



Review

Cardiorenal Interactions: A Review

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ABSTRACT

A complex interaction occurs between cardiac and renal function. They are intricately tied together, and a range of disorders in both the heart and kidneys can alter the function of the other. The pathophysiology is complex, and these conditions are termed cardiorenal syndromes. They can be acute and/or chronic in nature, they result in and from hemodynamic consequences, systemic congestion, and metabolic abnormalities, and they lead to dysfunction of both the heart and kidneys. The aim of this article is to provide a review for cardiologists and intensivists who are treating patients for whom cardiac and renal interactions may complicate their picture. We review acute kidney injuries, management of the complications of renal dysfunction, renal replacement therapy, and cardiorenal syndromes.

RÉSUMÉ

Il existe une interaction complexe entre la fonction cardiaque et la fonction rénale. Elles sont étroitement liées, et un éventail de troubles cardiaques et rénaux peuvent altérer la fonction de l'autre. Ces maladies dont la physiopathologie est complexe sont appelées syndromes cardiorénaux. Elles peuvent être aiguës et/ou chroniques de nature, elles entraînent des conséquences hémodynamiques, une congestion systémique et des anomalies métaboliques, ou résultent de celles-ci, et elles mènent à la dysfonction du cœur ou des reins. L'objectif du présent article est d'offrir une revue aux cardiologues et aux intensivistes qui traitent des patients dont les interactions cardiaques et rénales peuvent compliquer leur tableau. Nous passons en revue les atteintes rénales aiguës, la prise en charge des complications de la dysfonction rénale, le traitement de substitution rénale et les syndromes cardiorénaux.

The heart and kidneys are intricately linked, with the function (or dysfunction) of one organ directly impacting the other. Heart failure (HF) is increasingly prevalent, contributes to more frequent hospitalizations, impairs quality of life, and shortens life expectancy.^{1,2} As cardiac function worsens, an inability to meet the metabolic requirements of end-organs, including the kidney, occurs. Interactions between the heart and kidneys (cardiorenal syndromes) are common in HF hospitalizations, with kidney dysfunction complicating 32%–49% of HF admissions, and renal impairment being one

of the most powerful predictors of poor clinical outcomes in this population.^{3,4} Similarly, both acute and chronic renal failure are increasingly prevalent.^{5,6}

Acute Kidney Injury

Acute kidney injury (AKI) is a heterogeneous and complex syndrome characterized by a sudden decrease in glomerular filtration rate, an increase in serum creatinine concentration, or oliguria/anuria over less than 7 days.⁷ AKI occurs in approximately 20% of hospitalized patients, resulting in clinical complications including volume overload, electrolyte abnormalities, uremic complications, and drug toxicity.^{8–10} The incidence of AKI is higher in older adults, and those with more comorbidities are more likely to develop severe AKI.¹¹ In the critical care setting, sepsis is an independent and leading cause of AKI, accounting for approximately 50% of all cases.^{12–14} Furthermore, up to 40% of patients hospitalized with HF also have AKI,^{3,4,15,16} which is a major independent

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See page 881 for disclosure information.

risk factor for prolonged hospitalization, rehospitalization, and short- and long-term mortality.^{17,18}

The definition of AKI has evolved to include standard classifications that allow increased recognition of the condition and facilitate research.¹⁴ The Kidney Disease: Improving Global Outcomes (KDIGO) definition and staging system is currently being used to define AKI^{7,19} as one of the following: an increase in serum creatinine ≥ 26.5 $\mu\text{mol/L}$ (≥ 0.3 mg/dL) within 48 hours or an increase in serum creatinine to ≥ 1.5 times baseline (which is known or presumed to have occurred within the prior 7 days), or urine volume < 0.5 mL/kg/h for 6 hours. Even small increases of baseline creatinine were associated with worsening clinical outcomes in the post-cardiac surgery population, such as prolonged intensive care unit stay and increased mortality.²⁰ Addition of angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blockers (ARBs), and sodium glucose co-transporter 2 (SGLT2) inhibitors can result in an up to a 30% rise in creatinine levels; however, they are associated with clinical benefit and not renal injury.²¹ Volume status must be optimized, and any obstructive causes must be corrected. KDIGO also has the following staging criteria. Stage 1 is an increase in serum creatinine to 1.5 to 1.9 times baseline, or an increase in serum creatinine by ≥ 26.5 micromol/L (≥ 0.3 mg/dL), or reduction in urine output to < 0.5 mL/kg/h for 6 to 12 hours. Stage 2 is an increase in serum creatinine to 2.0 to 2.9 times baseline, or reduction in urine output to < 0.5 mL/kg/h for ≥ 12 hours. Stage 3 is an increase in serum creatinine to 3.0 times baseline or to ≥ 353.6 micromol/L (≥ 4.0 mg/dL), or a reduction in urine output to < 0.3 mL/kg/h for ≥ 24 hours, anuria for ≥ 12 hours, the initiation of kidney replacement therapy, or in patients aged < 18 years, a decrease in estimated glomerular filtration rate (eGFR) to < 35 mL/min per 1.73 m².

A few limitations are associated with the KDIGO AKI criteria. First, they do not distinguish between causes of AKI, as different etiologies are associated with different long-term outcomes. Second, many patients may not have creatinine measurements from the period 7 to 365 days prior to their hospitalization. Lastly, serum creatinine gives only an estimate of renal function in AKI and is a less-robust biomarker.²²⁻²⁵

AKI can be classified based on 3 main etiologic categories: prerenal, renal, and postrenal injuries (Fig. 1).^{26,27} Prerenal AKI is defined by renal hypoperfusion with a subsequent decrease in GFR and urine output without damage to the renal parenchyma. This is an adaptive response through the renin-angiotensin-aldosterone system (RAAS) to extrarenal insults.²⁸ GFR is maintained through a wide range of mean arterial blood pressures using the RAAS. Renal perfusion pressure below the lower limit of autoregulation will lead to decreased GFR and AKI.^{29,30} If a decrease in renal perfusion pressure occurs, the RAAS releases angiotensin II, which increases efferent arteriole constriction, sympathetic activity, arterial vasoconstriction, aldosterone secretion, and antidiuretic hormone (ADH) secretion.³¹ This mechanism leads to increased retention of sodium and water, which counteracts arterial underfilling. Arterial underfilling can be caused by arterial vasodilation, as occurs in septic shock, or by decreased cardiac output, as occurs in cardiogenic shock.³² In patients with chronic HF, increased neurohumoral stimulation leads to excessive sodium avidity, with subsequent extracellular

volume overload. At this stage, patients with chronic HF and cardiorenal syndromes typically have a low urinary sodium level before renal injury.³³

Medical Management of Acute Renal Failure Complications—for the Non-nephrologist

Volume overload

Diuretics. The medical therapy of volume overload involves diuretics, apart from sodium restriction (Fig. 2). If the patient has diuretic resistance or refractoriness to diuretics and still has volume overload with or without worsening renal function, then ultrafiltration is sought.

Loop diuretics. Furosemide is the most commonly prescribed of this class, which includes bumetanide, torsemide, and ethacrynic acid. The Diuretic Optimization Strategies Evaluation (DOSE) trial studied use of intermittent bolus administration of furosemide, compared to continuous infusion therapy. This trial utilized a 2:2 factorial design trial, with low-dose furosemide (total daily home dose intravenously), high-dose furosemide ($2.5 \times$ total daily home dose intravenously), intermittent bolus furosemide every 12 hours, and continuous infusion furosemide interventions. No differences were observed between intermittent boluses and continuous infusions for either renal function or symptoms at 72 hours. High-dose, vs low-dose, intermittent furosemide was found to reduce the time required on supplemental oxygen; however, no difference in mortality was seen.³⁴

Thiazide diuretics. Although loop diuretics are effective for most patients, some patients have reduced diuresis and loop diuretic resistance, and they require sequential nephron blockade with thiazide diuretics. Commonly prescribed thiazides include metolazone, hydrochlorothiazide, indapamide, and chlorthalidone. Classically, metolazone can be used synergistically with loop diuretics, usually 30 minutes prior to administration of the loop diuretic, to achieve a profound diuresis. Metolazone has a long half-life (approximately 20 hours) and should be started at a dose of 5 mg per 24 hours to achieve diuresis. Caution should be used with administration, as metolazone can result in significant hypomagnesemia, and hypokalemia can occur, requiring careful assessment of volume status.³⁵

Potassium-sparing diuretics. Spironolactone, epleronone, and amiloride are commonly prescribed potassium-sparing diuretics, which provide limited clinical diuresis. These medications lead to reduced sodium reabsorption, with decreased hydrogen and potassium secretion.³⁶

Diuretic resistance. Diuretic resistance is the attenuation of the maximal loop diuretic effect that ultimately limits sodium and chloride excretion. Diuretic resistance is associated with an increased risk of both rehospitalization after HF and mortality.³⁷⁻³⁹ Unbound loop diuretic must reach the urinary lumen of the ascending limb and inhibit the $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$ channel. An outpatient's oral bioavailability is the first major limiting factor and depends on the type of loop diuretic.

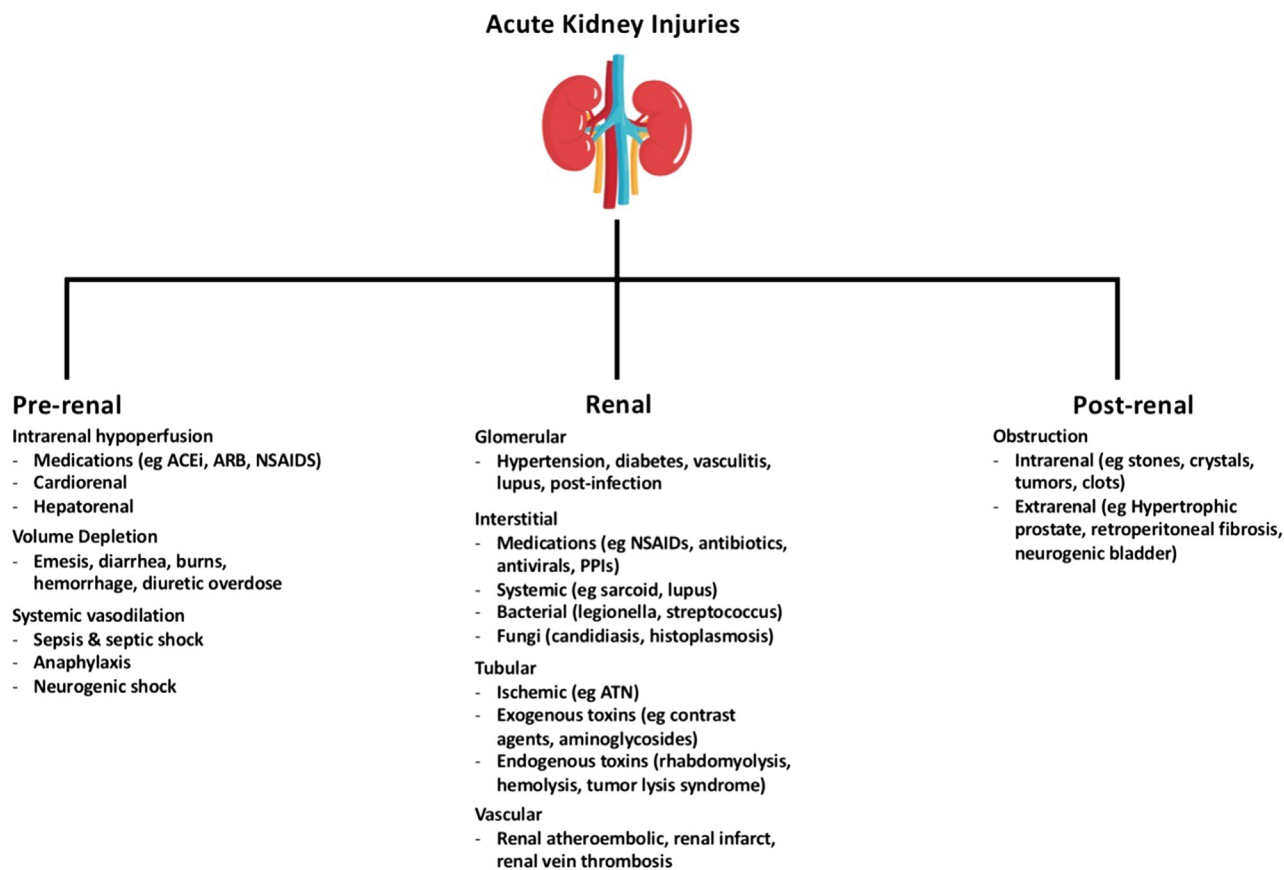


Figure 1. Acute kidney injuries. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ATN, acute tubular necrosis; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Bumetanide has a greater bioavailability than furosemide.⁴⁰ Furthermore, loop diuretics are mostly protein-bound, and hypoalbuminemia from poor nutritional status may result in reduced availability of loop diuretic to cross into the nephron. HF can reduce the peak effect of loop diuretic, as it results in increased proximal reabsorption of sodium, from increased RAAS system activation and expression of the Na⁺K⁺2Cl⁻ channel.⁴¹ Using multiple effective doses per day can prevent this from occurring. Loop diuretic use can result in the braking phenomenon, meaning reduced diuretic efficacy with each successive dose. The mechanism of this effect remains unclear; however, sodium loss is thought to play a role in the upregulation of proximal and distal sodium transporters, and therefore, sodium repletion can attenuate this compensation.^{37,42}

Hyperkalemia

Hyperkalemia occurs in < 10% of AKI cases but can be life-threatening. It can occur with renal injury involving any part of the nephron and can lead to unstable ventricular arrhythmias. Patients with symptoms of hyperkalemia, arrhythmias and cardiac conduction problems, or a severely elevated serum potassium level (K⁺ ≥ 6.5 mmol/L) should have prompt rapidly acting therapies.^{43,44} Intravenous calcium increases cardiac threshold potential and speeds impulse propagation, which in turn reverses myocyte depression and

promotes cardiac stabilization.⁴⁵ Intravenous calcium has a relatively rapid onset, acting within minutes, and has a short duration of 30 to 60 minutes. Insulin also should be used to reduce serum potassium.

Insulin decreases serum potassium by driving potassium intracellularly and increases the activity of Na-K-ATPase on cell membranes.^{46,47} Insulin effect on potassium usually starts within 30 minutes and lasts for 4 to 6 hours.⁴⁸ Insulin should be given intravenously and should be concomitantly administered with glucose to prevent hypoglycemia, which occurs in 6% to 18% of patients.⁴⁹ Hypoglycemia episodes post intravenous insulin administration can be avoided by checking on serum glucose every 15-30 minutes for 2 hours.

Potassium excretion from the body is required to further lower serum concentration. The most common gastrointestinal cation exchanger is sodium polystyrene sulfonate, but it has not been studied in HF and may result in worsening edema.⁵⁰ Patiromer (patiromersorbitex calcium/RLY5016) is a new potassium-lowering compound studied in the HF population that was effective at preventing hyperkalemia. Patiromer has not been studied in acute hyperkalemia.⁵¹ Lokelma is a novel selective cation exchanger that was evaluated in HF patients and found to be effective in reducing serum potassium, with a particularly rapid reduction in the first 48 hours of treatment.⁵² Dialysis is considered in patients with refractory hyperkalemia.

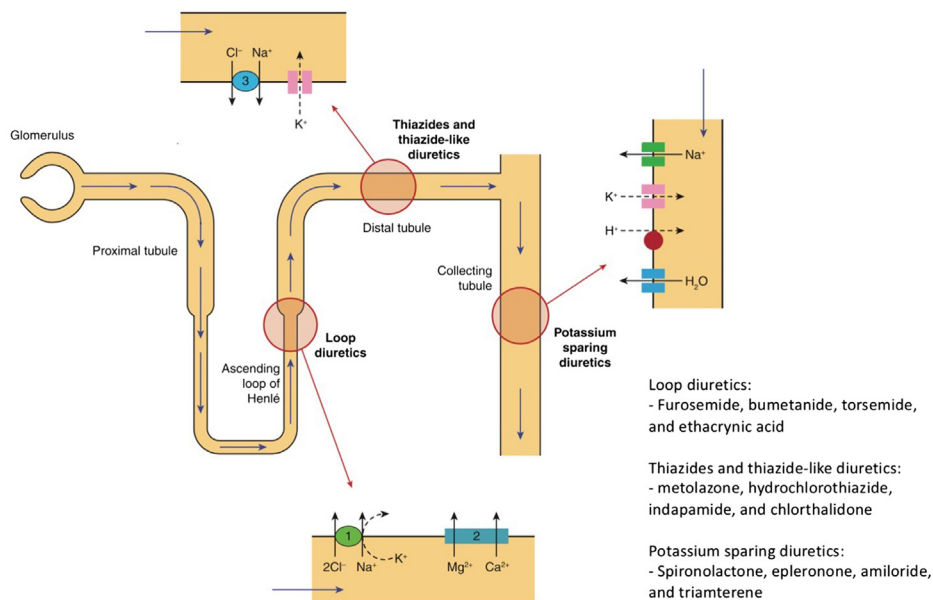


Figure 2. Nephron with diuretic mechanism of action. (Edited from open-access image from Shutterstock. ID: 314909174).

Metabolic acidosis

Acid-base balance is preserved by the renal excretion of daily acid load by the urinary excretion of hydrogen ions. Metabolic acidosis is characterized by a primary reduction in serum bicarbonate, with a secondary decrease in arterial partial pressure of CO_2 of 1 mm Hg for every 1 mmol decrease in serum bicarbonate, with a reduction in blood pH.⁵³ Treatment of metabolic acidosis is aimed at correcting and treating the underlying cause. In acute acidosis, when pH falls below 7.2, described effects include a reduction of myocardial contractility, increased ventricular arrhythmias, and resistance to inotropic and vasopressor effects of catecholamine infusions.⁵⁴⁻⁵⁶ However, controversy surrounds this topic, as patients with severe diabetic ketoacidosis had no impairment in left ventricular function.⁵⁷ If the clinician would like to treat metabolic acidosis, then options include oral and intravenous sodium bicarbonate, and refractory acidosis can be treated with dialysis.

Uremia

Uremia is a clinical syndrome characterized by elevated concentrations of urea and retained organic waste solutes cleared by the kidney. These abnormalities typically occur in parallel with renal dysfunction, chronic more often than acute.^{58,59} Treatment of uremia ultimately depends on improvement of cardiac function and restoration of renal perfusion. If renal function does not improve, then replacement of kidney function via dialysis can be considered.⁵⁹

In patients with uremia from end-stage renal disease (ESRD), pericardial diseases, including pericarditis, tamponade, and rarely, constrictive pericarditis may develop. Uremia may result in inflammation of the pericardial membrane, leading to symptoms of pericarditis; however, the mechanism is incompletely understood. Uremic pericarditis features may include pleuritic chest pain in the absence of

electrocardiogram changes.⁶⁰ In patients with chronic kidney disease (CKD) leading to ESRD, chronic pericardial effusions may develop as a result of volume overload.⁶¹ Treatment will depend on the hemodynamic status of the patient. If clinical signs of cardiac tamponade occurs, or evidence of a large pericardial effusion, consideration should be given to pericardiocentesis or pericardial window. Otherwise, the mainstay of therapy in uremic pericarditis is either initiation or intensification of dialysis therapy. Colchicine can be used cautiously with dose reduction in advanced renal dysfunction and dialysis patients.^{62,63} Pericardial effusion is often bloody in uremic patients, so clinicians should use caution and carefully consider anticoagulation options in patients starting hemodialysis.

Uremic encephalopathy can occur with both CKD and AKI, and it generally occurs when GFR falls below 15 mL/min, but these are not always correlated.⁶⁴ Although the exact toxin accumulation responsible for uremic encephalopathy has not been identified, it is likely related to impairment of amino acid metabolism in the brain and excessive parathyroid hormone.^{65,66} Urea levels are not well correlated with symptoms such as encephalopathy.^{64,67,68} Challenges that clinicians may encounter include distinguishing delirium and dementia from cardiovascular etiologies, such as a low perfusion state in HF, vs worsening uremic encephalopathy. The urea levels may go up with a low perfusion state but might not represent true uremic encephalopathy. Optimization of cardiovascular status should be done before referral for dialysis for possible uremic encephalopathy.

Renal Replacement Therapy for the Management of Acute Renal Failure Complications—for the Non-nephrologist

In both AKI and CKD patients, renal replacement therapies (RRTs) remain an important therapeutic option to reduce

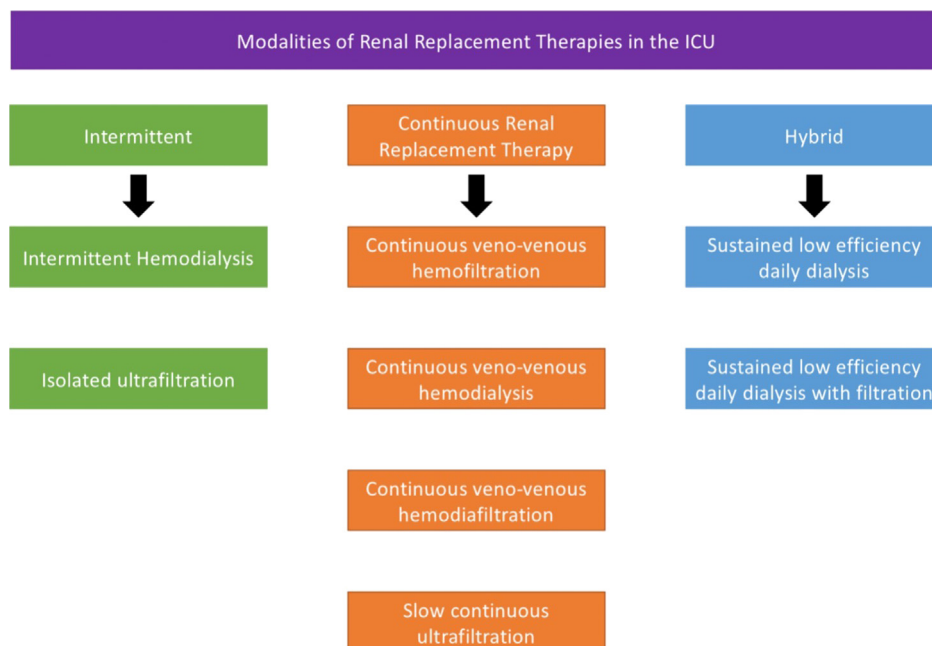


Figure 3. Types of renal replacement therapy in the intensive care unit (ICU).

mortality.⁶⁹ RRT can be delivered as peritoneal dialysis (PD), intermittent ultrafiltration, intermittent hemodialysis (IHD), slow low-efficiency daily dialysis (SLEDD), and continuous renal replacement therapy (CRRT), which includes slow continuous ultrafiltration, continuous veno-venous hemofiltration, continuous veno-venous hemodialysis, and continuous veno-venous hemodiafiltration (Fig. 3). RRT also ultimately includes kidney transplant.

Peritoneal dialysis

PD uses the peritoneum as a filter after the placement of a surgical Tenckhoff catheter. In patients who already have a PD catheter in place, this can be used if they are acutely admitted to the hospital and has the benefit of gentler ultrafiltration. Due to this gentler ultrafiltration, PD may have benefits in the HF population, especially those with right HF with ascites. Additionally, the peritoneal membrane is non-immunogenic and has the advantage of not causing an immune response.⁷⁰

Access for dialysis in acute renal failure

RRTs are dependent on vascular access and may include central venous catheters, arteriovenous grafts, and arteriovenous fistulas. In acute RRT starts, a large-bore double lumen central catheter line is inserted. Central catheter dialysis line diameters range from 8 to 13.5 Fr and provide pump flow rates of 300-400 mL/min, with larger luminal size providing a better flow rate. KDIGO has listed preferences of central venous catheter sites to optimize blood flow and reduce premature filter clotting. The right internal jugular is the first choice, followed by the femoral vein, then the left internal jugular, and lastly the subclavian.⁷¹ Tunneled catheters are used in patients who need long-term IHD, although arteriovenous access is preferred, with its lower infection risk.⁷²

CRRT vs IHD

Up to 13.5% of patients in critical care units are treated with some form of RRT.⁷³ IHD is a highly effective modality for solute and fluid removal. This removal is done over a short period of 3-5 hours, which can result in hemodynamic instability in already critically ill patients. CRRT provides similar solute and fluid removal over a 24-hour period, with less hemodynamic instability than IHD. The mortality rate does not differ between these 2 modalities.⁷⁴⁻⁷⁷ A pooled analysis of both observational and randomized trials showed that if IHD was the initial modality, then patients had a 1.7 times higher risk of dialysis dependency than if CRRT was the initial modality.⁷⁸ The major disadvantages of CRRT include cost, the need for trained personnel, and continuous anticoagulation. The CRRT is interrupted if the patient must be mobilized for any investigation or procedure, leading to frequent interruptions.

SLEDD therapy is a hybrid modality that provides extended RRT from 6-18 hours, but it is intermittent in nature. As with CRRT, SLEDD can be used as an RRT modality in patients who are too hemodynamically unstable to tolerate IHD. A meta-analysis comparing SLEDD and CRRT found similar mortality and rates of renal recovery.⁷⁹ Most decisions regarding IHD vs CRRT or SLEDD will be dependent upon patient hemodynamic stability and use of intravenous vasoactive agents. SLEDD is very useful when a patient has multiple procedures or tests that necessitate interruption of CRRT, and it can be used as an intermediate step in transitioning patients to IHD.^{80,81}

Ultrafiltration

In patients with AKI admitted to critical care units, fluid overload is commonly seen and is associated with increased

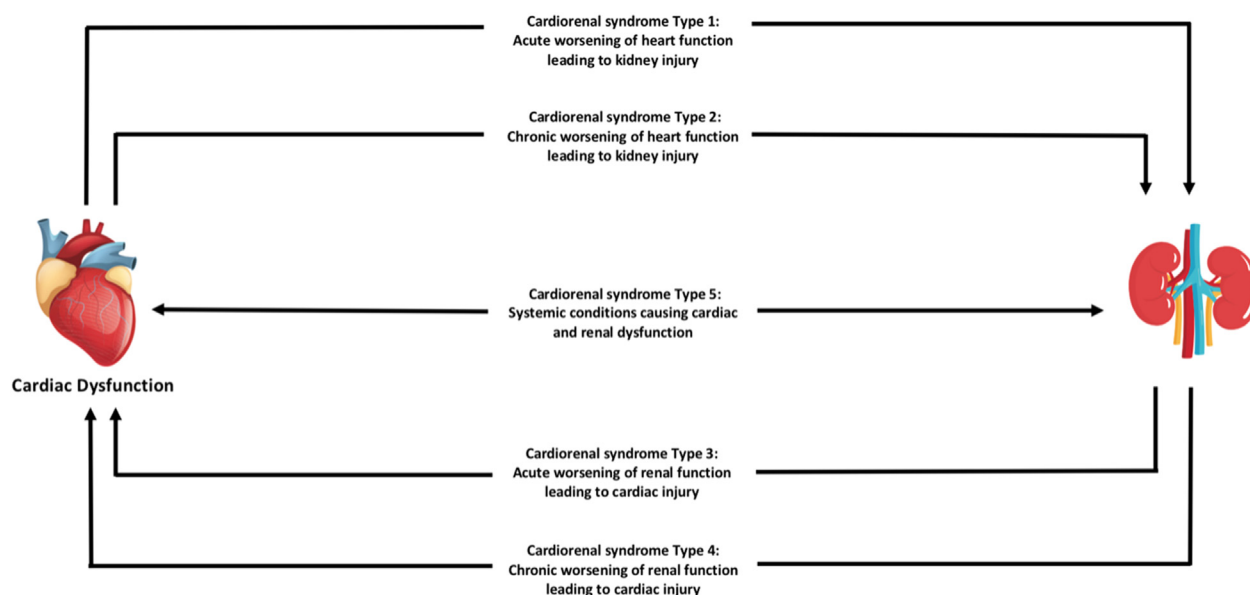


Figure 4. Cardiorenal syndromes.

mortality.⁸² Ultrafiltration (UF) can be utilized as an alternative to diuretics in diuretic-resistant patients. UF can be administered intermittently or through slow continuous UF. The evidence based on trial data is limited. The **Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD)** trial compared early venovenous UF with standard IV diuretic therapy. UF resulted in greater fluid and weight loss but no differences in dyspnea scores, creatinine level, or length of stay.⁸³ The **Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF)** found that pharmacologic therapy with IV loop-diuretics and other adjunct medication was superior to UF for conservation of renal function, with similar degrees of weight loss.⁸⁴ Excessive fluid removal can be complicated with hemodynamic instability, and slow UF may lead to prolonged organ edema and dysfunction; therefore, UF should be performed by trained nephrologists or intensivists with experience in this modality.

Anticoagulation and dialysis

As blood passes through the hemodialysis circuit and is exposed to thrombogenic surfaces, a risk of thrombosis is present. Anticoagulation during dialysis runs is therefore indicated, except for patients at high risk, as deemed by the prescribing nephrologist. For standard patients undergoing IHD, the usual anticoagulation regimens include unfractionated heparin or low-molecular-weight heparins. For those deemed to be too risky by the nephrologist, alternative agents are available, including regional citrate anticoagulation and saline flushes.

Citrate acts as a local anticoagulation agent in the dialysis circuit and can be used when other forms of anticoagulation are contraindicated. Citrate will chelate with ionized calcium in the pre-blood pump portion of the circuit. Calcium that is chelated out of the circuit is replaced with calcium chloride infusion. Any citrate that is not removed in dialysate is then metabolized by the liver to bicarbonate. In the setting of liver

dysfunction, citrate clearance is reduced and can result in citrate toxicity, with associated hypocalcemia. Clinicians should suspect citrate toxicity if the ratio of total serum calcium to ionized calcium is > 2.5 , which suggests that a significant amount of calcium is bound to citrate rather than free in the ionized form.⁸⁵ Citrate is mostly utilized as a regional anticoagulant in CRRT and is not commonly used in IHD.

Patients on systematic anticoagulation may forego the need for additional anticoagulation in the circuit during dialysis runs; however, many will still receive heparin to prevent filter clotting, at the discretion of the prescribing nephrologist. Warfarin and the direct oral anticoagulant rivaroxaban at 10 mg daily have established safety in patients with nonvalvular atrial fibrillation undergoing hemodialysis.⁸⁶

Cardiorenal Syndromes

Cardiorenal syndromes (CRSs) is a broad term used to describe the complex hemodynamic and neurohumoral connection that occurs with concomitant cardiac and renal dysfunction. In CRS, the disease process in one organ system may result in, accelerate, or worsen the decline of the other organ system; this effect can be acute or chronic in nature.⁸⁷ CRS encompasses from 25% to 50% of HF presentations and is associated with worse clinical outcomes.^{4,37,88-93} CRS has traditionally been classified into 5 categories as follows (Fig. 4):

- type 1 (acute cardiorenal syndrome)—acute HF, or cardiac dysfunction, results in AKI;
- type 2 (chronic cardiorenal syndrome)—chronic cardiac dysfunction causes progressive CKD;
- type 3 (acute renocardiac syndrome)—abrupt and primary worsening of kidney function due, for example, to renal ischemia or glomerulonephritis causes acute cardiac dysfunction, which may be manifested by HF;
- type 4 (chronic renocardiac syndrome)—primary CKD contributes to cardiac dysfunction, which may

be manifested by coronary disease, HF, or arrhythmia; and

- type 5 (systemic diseases)—acute or chronic systemic disorders (eg, sepsis or diabetes mellitus) that cause both cardiac and renal dysfunction.

Although this classification scheme is widely used, it does have limitations, including that it provides no description of the temporal relationship and mechanism of action of injury.⁹⁰

CRS type 1

The mechanism of action involved in CRS type 1 is thought to be multifactorial, including the previously mentioned hemodynamic derangements and neurohumoral effects.^{94,95} A typical clinical example of CRS type 1 includes acute decompensated HF, which leads to AKI or acute coronary syndrome resulting in cardiogenic shock and leading to AKI (acute cardiorenal).⁹⁵ Traditionally, the pathophysiology was believed to be that the decreased cardiac output from HF was initially contributing to worsening renal function due to decreased effective circulating volume. However, more recently, evidence has made apparent the fact that venous congestion plays a significant role, and it is thought to be the primary hemodynamic precipitant for deterioration in renal function.⁹⁶⁻⁹⁸ Elevated central venous pressure and right atrial pressure are independently associated with decreased renal function, with abnormal flow patterns in renal veins.^{98,99} Deterioration in renal function may lead to worsening volume overload, which results in further elevation of the renal venous and central venous pressures and further worsening clinical status.¹⁰⁰

Volume overload is a consequence of CRS; treatment is largely based on fluid removal with loop diuretics.¹⁰⁰ Diuretics will have differing effects based on the hemodynamic status of the patient. Traditionally, preservation of renal function (or at least the surrogate serum creatinine level) was a target of CRS diuretic management; however, increasing evidence in the literature suggests that holding diuretics to prevent worsening of renal decline may result in deleterious outcomes.^{101,102} With aggressive diuresis, as measured by hemoconcentration, the odds of developing an increased creatinine level go up. However, aggressive diuresis has also been shown to substantially reduce mortality and has a positive impact on survival. This finding further supports the concept that increasing serum creatinine alone is not independently linked with worsening clinical outcomes.^{103,104}

Patients with CRS and HF who are diuretic resistant (losing < 0.4 kg per 40 mg furosemide over 24 hours) are at higher risk for short- and long-term mortality and rehospitalization.^{39,105} HF reduces peak drug effect, which can sometimes be overcome with more frequent dosing of furosemide. Alternative loop diuretics, including bumetanide or torsemide, can be considered, with both drugs proving equally effective in reducing edema, with the effective dose ratio of bumetanide in comparison to furosemide being 1:25.¹⁰⁶ Typically, the next adjunct diuretic to furosemide is metolazone, typically given 30 minutes before furosemide to provide a synergistic diuretic effect.¹⁰⁷ Combining loop diuretics with spironolactone has been proposed and may provide more effective diuresis with fewer side effects than a high-dose loop diuretic alone.¹⁰⁸

The volume-overloaded state in CRS type 1 can lead to a hypervolemic hyponatremic state. Tolvaptan, a vasopressin receptor antagonist, can correct and restore serum sodium in patients with significant and symptomatic hyponatremia and hypervolemia. No evidence has been found of decreased hospitalization or mortality with tolvaptan; however, a subgroup *post hoc* analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial showed that patients with a serum sodium level of < 130 mmol/L had fewer clinical events with tolvaptan.^{109,110} To reduce the risk of hyponatremia, fluid restriction for any patient that is undergoing heavy diuresis is important.

UF, as outlined previously, has been studied as an option for volume management; however, currently the Canadian Cardiovascular Society guidelines do not recommend UF for management of diuretic-resistant volume overload in HF.²

CRS type 1 may be complicated by a low-cardiac-output state. This state can be objectively determined by measurement of serum lactate and central venous oxygen saturation, or through invasive hemodynamic monitoring such as Swan-Ganz right heart catheterization.¹¹¹ Inotropic agents in low-output states have not been shown to improve outcomes and may be associated with potential harm.¹¹²⁻¹¹⁴ In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial, patients with HF randomized to milrinone were found to have a greater number of atrial arrhythmias, symptomatic hypotension, and worsening HF.¹¹² Low-dose dopamine infusion has been studied in HF with renal dysfunction and was also found not to improve renal function or clinical outcomes.^{115,116} Intravenous inotropic and vasoconstrictor therapy should therefore be reserved for HF patients with low-output states or shock needing hemodynamic stabilization and as a bridge to definitive therapy, which may include coronary revascularization, cardiac surgery, mechanical circulatory support, and heart transplant.²

Vasodilators have been studied extensively but have not been credibly shown to significantly improve mortality, rehospitalization, or renal function. In patients with decompensated HF, high-dose IV nitrates (with low-dose furosemide) were compared with low-dose nitrates (and high-dose furosemide) and found to reduce rates of intubation by 60%.¹¹⁷ The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial tested nesiritide (recombinant human B-type natriuretic peptide) in decompensated HF. Dyspnea moderately improved at 6 and 24 hours; however, there was no change in clinical outcomes.¹¹⁸ Serelaxin is a human relaxin-2 hormone vasodilator that was also tested in acute decompensated HF. Infusion of serelaxin, compared to placebo, did not result in a lower incidence of death from cardiovascular causes at 180 days, or worsening HF at 5 days.¹¹⁹

Notably, distinguishing CRS type 1 from contrast-induced nephropathy is important. Many acutely ill cardiac patients undergo coronary angiograms and other radiographic studies. Contrast-induced nephropathy is a generally reversible AKI secondary to radiocontrast media causing a toxic acute tubular necrosis within 24-48 hours of exposure that resolves within 7 days. Contemporary literature suggests that this issue is much less prevalent than in the past due to the use of iso-osmolal radiocontrast media.

CRS type 2

Chronic heart failure, and other chronic abnormalities in cardiac function, can lead to progressive CKD (chronic cardiorenal).⁹⁵ Impaired renal function is independently associated with worse clinical outcomes, including increased cardiovascular death and hospitalizations for decompensated HF in both preserved, as well as reduced, left ventricular ejection fraction.^{120,121} In chronic HF, pre-existing micro- and macrovascular disease and chronically reduced renal perfusion are likely. Important to note is that chronic HF patients with preserved ejection fraction have a GFR similar to that of those with reduced ejection fraction.¹²² The **E**valuation **S**tudy of **C**ongestive **H**eart **F**ailure and **P**ulmonary **C**atheterization **E**ffectiveness (ESCAPE) trial found that elevated right atrial pressures were associated with a higher serum creatinine level; however, there was no link between other hemodynamic parameters, including cardiac index.¹⁶ Right ventricle hemodynamic assessment values, including right ventricular stroke work index, is prognostic of renal dysfunction in patients with HF, including in patients with both preserved and reduced ejection fraction.¹²³ This finding further emphasizes the importance of renal congestion in renal dysfunction.

The benefits of ACEis, ARBs, and angiotensin receptor neprilysin inhibitors (ARNIs) in patients with hemodynamically stable HF and renal impairment (CRS types 2 and 4) have been established in multiple trials. The **S**tudies of **L**eft **V**entricular **D**ysfunction (SOLVD) trial demonstrated a reduction in mortality and rehospitalization but an increase in serum creatinine.¹²⁴ A *post hoc* analysis of patients with CKD in addition to HF showed mortality benefits even in subjects with worse CKD.¹²⁵ This finding further emphasizes the importance of RAAS inhibition in chronic HF with renal dysfunction regardless of increases in creatinine. The benefits of implantable cardioverter defibrillators and cardiac resynchronization therapy pacemakers in stage 1-3 CKD are well established, but little to no evidence has been gathered in those with stage 4-5 CKD, which must be considered when implanting these high-cost therapies.

SGLT2 inhibitors are among the latest glucose-lowering therapeutic agents. They have been shown extensively to have cardiovascular mortality benefit in both HF with reduced ejection fraction and HF with preserved ejection fraction, independent of diabetes.¹²⁶⁻¹²⁸ Furthermore, SGLT2 inhibitors substantially reduced the risk of dialysis, transplantation, or death due to kidney disease.^{129,130}

CRS type 3

CRS type 3 is an acute and abrupt deterioration in renal function leading to acute cardiac dysfunction, such as acute kidney injury leading to volume overload, inflammatory surge, and metabolic disturbances leading to HF, arrhythmia, or ischemia (acute renocardiac).^{14,37,95} AKI can result in cardiac dysfunction through numerous mechanisms, such as acidemia volume overload and electrolyte abnormalities. Acidemia may impair vascular and cardiac energy metabolism and lead to cardiac dysfunction. Additionally, metabolic acidosis will lead to pulmonary vascular constriction, which can adversely affect hemodynamics by causing increased afterload of the right heart and subsequent acute right heart

dysfunction.¹³¹ Furthermore, acidemia is independently linked with decreased intracellular pH, which leads to an increase in the myocardial transient calcium amplitude and also alters Ca²⁺ binding to troponin C. This can result in cardiac myocyte dysfunction and apoptosis.¹³²⁻¹³⁵ Altered myocardial calcium signaling can lead to formation of a re-entry substrate by 2 mechanisms—promoting dispersion of excitability, and promoting dispersion of refractoriness, which is pro-arrhythmogenic.¹³⁶ Electrolyte abnormalities seen in CRS type 3, including hyperkalemia, are independently associated with arrhythmias.⁹³ AKI may result in a volume-overloaded state that can alter the Frank-Starling curve and lead to subsequent pulmonary edema. Uremia can also be an acute complication of severe AKI and may result in dysfunction in myocardial contractility, and could result in pericarditis.¹³⁷ Uremic pericarditis can be complicated with pericardial effusion accumulation and subsequent cardiac tamponade.¹³⁸ Clinicians should always consider uremic pericardial effusion and tamponade as an etiology of shock in patients with shock and chronic renal dysfunction, and if needed, arrange for prompt pericardiocentesis and dialysis.¹³⁹

Renal artery stenosis is a unique etiology of CRS type 3. Bilateral renal artery stenoses (or unilateral renal artery stenosis in solitary kidney) are prone to acute decompensated HF and flash pulmonary edema due to diastolic dysfunction from longstanding increases of blood pressure, upregulation of renin-angiotensin axis, and acute myocardial ischemia related to increased peripheral vasoconstriction.^{94,140,141} These patients are more likely to have diastolic dysfunction secondary to chronic hypertension and activation of the RAAS with sodium retention and vasoconstriction.¹⁴⁰⁻¹⁴² RAAS blockade with ACEi or ARB is generally required to manage hypertension, but the GFR is highly dependent on angiotensin, and therefore, worsening renal function may result.⁹⁵ Renal artery angioplasty with stenting is reserved for patients with uncontrolled hypertension resistant to medical management, progressive renal function loss, acute pulmonary edema, or fibromuscular dysplasia-related renal disease.¹⁴² RRT can be utilized in severe cases of AKI and CRS type 3.

CRS type 4

Patients with CKD may have secondary cardiac dysfunction, including ventricular hypertrophy, diastolic dysfunction, arrhythmias, and HF (chronic renocardiac syndromes).^{37,95} CKD is independently associated with an up to 30-fold increased risk of cardiovascular mortality, compared with control matched subjects without CKD, and up to 50% of those suffering from established ESRD are unlikely to survive a cardiovascular event.^{93,95,143-145} The paucity of CKD and ESRD population treatment studies may lead to difficult clinical scenarios for treating physicians.

ESRD patients on hemodialysis have an increased risk of bleeding secondary to uremia and systemic anticoagulation caused by intermittent heparinization.¹⁴⁶ Overall, an approximate doubling of bleeding risk occurs in patients with CKD.^{147,148} This bleeding concern likely contributes to decreased use of antiplatelet therapy in patients with CKD, despite the bleeding risk and significant clinical benefit.¹⁴⁹ CKD patients are found to have more diffuse coronary

Table 1. Cardiorenal syndrome type 5

| Acute | Chronic |
|---|------------------------------|
| Sepsis | Amyloidosis |
| Infective endocarditis | Systemic lupus erythematosus |
| Drugs/Toxins (eg, cocaine, CCB, chemotherapy) | Diabetes mellitus |
| Vasculitis/Thrombotic microangiopathy | Chronic liver disease |
| Endocrine (pheochromocytoma) | Sarcoidosis |

CCB, calcium channel blocker.

artery disease, vulnerable plaques, and a greater tendency for thrombosis.^{150,151}

CRS type 5

CRS type 5 is characterized by a systemic disorder or acute systemic insult resulting in simultaneous cardiac and renal dysfunction. Data are limited on how simultaneous dysfunction of renal and cardiovascular systems mechanistically work and their clinical outcomes.^{93,95} CRS type 5 can develop with both previous and no previous renal and cardiac dysfunction. In the setting of sepsis, inflammation and microvasculature alterations can result in alternation of organ function leading to cardiac and renal involvement. Many systemic conditions can lead to CRS type 5, including sepsis, amyloidosis, diabetes, and systemic lupus erythematosus; these can be categorized into acute and chronic causes (Table 1). It is important to treat the underlying etiology and optimize cardiac and renal function.

Conclusion

A complex interplay occurs between the heart and the kidneys, and the functionality of one has a direct impact on the other. It is important for cardiologists, nephrologists, and intensivists to recognize these complex interactions and their role in diagnosing and managing these challenging patients. Understanding renal function, chronic and acute renal failure and associated complications, and cardiorenal syndromes is vital for clinicians to help care for these patients. Clinicians should be aware of the complications of renal dysfunction—including volume overload, the appropriate utilization of high-dose loop diuretics, and the synergistic effect of additional diuresis with metolazone—and the utility of early consultation with the nephrology department about RRTs and UF options, including many of the nuances involved in management, and of recognition of cardiorenal syndromes and the importance of approaching from a multidisciplinary perspective.

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