KIM-1), N-acetyl-D-glucosaminidase (NAG), Ischemia modified albumin (IMA), Renin-angiotensin-aldosterone system (RAAS), Sympathetic nervous system (SNS), Myocardial depressant substance (MDS), Brain natriuretic peptide (BNP), N-terminal pro hormone of brain natriuretic peptide (NT-proBNP), Interleukin-18 (IL-18), creatine kinase –MB (CK-MB), Myeloperoxidase (MPO), Pulmonary vasoconstriction (Pulmonary VC), glomerular filtration rate (GFR). (Figure produced by Sabry A. Omar)

OUTCOME OF CARDIORENAL SYNDROME

CRS type 1 is the most frequent disorder involving the heart and the kidney and is more frequent in patients with acute decompensated heart failure. Although CRS is less frequent in acute coronary syndrome patients, it is associated with longer hospital stays and with higher in-hospital mortality in these patients. Newsome et al reported a greater likelihood of progression to end-stage renal disease in patients with acute coronary syndrome complicated by acute kidney injury.²⁷ In patients surviving ST elevation myocardial infarction, Goldberg found that persistent and increasing severity of acute kidney injury was associated with a higher risk of death.²⁸ Gottlieb et al reported that 47% of patients admitted with acute decompensated heart failure developed CRS type 1 after three days of hospitalization; Cowie and coworkers found that 50 % developed CRS type 1 after four days.^{29,30} Kociol retrospectively studied 20,063 Medicare beneficiaries hospitalized for acute decompensated heart failure and found that 17.8% developed acute kidney injury (defined as an increase in Cr of 0.3 md/dl) and that 64.5% of those patient with acute kidney injury were readmitted and 35.4% died within one year.³¹ After adjustment for covariates, he found that acute kidney injury was associated independently with long-term mortality. Aronson et al reported that persistent worsening renal function after admission for acute decompensated heart failure was more likely in those with worse baseline kidney function. He investigated this outcome in a cohort of 467 patients admitted with acute decompensated heart failure. Worse renal function was defined as an absolute increase in serum creatinine of 0.5 mg/dl. Transient deterioration was defined as a return to baseline within 30 days and persistent worsening renal function as a sustained increase in serum creatinine of 0.5 mg/dl beyond 30 days. Transient and persistent deterioration in renal function occurred in 7.9% and 14.3%, respectively. At six months, mortality was 17.3 %, 20.5%, and 46.1% in those with neither, transient, and persistent worsening renal function, respectively ($P < 0.0001$ for persistent vs. no change in renal function). This study strongly demonstrates a poor prognosis in patients with acute decompensated heart failure who have a persistent decrease in kidney function.³²

In a study of acute kidney injury, the adjusted odds ratio for death from cardiac failure (7.7) was greater than the ratio from other causes, including hepatic failure (6.3), massive transfusion (5.3), age older than 60 years (3.7), respiratory failure (3.6), or neurologic failure (3.0).³³ This study demonstrates that patients with acute kidney injury have complicated clinical courses and that cardiac mortality is frequent.

TREATMENT

Prevention of CRS is important since once the syndrome has started it is difficult to treat, is not completely reversible in some cases, and is associated with poor outcomes. Blood pressure control, use of drugs that block the renin–angiotensin–aldosterone system, aldosterone receptor blockers, beta adrenergic blockers, coronary artery disease risk factor modification and compliance with dietary and drug treatments, and a combination of nitrates and hydralazine when needed are the most basic preventive strategies suggested by the American Heart Association / American College of Cardiology for Stage A and B heart failure.^{34, 35}

Therapeutic approaches to patients with CRS are complex (Table 2). Vasodilators and loop diuretics are frequently used in cases of acute decompensated heart failure with CRS type 1.³⁶ However, loop diuretics predispose patients to electrolyte imbalance and hypovolemia leading to neurohumoral activation, reduced renal glomerular flow, and higher serum urea and creatinine levels. Felker reported that there were no significant differences in symptoms or rates of re-hospitalization or death when diuretic therapy was administered by bolus compared to continuous infusion or at a high dose compared to a low dose in patients with acute decompensated heart failure.³⁷ In this trial, serum creatinine increased by 0.3 mg/dL or more less frequently in those randomized to the bolus and lower-dose diuretic groups, suggesting less aggressive diuresis when feasible is a better strategy. In a randomized trial involving patients hospitalized for acute decompensated heart failure, worsening renal function, and persistent congestion, Bradley found

that a stepped pharmacologic-therapy algorithm was superior to ultrafiltration for the preservation of renal function. Weight loss at 96 hours was similar with the two approaches, but ultrafiltration was associated with higher rates of adverse events.³⁸ An earlier ultrafiltration vs. intravenous diuretics trial for patients hospitalized for acute decompensated heart failure with two or more signs of hypervolemia compared the safety and efficacy of veno-venous ultrafiltration and standard intravenous diuretic therapy for acute decompensated heart failure patients; this study had a different outcome.³⁹ Two hundred patients were randomized to ultrafiltration or intravenous diuretics. At 48 hours, weight loss (5.0 ± 3.1 kg versus 3.1 ± 3.5 kg; $P = .001$) and net fluid loss (4.6 L versus 3.3 L; $P = .001$) were greater in the ultrafiltration group. At 90 days, the ultrafiltration group had fewer patients rehospitalized for heart failure (16 of 89 [18%] versus 28 of 87 [32%]; $P = .037$), fewer heart failure rehospitalizations per patient (0.22 ± 0.54 versus 0.46 ± 0.76 ; $P = .022$), and fewer rehospitalization days per patient (1.4 ± 4.2 versus 3.8 ± 8.5 ; $P = .022$). Changes in serum creatinine were similar in the two groups throughout the study. This trial showed that ultrafiltration produces greater weight and fluid loss than intravenous diuretics and reduces 90-day heart failure rehospitalizations and emergency department visits in patients with acute decompensated heart failure. These results support the hypothesis that removal of isotonic fluid by ultrafiltration rather than hypotonic urine by intravenous diuretics may explain the improved clinical benefits of ultrafiltration.⁴⁰ However, ultrafiltration increases the complexity of care.

For CRS type 2 angiotensin converting enzyme inhibitors, beta-blockers, angiotensin receptor blockers, and aldosterone antagonists significantly reduce mortality and morbidity in congestive heart failure.^{41,42} In patients unable to tolerate these agents, hydralazine and nitrates can be used. Digoxin and diuretics improve symptoms in congestive heart failure but have no effect on mortality.⁴³ However, vasodilators (e.g., nesiritide) can affect renal function and in some cases exacerbate renal injury.⁴⁴ Vasopressin receptor 2 antagonists can improve hyponatremia in heart failure patients but have no clear survival benefit.⁴⁵ Intra-aortic balloon pumps can be used for persistent

hypotension in patients with acute decompensation. Depending upon pre-existing comorbidity and the underlying etiology, left ventricular assist devices can be used as a bridge to transplantation or cardiac surgery.

Management of CRS type 3 depends on optimal fluid status and perfusion pressures. To prevent kidney injury from low perfusion, volume depletion should be corrected. The core management of CRS type 3 is intravascular and extravascular volume control with either use of diuretics and various forms of renal replacement therapy or extracorporeal therapy and solute removal. In the setting of acute kidney, prevention of left ventricular volume overload is critical to maintain adequate cardiac output and systemic perfusion and also to protect against the vicious cycle that will worsen both cardiac and renal function. Because no evidence based guidelines have been proven effective in the management of CRS type 3, the best approach is prevention. Optimization of fluid, avoidance of nephrotoxic agents, and correction of underlying disorders are the basic principles.

In CRS type 4 the presence of traditional cardiovascular risk factors represents an obvious target for therapy. Additional management strategies have mostly targeted those risk factors that are particular to or exaggerated in chronic kidney disease patients; these risk factors include anemia, hypertension, dyslipidemia, smoking, albuminuria, hyperhomocysteinemia, and malnutrition. The Study of Heart and Renal Protection (SHARP) trial included 3,023 end stage renal disease patients and 6,247 chronic kidney disease patients not on dialysis, and preliminary results showed a significant benefit with the combination of simvastatin and ezetimibe.⁴⁶ In another study, 245 patients were randomized to three times weekly (conventional) or six times weekly (frequent) hemodialysis and followed up for 12 months. The frequent dialysis group had better outcomes, and the hazard ratio for death or increased left ventricular mass was 0.61 (95% CI, 0.46- 0.82). Important improvements in serum phosphate, control of hypertension, and avoidance of intradialytic hypotension were also noted in the frequent dialysis group. These results would strongly suggest that frequent dialysis may have an important role to play in the prevention and treatment

Table 2 Cardiorenal syndrome treatment

Type	Treatment
CRS type 1	Vasodilators and loop diuretics are frequently used in cases of acute decompensated heart failure with CRS type 1. ³⁴ Ultrafiltration can be used if volume overload persists.
CRS type 2	Angiotensin converting enzyme inhibitors, beta-blockers, angiotensin receptor blockers, and aldosterone antagonists significantly reduce mortality and morbidity in congestive heart failure. ^{39,40} In patients unable to tolerate these agents, hydralazine and nitrates may be an option. Left ventricular assist devices can be used as a bridge to transplantation or cardiac surgery.
CRS type 3	The core management of CRS type 3 is intravascular and extravascular volume control with either use of diuretics and various forms of renal replacement therapy or extracorporeal therapy and solute removal. Optimization of fluid, avoidance of nephrotoxic agents, and correction of underlying disorders are the basic principles. Because no evidence based guidelines have been proven effective in the management of CRS type 3, the best approach is prevention.
CRS type 4	Management strategies have mostly targeted cardiovascular risk factors that are particular to, or exaggerated in, chronic kidney disease patients, such as anemia, hypertension, dyslipidemia, smoking, albuminuria, hyperhomocysteinemia, and malnutrition. Frequent dialysis in one study showed an important role in the prevention and treatment of CRS type 4.
CRS type 5	Treatment of the underlying disease(s) is the mainstay of treatment for CRS type 5. Associated cardiac and renal complications warrant appropriate therapy as indicated on an individual basis. For example, removal of the source of infection, antibiotic therapy, and other supportive measures in early goal directed therapy are indicated in patients with septic CRS type 5.

of CRS type 4.⁴⁷

Treatment of the underlying disease(s) is the mainstay of treatment for CRS type 5. Associated cardiac and renal complications warrant appropriate therapy as indicated on an individual basis. For example, removal of the source of infection, antibiotic therapy, and other supportive measures in early goal directed therapy are indicated in patients with septic CRS type 5.

KEY POINTS

1. Acute and chronic cardiac dysfunction can have adverse effects on renal function.
2. Acute and chronic renal dysfunction can have adverse effects on cardiac function.
3. The development of dysfunction in a second organ (renal) as a consequence of the primary disorder (cardiac) increases morbidity and mortality.

der (cardiac) increases morbidity and mortality.

4. The cardiorenal syndrome classification may help clinicians organize their thinking about pathogenesis and patient management.

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