

CHAPTER 111

Cardiorenal Syndrome Type 1

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OBJECTIVES

This chapter will:

1. Describe the pathophysiologic pathways of heart and kidney interaction.
2. Characterize the effect of heart failure on the kidney.
3. Identify risk factors and preexisting comorbid conditions.
4. Describe the clinical outcomes and potential therapeutic interventions.

Combined disorders of heart and kidney are classified as cardiorenal syndromes (CRS). According to the new classification, the cross-talk between the heart and the kidney perpetuates a disorder in which a vicious circle produces progressive dysfunction of these two organs.¹ An initial insult or injury in one organ often results in secondary dysfunction in the other. Although generally defined as a condition characterized by the occurrence of acute kidney injury (AKI) secondary to acute decompensated heart failure (ADHF), the term CRS also is used to describe the negative effects of acute or chronic renal dysfunction on the heart (renocardiac syndrome). CRS are thus disorders of the heart and kidneys, in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. The current definition has been expanded into five subtypes whose etymology reflects the primary and secondary pathology, the time frame and simultaneous cardiac and renal co-dysfunction secondary to systemic disease. This new conceptual model of CRS provides a platform to examine complex organ cross-talk and introduce the possibilities of new prevention, treatment, and recovery strategies.² Approximately one third of heart failure (HF) admissions may be complicated by AKI, resulting in a threefold increase in length of stay and a greater likelihood of rehospitalization. CRS type 1 (CRS-1) refers primarily to an episode of ADHF or acute coronary syndrome (ACS) leading to AKI. Both components of the syndrome contribute to morbidity and mortality. The pathophysiology of renal function impairment is complex, and it may depend on several mechanisms including reduced cardiac output (CO), passive congestion of the kidneys, altered neurohormonal

response (combined renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) activation, dysregulation of the immune system with humoral and cellular signaling in response to inflammation and oxidant stress, iatrogenic factors such as contrast media. An imbalance in this cohort of mechanisms often causes deterioration in cardiac and renal function. To fully understand the nature of CRS-1, its natural history, the involved risk factors, and the associated morbidity and mortality, it is essential to comprehend fully the above-mentioned interactions and their pathophysiologic foundations.

EPIDEMIOLOGY

CRS-1 (acute CRS) occurs in approximately 25% of patients admitted with ADHF with important implications for diagnosis, prognosis, and management.

HF affects 2% of the adult population³ and represents an important cause of hospital admission. It is the leading cause of hospitalization among adults over the age of 65 representing an important component of healthcare expenditure. A third of these admissions are complicated by AKI, resulting in a threefold increase in length of stay, a greater likelihood for hospital readmission, and a 22% higher mortality rate. Some degree of chronic kidney disease (CKD) is already present in approximately 25% of patients with chronic HF, independent of their level of left ventricular function. Patients with preexisting renal disease, common in cardiac patients, fare even worse. CRS-1 is characterized by acute worsening of cardiac function leading to AKI (damage or dysfunction). Although even small acute changes in serum creatinine may increase mortality, the risk increases as the kidney function worsens. Acute cardiac events that may contribute to AKI include ACS, cardiogenic shock, ADHF, and cardiac surgery. It may occur at any time during the hospital admission but is usually evident early. The frequency has ranged from 24% to 45% with ADHF and 9% to 19% in patients with ACS. In the Acute Decompensated Heart Failure National Registry (ADHERE) of 105,000 individuals admitted for ADHF, 21% had serum creatinine concentrations greater than 2.0 mg/dL, 30% had a history of renal insufficiency, and 9% had creatinine concentrations in excess of 3.0 mg/dL.⁴ McAlister et al.⁵ found that only

17% of 754 outpatients with HF had creatinine clearances of more than 90 mL/min. In their cohort, 39% with New York Heart Association (NYHA) class IV symptoms and 31% with NYHA class III symptoms had creatinine clearance less than 30 mL/min. These numbers assume greater significance, considering that there are millions of hospitalizations for ADHF in the United States annually.

Seven observational studies have reported on the frequency and outcomes of CRS-1 in the setting of ADHF and five in ACS.⁶ Depending on the population, 27% to 40% of patients hospitalized for ADHF develop AKI as defined by an increase in serum creatinine of at least 0.3 mg/dL.⁷ Risk predictors for this complication include reduced baseline renal function, diabetes, and prior HF.⁸ These patients experience more complicated hospital courses, longer inpatient stays, and higher mortality.

The reported incidence of CRS varies widely because of variation in definitions used, differences in the populations under study, and the time frame of the investigation. CRS-1 has been defined as increases in serum creatinine (SCr) ≥ 26.5 $\mu\text{mol/L}$ (0.3 mg/dL), ≥ 44.2 $\mu\text{mol/L}$ (0.5 mg/dL),⁹ $\geq 25\%$ relative to SCr at the time of hospital admission, $\geq 50\%$ at the time of hospital admission, and as the combined increase of ≥ 26.5 $\mu\text{mol/L}$ (0.3 mg/dL) and $\geq 25\%$ increase. Studies also have evaluated CRS-1 as even smaller increments of rise in SCr (≥ 8.8 $\mu\text{mol/L}$ (0.1 mg/dL) or as the rate of decline in estimated glomerular filtration rate (GFR).¹⁰ Aronson et al. evaluated CRS-1 defined by a 50% increase in blood urea nitrogen above admission values.¹¹ Today, the occurrence of AKI (described according to new criteria including biomarkers and serum creatinine and urine output) after any acute cardiac event should be classified as CRS-1. Thus it is likely that the incidence of this disorder is probably higher than what has been reported in the past, where the concept of worsening renal function was limited to more restrictive criteria.

In a cohort with ADHF, Gottlieb et al. showed that 47% developed CRS-1 within 3 days of hospitalization.¹² Cowie et al. found that 50% occurred within 4 days,¹³ whereas two observational studies found that 70% to 90% of all CRS-1 had occurred within the first week of hospitalization.¹³ Study durations range from 1 for 2 weeks¹⁴ and up to 6 months.¹⁵ These variations further confound precise estimation of the significance of CRS-1. In a retrospective study of 20,063 Medicare beneficiaries hospitalized for ADHF, Kociol et al. found that 17.8% developed AKI (defined as an increase in SCr ≥ 27 $\mu\text{mol/L}$), with 64.5% readmitted and 35.4% dying within 1 year.¹⁶ After adjustment for covariates, AKI was associated independently with long-term mortality. AKI associated with ACS increases the risk of poor outcome.

Newsome et al. reported a greater likelihood of progression to end-stage renal disease (ESRD) in those with ACS complicated by AKI.¹⁷ In patients surviving ST elevation myocardial infarction (STEMI), Goldberg et al. found increasing severity of and persistent AKI were associated with higher risk of death.¹² This would imply, similar to studies with ADHF, that there is a relationship between the duration and severity of AKI and mortality. Their data suggest that AKI further exacerbates cardiac injury. This association also may promote a decline in kidney function. In another study, a small cohort of 141 patients with reperfused anterior STEMI, those developing AKI had higher plasma norepinephrine, B-type natriuretic peptide (BNP), interleukin-6 (IL-6) levels in the 2 weeks after reperfusion.¹³ Moreover, those developing AKI have higher risk of in-hospital death ($p = .004$) and major adverse cardiac events ($p = .02$) that correlated with greater observed left ventricular (LV) remodeling. This would imply that the

observed heart-kidney interface in CRS-1 may act synergistically to accelerate further injury and/or dysfunction.

Two studies recently have evaluated the association of biomarkers for predicting AKI/CRS-1 in patients with ADHF.¹⁷ In a small cohort of 91 ADHF patients, serum neutrophil gelatinase-associated lipocalin (NGAL) was measured at the time of admission. In total, 35 patients with CRS-1 (38%) developed AKI defined as an increase in SCr ≥ 26.5 $\mu\text{mol/L}$. Serum NGAL was significantly higher (194 ng/mL vs. 128 ng/mL, $p = .004$) in patients developing AKI. Those with an admission serum NGAL of at least 140 ng/mL had a 7.4-fold increased risk of developing CRS-1. In another small cohort of 125 HF patients, Pfister et al. found elevated baseline N-terminal (NT)-pro-BNP predicted subsequent AKI.¹⁸

RISK FACTORS AND PATIENT'S SUSCEPTIBILITY

There are a host of predisposing factors that create baseline risk for CRS-1 as shown in Fig. 111.1.¹⁹

Obesity and Metabolic Syndrome

We are in the midst of a worldwide obesity pandemic, in which the mass of the human body is undergoing morphologic changes far more rapidly than evolutionary adaptive changes can occur. Thus there are developing epidemics of at least 26 chronic diseases, including type 2 diabetes mellitus (DM), hypertension, obstructive sleep apnea, atrial fibrillation, heart failure (HF), hyperuricemia, and CKD, directly or indirectly related to excess adiposity. It has been shown that the number of adipocytes in the human body can increase tenfold in number and in size. With such a dramatic increase in fat mass, cytokines and adipokines are produced in large quantities to ensure homeostasis of this expanding organ. Many of these cytokines will be discussed later, and as a side effect, may cause cardiac and renal injury: for example, IL-6 and tumor necrosis factor- α (TNF- α), which are secreted by adipocytes. Indeed, the production of IL-6 by abdominal adipocytes into the portal circulation and transit to the liver is the most important stimulus for release of high-sensitivity C-reactive protein (hs-CRP). Thus hs-CRP levels are highest in obese individuals and fall to a greater extent with weight loss than any other intervention.²⁰

Growth of adipocytes and increase in fatty acid content of visceral locations has been demonstrated consistently to be related to obesity, generating diseases more so than peripheral fat stores in the subcutaneous space. Epicardial fat has been shown in multiple studies to be involved directly in vascular inflammation of the epicardial coronaries, associated with the metabolic syndrome, and implicated in myocardial dysfunction and chamber enlargement. Body mass index, a global measure of excess adiposity, is associated with abnormalities on echocardiography, including left atrial dilatation, left ventricular hypertrophy and dilation, and impaired relaxation. These findings suggest that changes in the lipid content within cardiomyocytes are playing a role in these pathologic steps of cardiac remodeling.

Obesity-related glomerulopathy has been long described as a condition of hyperfiltration in obese individuals without DM that ultimately leads to CKD and predisposes to CRS-1. In addition, the cardiometabolic syndrome in the absence of frank DM has been associated with three- to sevenfold increased risk of CRS-1 in a variety of clinical settings.

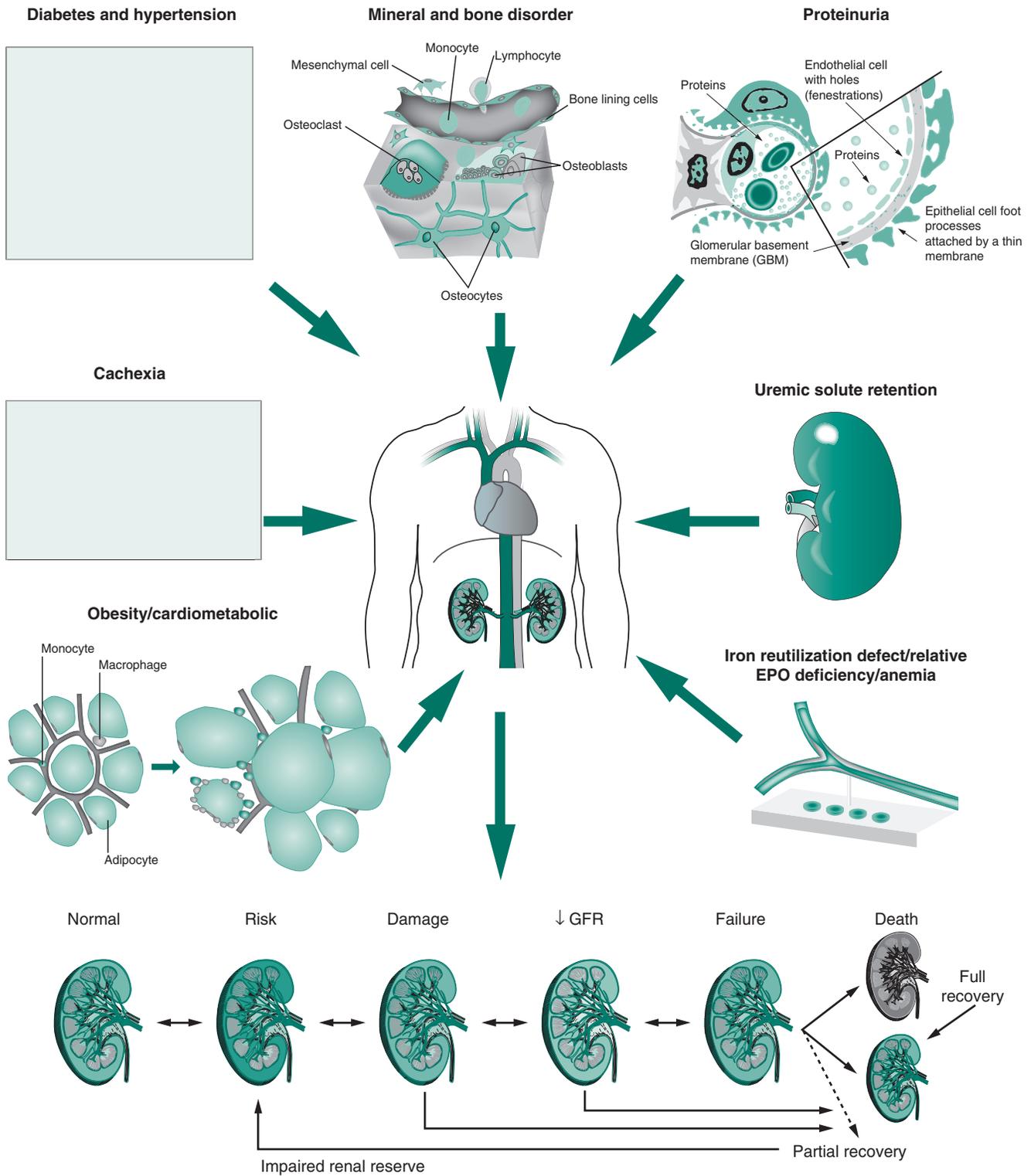


FIGURE 111.1 Predisposing factors for cardiorenal syndromes.

Cachexia

Together with obesity and metabolic syndromes, combined disorders the heart and kidney are also likely to develop in presence of some degree of cachexia and sarcopenia. Cachexia has been proposed as a possible mechanism contributing to worsening of such pathologic organ cross-talk via $TNF-\alpha$ and other proinflammatory cytokines. In these circumstances, a vicious cycle could arise, in which cachexia

associated with either HF or CKD may contribute to further damage of the other organ. In chronic CRS, activation of the immune and neuroendocrine systems contributes to the genesis of cachexia, which in turn can affect the heart and kidney function negatively. In patients with cardiac cachexia, sustained activation of the immune and neuroendocrine systems, tissue oxidative stress, and increased renal vascular resistance can increase and therefore impair renal perfusion and oxygen use, leading to worsening renal

function (WRF). Similarly, in renal cachexia, increased levels of proinflammatory cytokines can cause endothelial dysfunction, progressive left ventricular systolic dysfunction, and myocardial cell death, resulting in increased myocardial fibrosis reflected by elevated levels of plasma galectin-3. Thus we speculate that the occurrence of chronic CRS could represent a fundamental step in the genesis of cachexia, that is, renal and cardiac dysfunction closely related to the occurrence of a systemic final common pathway to serious complications such as infection or death.

Hypertension and Diabetes

Hypertension and type 2 DM account for the majority of CKD and ESRD in developed countries. As renal filtration function declines, there is greater salt and water retention, neurohormonal activation, and worsened HTN. Lack of blood pressure control is related directly to accelerated loss of nephrons and reductions in glomerular filtration rate (GFR).²¹ Diabetes, through many mechanisms, contributes to glomerular dysfunction, damage, and ultimate loss of functioning filtration units and further contributes to CKD. Increased blood pressure upon initial evaluation, probably as a reflection of neurohormonal activation, in patients with ADHF has been associated consistently with CRS-1. Conversely, in the setting of hypotension and shock, there is a massive elevation of catecholamines and a failure of the heart to respond with an increase in cardiac output. This latter scenario accounts for less than 2% of CRS-1.

Proteinuria

Endothelial, mesangial, and podocyte injury in the presence of hypertension and DM results in excess quantities of albumin in Bowman's space, and with increased quantities of albumin in the urine, the proximal tubular cells have an increased workload of reabsorption. This phenomenon has been suggested to lead to apoptosis of renal tubular cells, further nephron loss, and progression of kidney disease. Indeed, albuminuria and gross proteinuria have been associated consistently with the risk of AKI in a variety of settings. Albuminuria in the general population is predictive of the development of HF, especially in those patients with established HF; it is present in approximately 30% and associated with hospitalizations and mortality. These observations suggest the common soil for CRS lies within common cell types in both organs, namely, the endothelial cells. The endothelial cell is the earliest target of atherosclerosis, allowing further accumulation of lipid material, oxidation, recruitment of monocytes and macrophages, and progression of the disease process in the vasculature and the kidneys. Microalbuminuria thus is a risk marker for cardiovascular disease (CVD) and CKD and is probably a pathogenic factor in the progression of CKD.

Uremic Solute Retention

Studies have demonstrated that uremia causes myocyte dysfunction manifested by impaired movement of calcium in the cytosol leading to impaired contraction of myocyte elements. Uremia also may contribute to loss of skeletal and cardiac myocytes and be partially responsible for myopathy of both muscle types. In addition, uremia directly contributes to accelerated fibrosis and adverse cardiac remodeling after myocardial infarction. Relief of chronic uremia with renal

transplantation has been associated with many changes, including improvement in left ventricular systolic function, reduction in left ventricular mass, and reduction in left ventricular size. Hyperuricemia is associated with uremia and has been associated with atherosclerosis and cardiovascular death in multiple studies.²² Observational studies of patients with gout and HF have shown that allopurinol is associated with improved outcomes.²³ Small randomized trials suggest that lowering uric acid may influence the natural history and symptoms of CKD and cardiovascular disease.^{24,25} Therefore as a predisposing factor related to uremia, hyperuricemia warrants additional attention as a potential treatment target.

Anemia

Anemia is common in HF and is associated with increased mortality, morbidity, and WRF. The pathogenesis of anemia in HF is multifactorial, encompassing hemodilution as a result of water retention, blockade of normal iron transport, inflammation/cytokine-induced erythropoietin deficiency and tissue resistance, malnutrition, cachexia, and vitamin deficiency amplified in the presence of preexisting CKD. The triad consisting of anemia, HF, and CKD has been named cardiorenal-anemia syndrome. However, the presence of anemia is a consequence of CRS and an important factor affecting progression of organ damage and worsening of renal and cardiac function. Neurohormonal and inflammatory pathways have an impact on endogenous erythropoietin production and bone marrow resistance. Furthermore, reduced responsiveness to erythropoietin in patients with HF and CKD has been associated with high levels of hepcidin-25, a key regulator controlling iron intestinal absorption and distribution through the body. High levels of cytokines induce the iron utilization defect by increasing hepcidin-25 production from the liver, which blocks the ferroportin receptor and impairs gastrointestinal iron absorption and iron release from macrophage and hepatocyte stores. Hepcidin-25 may be useful in predicting erythropoietin responsiveness in stable chronic HF patients.²⁶ Thus attempts to control anemia in HF will have to take into consideration blockade of iron transport and the body, and attempts to overcome this problem with supplemental iron as well as erythropoiesis-stimulating agents (ESA) such as erythropoietin and darbepoetin. Many studies of anemia in HF with ESA and/or enteric or intravenous iron have shown a positive effect on hospitalization, New York Heart Association functional class, cardiac and renal function, quality of life, exercise capacity and reduced B-type natriuretic peptide (BNP). These short-term findings should be tempered with the sobering realization that long-term use of ESA and iron therapy in CKD in an attempt to raise hemoglobin over years of time has been associated consistently with higher rates of cardiovascular events, including HF in CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) and stroke in the TREAT (Trial to Reduce Cardiovascular Events with Aranesp) trials.²⁷

Repeated Episodes of Subclinical Acute Kidney Injury

It is highly probable that some individuals undergo repeated episodes of either subclinical or unrecognized episodes of AKI over the course of a lifetime. With each episode, there is injury to nephron units with partial recovery of some and permanent death to others. Because of the kidneys' ability to alter blood flow and filtration, the clinician would

not be able to detect these events with the measurement of serum creatinine. Such AKI events could occur with episodes of extreme dehydration (e.g., with self-limited gastrointestinal or viral syndromes), after elective surgeries, with toxic therapies for other diseases (e.g., chemotherapy, antibiotics), and with the use of iodinated contrast agents for a variety of imaging studies. Thus repeated subclinical AKI in the past may explain why some individuals with seemingly no baseline CKD or risk factors develop CRS in the setting of ADHF.

Cardiac and Renal Fibrosis

Increased stress or injury to the myocardium, glomeruli, and renal tubular cells, resulting from uncontrolled hypertension, DM, and other factors discussed in this section, has been associated with tissue fibrosis. Responses to acute and chronic damage can involve recruitment of immune cells, production of cell signaling proteins from local pericytes, mast cells, and macrophages, resulting in activation of resident fibroblasts and myofibroblasts, and in the final common pathway, the deposition of procollagen into the extracellular matrix, which is irreversibly cross-linked to collagen generating cardiac and renal fibrosis. There are a multitude of regulators involved in the pathophysiology of cardiac fibrosis. The galectin classes of carbohydrate-binding proteins are important participants in this process. Various subtypes bind to specific carbohydrate molecules, which activate a particular cellular signaling process. Galectin-3 is the most well-studied galectin subtype and released by activated macrophages directly in the myocardial extracellular space and bloodstream.

Galectin-3 (also known as MAC-2 Ag), one of 14 mammalian galectins, is an approximately 30 kDa glycoprotein with a carbohydrate-recognition-binding domain of approximately 130 amino acids, which enables the binding of β -galactosides. It is encoded by a single gene, LGALS3, located on chromosome 14, locus q21–q22, and expressed in the nucleus, cytoplasm, mitochondrion, cell surface, and extracellular space. Galectin-3 as a paracrine signal is involved in cell adhesion, activation, chemoattraction, growth and differentiation, cell cycle, and apoptosis in multiple diseases including cancer, liver disease, rheumatologic conditions, and CRS. In the myocardium and the kidney, angiotensin II (Ang II) and aldosterone represent a major stimulus for macrophages to secrete galectin-3, which in turn works as a paracrine signal on fibroblasts to help translate the signal of transforming growth factor- β (TGF- β) to increase cell cycle (cyclin D1) and direct the proliferation of pericytes and fibroblasts and the deposition of procollagen 1. These observations strongly suggest that fibrosis is a critical participant in the pathogenesis and progression of CKD and HF. Because the tissue secretion of galectin-3 is sufficiently high, it can be detected as a signal in blood and thus has been developed as a key advance for the clinical assessment of patients at risk for cardiorenal syndromes.

PATHOPHYSIOLOGY

Four subtypes of HF are hypertensive pulmonary edema with preserved left ventricular systolic function, ADHF, cardiogenic shock, and predominant right ventricular failure. Any of these can represent a cause of AKI and CRS-1 with different mechanisms (Fig. 111.2). Renal hypoperfusion can play an important role, although worsening renal

function also has been observed in patients with preserved left ventricular ejection fraction, and diastolic dysfunction may be an important mechanism of kidney congestion. Increased intraabdominal pressure also has been invoked. Vascular factors such as nitric oxide, prostaglandin, natriuretic peptides, and endothelin may modulate renal perfusion independently of cardiac hemodynamics. The heart, kidneys, renin-angiotensin system (RAAS), SNS, immune system, and endothelium interact through intricate feedback loops, as shown in Fig. 111.3. An imbalance in this complex system may cause deterioration in cardiac and renal function. If CO and mean arterial pressure fall, so does renal blood flow, activating the RAAS, reducing nitric oxide in the endothelium, activating the sympathetic nervous system (SNS), and inducing inflammatory mediators. All of these cause structural and functional damage to the kidneys and heart. Creatinine rise is a marker of illness severity because it reflects activation of hormonal, immunologic, inflammatory, and oxidative processes.

Recently, researchers focused on the role of inflammatory markers as links between cardiovascular and kidney disease, reduction in CO, renal blood flow, and perfusion pressure.

The clinical importance of each of these mechanisms is likely to vary from patient to patient, depending on the type of HF (e.g., acute cardiogenic shock, hypertensive pulmonary edema, or ADHF). These are modified further by complications such as valvular disease or endocarditis. In ADHF, AKI seems to be more severe in patients with impaired left ventricular ejection fraction. Indeed, the incidence in cardiogenic shock is greater than 70%.

In the Prospective Outcomes Study in Heart Failure (POSH) study, elevated creatinine conferred a higher 6-month mortality only in patients with ADHF complicated by circulatory shock, hypotension, cardiac arrest, sepsis, or ACS.^{28,29} Those with an increased serum creatinine of at least 0.3 mg/dL but no other complications did not have higher mortality in the hospital at 30 or 180 days. Thus much of CRS-1 mortality is due to other factors. CRS-1 in ADHF rarely occurs in the prehospital phase and generally is observed during hospitalization. This implies that some factor associated with hospitalization, such as diuresis, precipitates CRS. In fact, loop diuretics have been identified as one of the modifiable in-hospital determinants of CRS-1 probably by further activation of the RAAS as well as worsening intrarenal hemodynamics.²⁹ Testani et al.³⁰ have shown recently in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial that the use of higher doses of loop diuretics, causing hemoconcentration, resulted in a fivefold increased rate of worsening renal function. Nevertheless, in this prospective trial of hemodynamic monitoring, aggressive diuresis was associated with a 69% reduction in mortality at 180 days.

Several studies have related the presence of an elevated central venous pressure and renal venous congestion to the development of CRS-1. Normally, increased atrial pressure suppresses arginine-vasopressin (AVP) release and enhances water diuresis, decreases renal sympathetic tone, and augments natriuretic peptide secretion. However, in patients with HF, neurohormonal activation overwhelms these atrial–renal reflexes, as is shown by persistent renal sodium and water retention despite elevated atrial pressures. Transmission of venous congestion to the renal veins further impairs the GFR.

The specific physiology underlying this direct link between increased venous pressure and GFR is unclear, but there are a number of possibilities. Renal venous pressure increases in response to increased central venous pressure and causes an increase in renal interstitial pressure. The

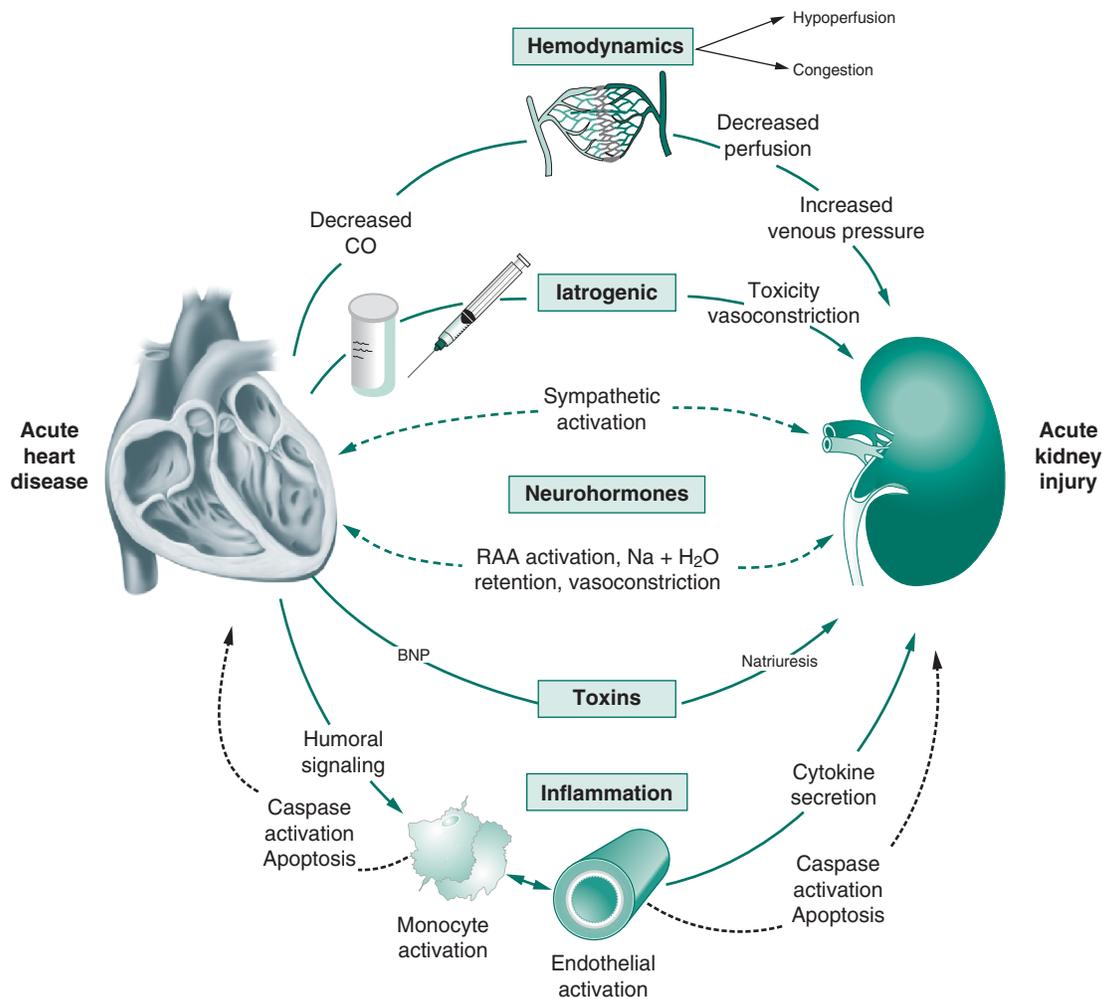


FIGURE 111.2 Pathogenic mechanisms for type 1 cardiorenal syndrome. *BNP*, Brain natriuretic peptide; *RAA*, Renin angiotensin aldosterone.

resulting hypoxia may lead to impairment of GFR. Increased renal venous pressure also may raise systemic angiotensin II concentrations. This will lead to a further fall in GFR, either directly or by modulation of the SNS. Increased SNS activity influences GFR by changing the filtration coefficient. Furthermore, increased SNS activity triggers angiotensin II release, which also reduces GFR. Thus the ability of atrial natriuretic peptide (ANP) to preserve GFR by decreasing sensitivity of the tubuloglomerular feedback mechanism is blunted in HF, thereby compromising GFR. SNS-activation and angiotensin II are mediators of the blunted response to ANP observed in HF.

Coronary revascularization also can lead to CRS-1. Almost every patient undergoes coronary angiography in the hours to days before surgery. Iodinated contrast causes renal vasoconstriction and direct renal tubular toxicity. As a result, acute contrast-induced nephropathy occurs in 15% of patients. Cardiac surgery then exposes the kidneys to hypothermic, pulseless reduced perfusion for 30 to 90 minutes, which can superimpose further ischemic injury in the setting of a proinflammatory state. It is also possible that the extracorporeal circuit used in cardiopulmonary bypass surgery activates systemic factors that further induce AKI; however, attempts to limit this exposure have not resulted in significantly reduced rates of AKI. Thus cardiopulmonary bypass surgery-associated AKI occurs in 30% of patients. In this setting, CRS-1 appears

to cause a three- to fourfold increase in mortality despite the availability of dialysis. These patients commonly have additional risk factors, including diabetes, HF, older age, and larger contrast volumes. The result is longer hospital stay, higher mortality, and further kidney damage. Some ultimately require long-term dialysis or renal transplantation. Each single mechanism requires a deeper analysis to better understand the cross-talk between heart and kidney and its pathophysiologic implications.

ACUTE PATHWAYS OF CARDIORENAL SYNDROME TYPE 1

Several pathways have been identified in the process linking acute heart disorders and acute kidney injury or dysfunction (see Fig. 111.1). In this section, we explore each of them in detail.

Hemodynamic Alterations and Venous Congestion

Registry data have shown that it is the pulmonary congestion that brings patients to the hospital. In the ADHERE (Acute Decompensated Heart Failure National Registry) registry,

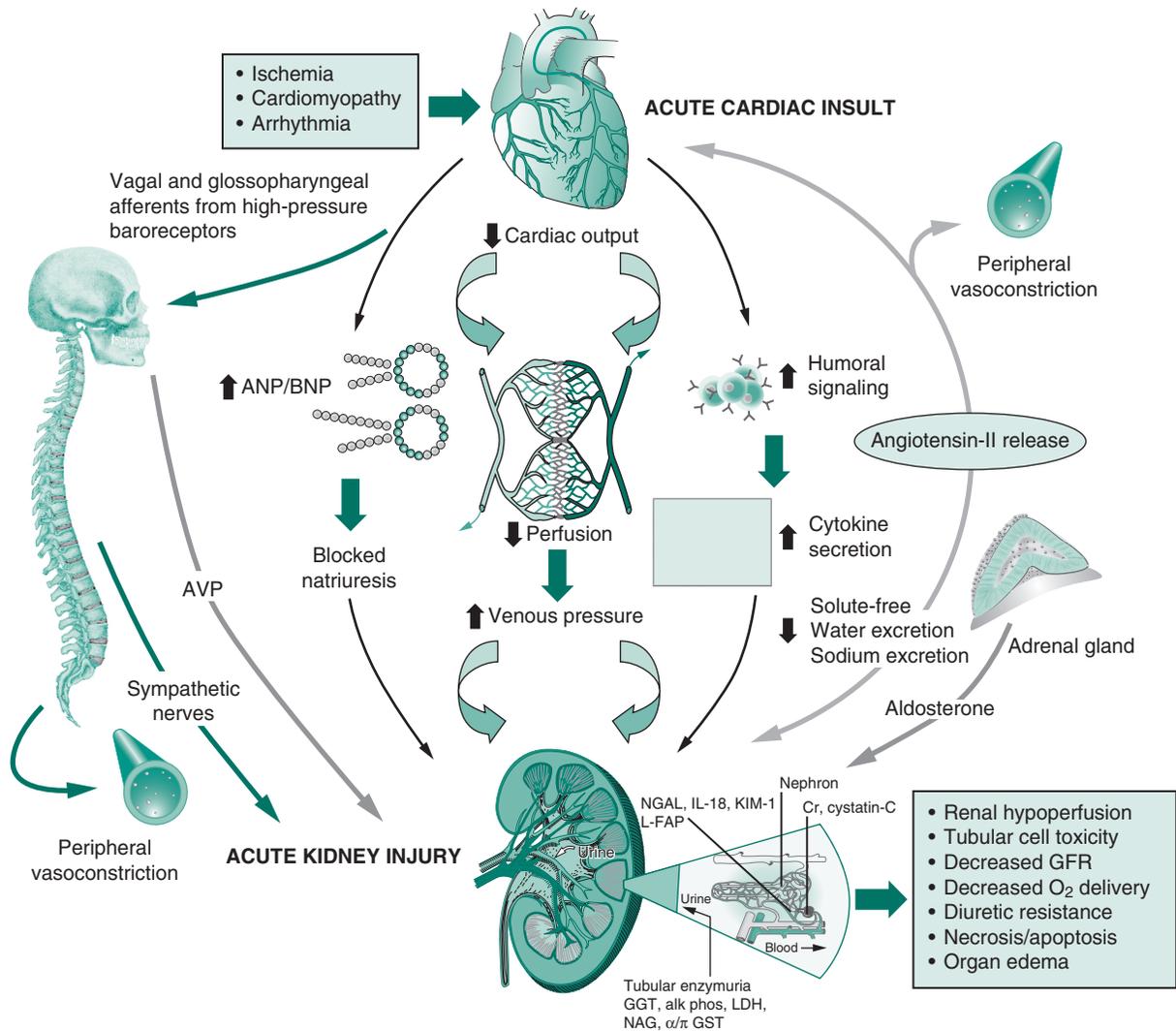


FIGURE 111.3 Hemodynamic, humoral, cellular and neurohormonal signals involved in the pathogenesis of acute kidney injury after an acute cardiac insult. ANP, Atrial natriuretic peptide; AVP, arginine vasopressin; BNP, brain natriuretic peptide; Cr, creatinine; IL-18, interleukin 18; GGT, gamma glutamyl transpeptidase; GST, glutathione transferase; KIM-1, kidney injury molecule-1; L-FAP, liver binding protein; LDH, lactic dehydrogenase; NaG, N-Acetyl-β-D Glucosaminidase; NGAL, neutrophil galactinase-associated lipocalin.

50% of patients who were admitted to the hospital had a systolic blood pressure of 140 mm Hg or higher and only 2% had a systolic blood pressure (BP) of less than 90 mm Hg.³¹ The increase in BP is likely a reflection of sodium retention and SNS activation. Dysfunction of the left ventricle is particularly sensible to afterload variations, and therefore an increase in blood pressure can worsen abruptly left ventricular filling pressures, leading to pulmonary congestion irrespective of total intravascular volume. Subsequently, a vicious cycle arises, in which cardiac remodeling leads to functional mitral regurgitation, further increase in left atrial pressure, and pulmonary hypertension. Experimental animal data as far back as the 1930s have demonstrated that temporary isolated elevation of central venous pressure can be transmitted back to the renal veins, resulting in direct impairment of renal function.³² Chronic passive congestion of the kidneys results in attenuated vascular reflexes over time (Fig. 111.4). As with the heart, venous congestion is one of the most important hemodynamic determinants of CRS and has been associated with the development of renal dysfunction in the setting of ADHF. However, the ESCAPE trial found no relationship with

baseline or changes in hemodynamics on renal outcomes.³³ It is observed commonly that coexisting renal dysfunction may complicate the treatment course of HF. The use of intravenous loop diuretics often alleviates congestion at the cost of WRF within days of hospitalization and is a strong independent predictor of adverse outcomes. Although loop diuretics provide prompt diuresis and relief of congestive symptoms, they provoke a marked activation of the SNS and RAAS result in renovascular reflexes and sodium retention and thus are considered a primary precipitant of CRS. This places the patient with ADHF at risk for CRS in a narrow therapeutic management window with respect to fluid balance and blood pressure as shown in Fig. 111.5.

Neurohormonal Activation

The RAAS has an important role in the initiation and maintenance of vascular, myocardial, and renal dysfunction leading to edema in HF. Increased renin secretion occurs early in biventricular failure, which leads to stimulation of angiotensin II. This eight-amino acid oligopeptide has

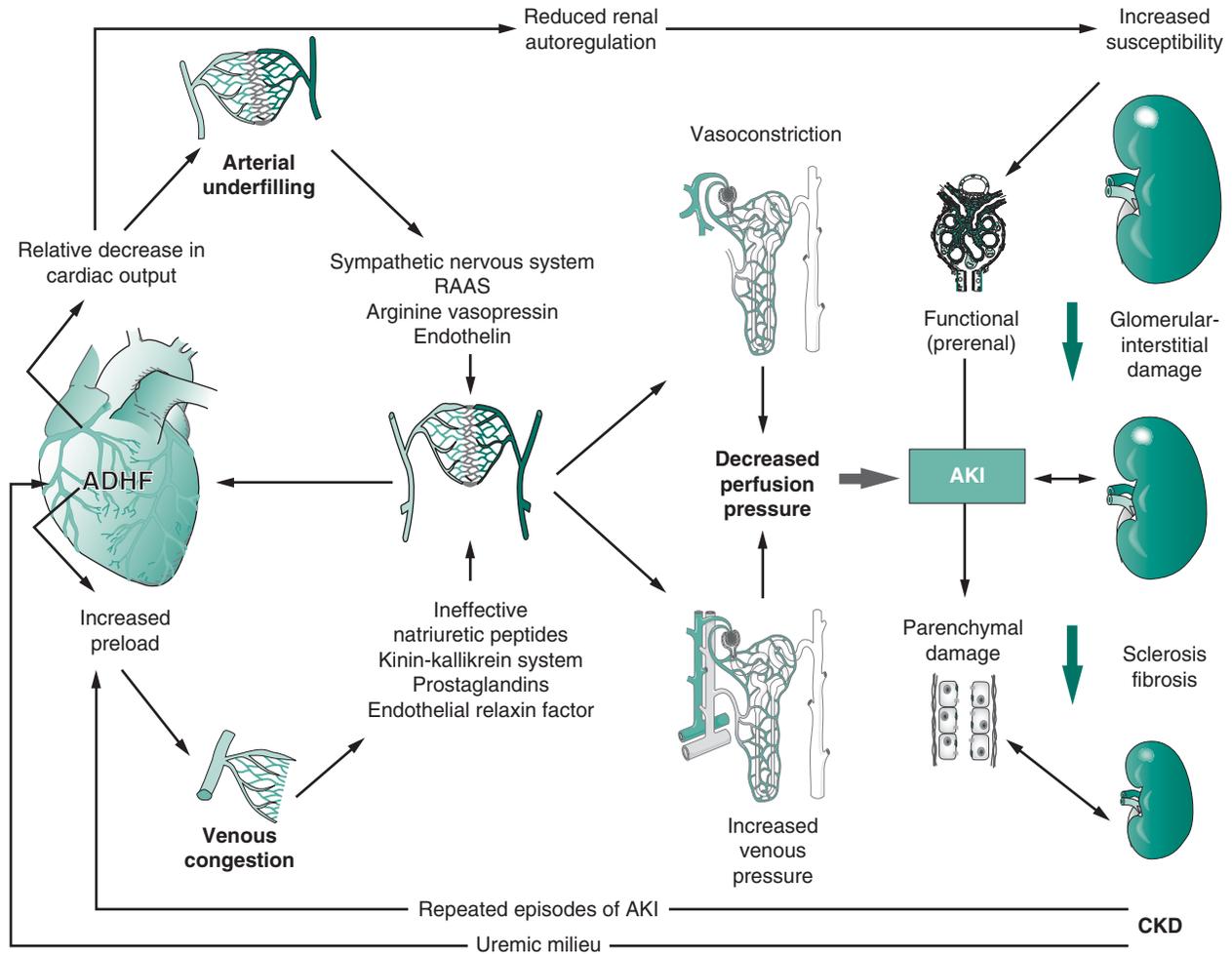


FIGURE 111.4 Hemodynamic adaptations in case of acute decompensated heart failure leading to either low cardiac output state or severe diastolic dysfunction.

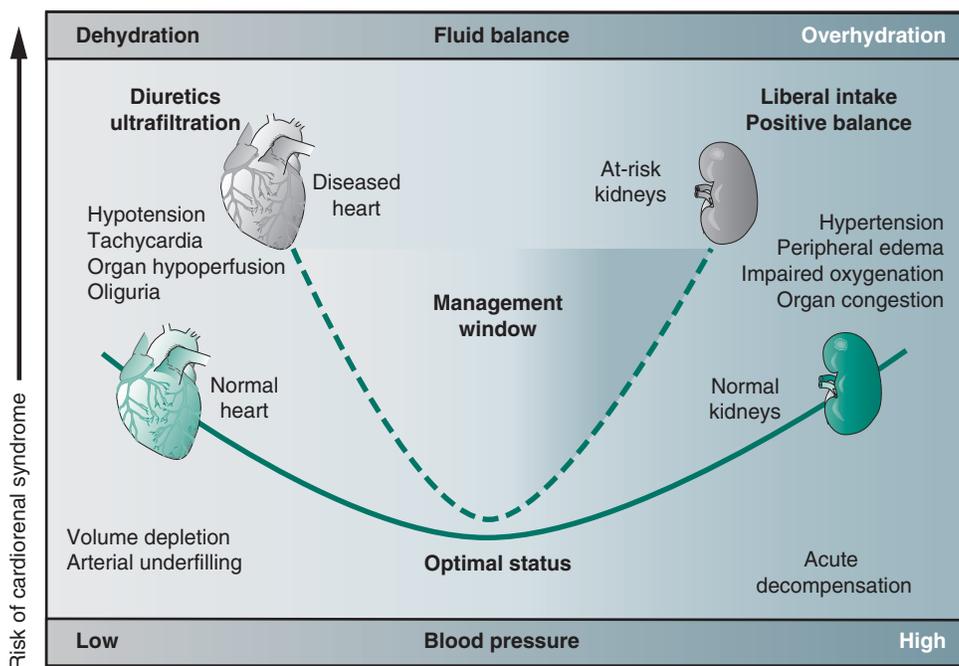


FIGURE 111.5 Narrow management window for volume and blood pressure in patients at risk for cardiorenal syndrome type 1.

many physiologic effects, which include stimulation of central neural centers associated with increased thirst and heightened activity of ganglionic nerves via its effects on the autonomic nervous system. It is a systemic vasoconstrictor to compensate for the initial decrease in stroke volume associated with ventricular failure while increasing contractility. Angiotensin II also is known to be a potent stimulator of the SNS, which increases systemic vascular resistance, venous tone, and congestion. Angiotensin II has direct trophic effects on cardiomyocytes and renal tubular cells that promotes cellular hypertrophy, apoptosis, and fibrosis. Angiotensin II accounts for approximately 50% of the stimulation of aldosterone release from the adrenal gland, which increases renal sodium reabsorption and causes sodium retention. In normal subjects an “escape” from renal salt-retaining effects of aldosterone occurs usually after 3 days, thus avoiding edema formation. This aldosterone escape phenomenon, however, does not occur in HF patients, and the continued sodium retention contributes to the pulmonary congestion and edema, particularly in those with angiotensin-converting enzyme DD genotype. Aldosterone stimulates macrophages in heart and kidney tissue to secrete galectin-3, which in turn stimulates fibroblasts to secrete pro-collagen I and III that is cross-linked to collagen resulting in fibrosis.³⁴ Moreover, patients with biventricular failure also may have poor hepatic perfusion and decreased clearance of aldosterone, thereby contributing to an elevation in the plasma aldosterone concentration.

As a result of SNS activation, catecholamines play a vital role in the pathogenesis and progression of HF. It is well known that elevated plasma NE levels in patients with HF correlate with increased mortality. Meanwhile, renal effects occur secondary to activation of the SNS. Stimulation of adrenergic receptors on proximal tubular cells enhances the reabsorption of sodium, while adrenergic receptors in the juxtaglomerular apparatus stimulate the RAAS.

Hypothalamic-Pituitary Stress Reaction

Activation of corticotrophin-releasing factor neurons in the paraventricular nucleus of the hypothalamus is necessary for establishing the classic endocrine response to stress. Stress is defined as anything that disrupts homeostatic balance; for example, ADHF. Any stressor that activates the hypothalamus-pituitary-adrenal axis leads to an increase in concentrations of the adrenal stress hormone, cortisol. One of the major hypothalamic stress hormones, which are stimulated by different stressors including osmotic and nonosmotic stimuli (cytokines), is arginine vasopressin (AVP). Measurement of circulating AVP levels has been challenging because it is released in a pulsatile pattern, unstable, and is cleared rapidly from plasma. AVP is derived from a larger precursor peptide (pre-provasopressin) along with copeptin, which is released from the posterior pituitary in an equimolar ratio to AVP and is more stable in the circulation and closely reflects AVP. Copeptin levels have been found to closely mirror the production of AVP and have been proposed as a prognostic marker in acute illness. Copeptin is elevated in several scenarios leading to CRS including sepsis, pneumonia, lower respiratory tract infections, stroke, and other acute illnesses. AVP stimulates the V_{1a} receptors of the vasculature and increases systemic vascular resistance, whereas stimulation of the V_2 receptors in the principal cells of the collecting duct increases water reabsorption and leads to hyponatremia. AVP also enhances urea transport in collecting ducts of the nephron, thereby increasing the serum blood urea nitrogen. The clinical

consequences of these changes include sodium and water retention, pulmonary congestion, and hyponatremia, which occurs in low-output and high-output cardiac failure. It is important to recognize that hyponatremia is a relatively late sign of AVP overstimulation, and thus earlier modulation of this system is an important consideration in treatment. The arterial underfilling occurs secondary to a decrease in cardiac output in low-output HF and arterial vasodilatation in high-output HF, both of which decrease the inhibitory effect of the arterial stretch baroreceptors on the SNS and the RAAS. Decreased baroreceptor sensitivity also contributes to stimulation of RAAS and SNS. Thus a vicious cycle of worsening HF and edema formation occurs.

Inflammation and Immune Cell Signaling

Inflammation classically has four components: (1) cells, (2) cytokines, (3) antibodies, and (4) complement. Thus the term *inflammation* in CRS has been termed “low-grade” or better described as an imbalance between the immune system cell signaling pathways promoting and inhibiting inflammation. Over the past 30 years there has been increasing evidence on the role of activation of the inflammatory response in the pathogenesis of different types of heart disease, including HF. An early work of Levine et al. showed that in patients with severe HF, circulating levels of TNF- α were much higher than normal. Numerous studies showed activation of inflammation at various levels in HF patients. Further support for the inflammatory cause of HF came from the demonstration that inflammatory cytokines also may be produced by cardiomyocytes, following ischemic or mechanical stimuli, but also the innate immune response, represented by Toll-like receptors, pentraxin-like C-reactive protein, and pentraxin 3. These findings suggest that in HF, an immune-dysregulation may exist; cytokines could not only produce distant organ damage such as AKI but also may play a role in further damaging myocytes. There is evidence supporting the prognostic value of various circulating markers of inflammation, particularly C-reactive protein, pentraxin 3, TNF- α , IL-1, and IL-6. Excessive elevations of cytokines and markers of inflammation have been documented consistently in ADHF. Inflammatory activation may have a role in HF by contributing to vascular dysfunction and fluid overload in the extravascular space.³⁵ The amount of fluid in the pulmonary interstitium and alveoli is controlled tightly by an active process of reabsorption. Recent studies have shown that inflammation interferes with this process and thus leads to pulmonary fluid overload despite no increase in total body fluid. This mechanism could be a cause for inadequate renal perfusion pressures, peritubular edema, pathologic reduction of glomerular filtration, and finally a mixed inflammatory and ischemic tubular damage.

Role of the Gut and Endotoxemia

Underperfusion of the intestine and the hematogenous release of endotoxin in patients with HF have been proposed as a mechanism for progression of HF and CRS-1, particularly in patients with cachexia. In HF, blood flow presumably is shunted away from the splanchnic region, and ischemia is pronounced particularly at the tips of the intestinal villi; in states of intestinal underperfusion, the paracellular permeability of the intestinal wall is increased as a result of hypoxia and local production of lipopolysaccharide, and systemic endotoxemia occurs. Disruption

of intestinal function and translocation of gram-negative bacteria or lipopolysaccharides as well as cytokines (TNF- α , IL-1, and IL-6) can exacerbate myocyte dysfunction. They exert their cardiopressive effects primarily by altering myocardial intracellular calcium, reducing mitochondrial activity, and causing imbalance of autonomic nerve activity, thus affecting many other organs including the kidneys.³⁶ When cardiomyocytes are exposed to LPS, nitric oxide and cGMP are increased. This effect is mediated by the Toll-like receptor 4 and results in depression of excitation depression coupling and of the peak velocity of cardiomyocyte shortening. Further abnormalities of cardiomyocytes have been documented (e.g., disturbed mitochondrial respiration, reduction in resting membrane potential, Na⁺, K⁺ gradient, and impaired substrate metabolism, increased expression of metalloproteinases and their inhibitors, decreased adrenergic responsiveness, and many others). This sequence of pathologic events is far more evident in acutely ill patients with sepsis, liver cirrhosis, ischemia reperfusion after burns, and cachexia.

Superimposed Infection

Superimposed infection, often pneumonia, is a common precipitating or complicating factor in ADHF. An inflammatory pathogenesis can be a common key feature for the kidneys and cardiovascular system during sepsis, leading to cell ultrastructural alterations and organ dysfunction. Murugan et al. recently demonstrated that AKI is associated

to pneumonia via an inflammatory pathogenesis. In this paper, the outcomes of AKI were associated adversely to IL-6 plasma concentration. Proinflammatory cytokines such as TNF- α , IL-1, and IL-6 induce myocardial dysfunction, cause microcirculatory damage, and contribute to altered tissue perfusion and oxygen delivery/consumption, thus contributing to heart and kidney failure. Enhanced endothelial expression of leukocyte adhesion molecules and alteration of endothelial cells contacts can increase microvascular permeability, thus leading to extravascular fluid shift, fluid overload, hypovolemia, reduced venous return, and lower cardiac output. Interstitial edema further reduces oxygen delivery to tissues, and fluid overload is an independent risk factor for mortality among septic patients with AKI. The pathogenesis of interstitial edema involves the glycocalyx, which is a thin (0.5–1.2 μ m) molecular structure that lies beneath capillary endothelial cells and regulates capillary flow, leukocyte adhesion and migration, platelets adhesion, and coagulation. Glycocalyx disruption resulting from sepsis and cytokines contributes to increased permeability, in systemic and renal microcirculation, increasing leukostasis, microthrombosis, fluid shift, and interstitial edema.

Iatrogenic Interventions

Among the mechanisms involved in organ cross-talk between heart and kidney, we must consider iatrogenesis (Fig. 111.6). In several clinical conditions, drugs required to treat DM,

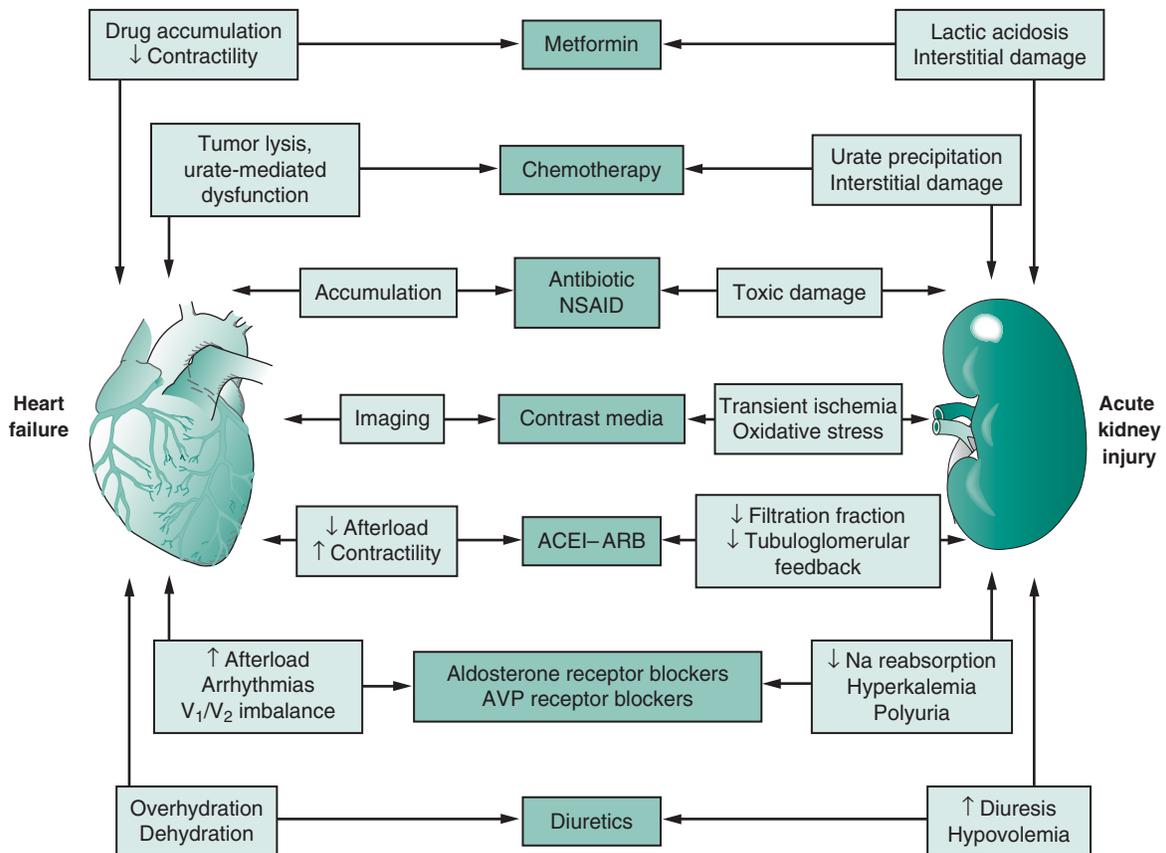


FIGURE 111.6 Selective sources of iatrogenesis causing either cardiac, renal, or cardiorenal impairment and damage in patients with acute decompensated heart failure. ACEI, angiotensin convertin enzyme inhibitors; ARB, angiotensin receptor blocker; NSAID, non steroidal antiinflammatory drugs; V₁, vasopressin receptors type 1; V₂, vasopressin receptors type 2.

oncologic diseases, infections, HF, or fluid overload may affect the delicate balance between the heart and the kidney, leading to progressive deterioration of both. Metformin is an antidiabetic drug that can result in lactic acid accumulation and worsen heart function because of a negative inotropic effect. Chemotherapeutic agents used in solid tumor treatments may induce a tumor lysis syndrome with a sudden increase in circulating uric acid levels.³⁷ Such an effect, although less dramatic, also may be induced by diuretic therapy. Uric acid as discussed above is potentially toxic to the myocardium as well as for the tubulointerstitial component of the kidney. Antibiotics may cause interstitial nephritis and tubular dysfunction and contribute to progressive renal insufficiency, especially when glomerular filtration is stressed by a low cardiac output and activation of the RAAS. Iodinated contrast causes a much different form of AKI characterized by transient vasoconstriction and decreased perfusion followed by direct tubular toxicity as the contrast is taken up by proximal tubular cells and transported into the interstitium in the kidney. Contrast-induced nephropathy can be an important cause of a negative feedback on the heart with progressive worsening of cardiac disease resulting from uremic complications. Cardiac surgery is a well-recognized antecedent to type 1 CRS and AKI particularly if the patient has received contrast in the days before the operation. Because this is one of the timed forms of AKI, there has been considerable effort in demonstrating the novel markers of AKI (NGAL, kidney injury molecule-1 [KIM-1], liver-type fatty acid binding protein [LFABP], N-acetyl- β -D-glucosaminidase [NAG], and others) serve as baseline risk predictors and diagnostic indicators of kidney damage after cardiac surgery.

Progressive salt and water retention alter intraglomerular hemodynamics and thereby influence physiologic tubuloglomerular feedback. Patients already may be undergoing treatment with angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), direct renin inhibitors, and or aldosterone blockers, all of which may affect tubuloglomerular feedback negatively. However, holding these agents, although temporarily causing less creatinine retention in the blood pool, has been associated with worsening of HF over the longer term. Combinations of ACEI, ARB, direct renin inhibitors, and especially aldosterone blockers when GFR is reduced below 45 mL/min, may lead to secondary hyperkalemia. Nonsteroidal antiinflammatory agents reversibly inhibit cyclooxygenases 1 and 2, impair prostaglandin synthesis, and result in sodium and fluid retention and tissue edema, which consistently worsen HF outcomes.³⁸ In the kidney, edema may result in impaired oxygenation and metabolite diffusion, distorted tissue architecture, obstruction of capillary blood flow, and lymphatic drainage, and disturbed cell-cell interactions that then may contribute to progressive organ dysfunction.

The cornerstone of treatment for ADHF is the use of oral and intravenous loop diuretics. These agents represent a double-edged sword because they may resolve congestion but worsen renal perfusion by arterial underfilling and heightened activation of the SNS and RAAS leading to CRS-1.

Although registry data have demonstrated that earlier diuretic use decreases mortality in severe ADHF, there is an overall relationship between increased loop diuretic dosing and mortality. Felker et al., in a small randomized trial of ADHF, demonstrated that higher doses and continuous infusions of furosemide resulted in more patients developing AKI (rise in Cr > 0.3 mg/dL) with no improvement in hospitalization or death.³⁹ These arguments suggest

the clinician needs better guidance on the use of loop diuretics in ADHF. Two such sources of guidance include the use of bioimpedance to estimate body water as well as novel biomarkers of AKI such as NGAL, which rises in the setting of diuretic-induced AKI.

Oxidative Stress

Oxidative stress is a final common pathway for cellular dysfunction, tissue injury, and organ failure. The mechanisms discussed above all render the heart and kidney vulnerable to loss of control over normal cellular oxidative reactions necessary for cellular function. The most widely recognized chemical reactions generating reactive oxygen species are the Haber-Weiss and Fenton equations. These equations require oxygen, water, hydrogen, and a metal catalyst in the form of such metals as iron and copper. Because iron is the most abundant metal element in cells, it is believed that labile iron is the major stimulus for oxidative stress that results in tissue injury.⁴⁰ The release of poorly liganded labile iron, which remains unbound in a fraction, has been implicated in acute ischemic cardiac and a variety of injury models in the kidney. Importantly, labile iron transitioning from Fe²⁺ to Fe³⁺ facilitates the production of hydrogen peroxide and the dangerous hydroxyl radical, which overwhelm the homeostatic antioxidant defense mechanisms in cells. Attempts to slow these reactions may have benefit, particularly for the kidney and include alkalization, cooling, and binding the iron catalyst. It is important to recognize in probably every case of CRS that oxidative stress and injury to the heart and kidneys is playing a potentially reversible role and that these mechanisms represent a final common pathway for tissue damage and organ failure. Thus therapeutic attempts to substantially attenuate oxidative stress, in theory, hold promise for large benefits in patients with CRS.

Failure of Counterregulatory Mechanisms

The regulatory and counterregulatory systems in ADHF have been studied extensively over the past several decades. In response to wall tension, the cardiomyocyte produces large quantities of natriuretic peptides that work to reduce wall tension, vasodilate, and promote natriuresis and diuresis.⁴¹ Ischemia also is recognized as a stimulus for natriuretic peptide production. Natriuretic peptides, working via NP receptors in the glomerulus and the renal tubules, activate cyclic-CMP and reduce sodium reabsorption. When given in supraphysiologic doses, BNP reduces levels of catecholamines, Ang II, and aldosterone. However, this counterregulatory set of functions appears to be overwhelmed in CRS-1, and thus the patient worsens clinically and develops oliguria in the setting of markedly elevated levels of natriuretic peptides.⁴²

The kidney also produces counterregulatory proteins that work to reduce cellular injury. The most notable protein is NGAL, or siderocalin-2. In the setting of tubular injury, unbound or labile iron is released from the cytosol, where it catalyzes the major oxidative stress reactions discussed above. NGAL works to mop up this poorly liganded iron and reduce oxidative stress. This is probably a vestigial function that also helped reduce iron availability and check bacterial growth in the setting of pyelonephritis. As with the natriuretic peptides, this counterregulatory protein has been shown to be a useful diagnostic tool for AKI and is elevated in patients with CRS-1.⁴³

TREATMENT

CRS-1 requires a full understanding of the pathophysiologic foundations of the clinical picture that often represent a clinical challenge. Preservation of renal function should receive the same priority as maintaining cardiac function. Many of the current therapies for HF, such as diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), may have deleterious effects on kidney function, and aldosterone antagonists often are withheld because of the fear of hyperkalemia. Few agents used in the treatment of ADHF have been shown to improve clinical outcomes.

Diuretics improve symptoms of ADHF but have not been shown to reduce long-term morbidity and mortality. In fact, they often represent the main cause of worsening renal function resulting from neurohormonal activation. Diuretic responsiveness may be impaired in these patients. Data are limited, because most large HF trials have excluded patients with advanced renal dysfunction. Diuretics may best be given in ADHF patients with evidence of systemic fluid overload with the goal of achieving a gradual diuresis. Dosing should take into account renal function, systolic blood pressure, and history of chronic diuretic use. Diuresis may be augmented by the addition of a thiazide diuretic, acetazolamide, or spironolactone, or the use of continuous infusions of loop diuretics. Continuous infusion of a loop diuretic may be guided by techniques for fluid status assessment such as bioimpedance vector analysis (BIVA) and BNP monitoring.⁴⁴ Measurement of CO and venous pressure also may be helpful. According to a recent study performed by Felker et al., it was found that among patients with ADHF, there were no significant differences in patients' symptoms or rates of rehospitalization or death when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose.⁴⁵ In this trial, there was a considerably lower rate of a rise in serum creatinine of 0.3 mg/dL or more in those randomized to the bolus and lower-dose groups, again suggesting less aggressive diuresis when feasible is a rational strategy. A novel approach is the limited administration of hypertonic saline and high doses of loop diuretics. Reportedly, this produces a reduction of neurohormonal activation with significant increases in diuresis and natriuresis. Length of stay and readmission rates were reduced. The effect of this regimen on kidney function in patients with ADHF currently is being investigated.

If fluid overload persists, despite an optimized CO, removal of isotonic fluid can be achieved by ultrafiltration. This procedure results in increased sodium removal without an increase in sodium delivery to the distal nephron, which would activate the tubuloglomerular feedback (TGF) system. Theoretically, this should cause less activation of the RAAS and the SNS. The UNLOAD trial compared ultrafiltration with intravenous diuretics in patients with ADHF. Ultrafiltration induced more weight loss and reduced rehospitalization rates without worsening renal function. A smaller trial found no difference in fluid balance, GFR, and renal plasma flow. The role of ultrafiltration in patients with CRS currently is being assessed in a multicenter trial.

Interventions that inhibit the activity of the RAAS reduce morbidity and mortality in patients with HF and slow or even halt the progression of CKD, especially diabetic nephropathy. However, ACEIs and ARBs are underused in patients with CRS because of the fear of worsening kidney function. Patients with moderate renal dysfunction appear to have a survival benefit, despite the transient worsening

of kidney function that occurs in up to 30% of the patients. In those with severe renal dysfunction, the trade-off between efficacy and safety remains unknown, and close monitoring of kidney function is advised. The presence of AKI with or without hyperkalemia also may discourage the prescription of ACEIs and aldosterone inhibitors. This is unfortunate because the potential benefits of these interventions will likely outweigh their risks even in these patients, provided there is a close monitoring of renal function and potassium levels.

Beta blockers are often beneficial in the appropriate patient. Caution is needed, for in some patients with fixed stroke volume, tachycardia is necessary to maintain CO. Blockade of such compensatory tachycardia and sympathetic system-dependent inotropic compensation can precipitate cardiogenic shock and can be lethal. Particular concern applies to beta blockers that are excreted by the kidney, such as atenolol or sotalol, especially if combined with calcium antagonists. These considerations should not inhibit the slow, careful titration of beta blockers once patients are hemodynamically stable. This aspect of treatment is particularly relevant in patients with CRS due to under treatment after myocardial infarctions. In the setting of CRS type 1, combination therapy with beta blockers and ACEI should be done with attention when trying to optimize and stabilize the patient's clinical status.

Natriuretic peptides induce vasodilation and natriuresis. Unlike diuretics, they decrease neurohormonal levels and have antifibrotic, antihypertrophic, antiinflammatory, lusitropic, and aldosterone-inhibiting properties. However, despite symptom relief in HF, a beneficial effect of nesiritide, a recombinant B-type natriuretic peptide on mortality could not be established. Conflicting results with regard to the effect on kidney function (no effect or worsening) exist, but no study in patients with HF has shown an improvement in kidney function. The ongoing phase III Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF) hopefully will provide a definite answer.⁴⁶ Urodilatin is an A-type natriuretic peptide that can improve symptoms but did not affect mortality or kidney function in patients with ADHF.⁴⁷

Other newer strategies that target renal function in patients with HF are adenosine receptor antagonists and vasopressin antagonists. Renal TGF is a normal homeostatic mechanism that maintains electrolyte and fluid homeostasis. In the setting of HF, the TGF may become maladaptive and result in diuretic resistance and decreased GFR. The TGF is mediated through the adenosine receptor subtype 1. Blocking this receptor may enhance diuresis and natriuresis with maintained or increased GFR and reduce loop diuretic requirements, as suggested by phase II protocols in patients with CRS. The complexity of adenosine physiology requires careful consideration in using such drugs. Larger phase III trials are ongoing. Blockade of the vasopressin V2 receptor in the collecting duct results in increased free water excretion, which theoretically may correct fluid retention and hyponatremia in HF. Tolvaptan, an oral selective V2 receptor blocker, has been shown to result in symptomatic improvement of patients hospitalized for ADHF, without worsening kidney function. However, mortality or HF readmission was not affected.⁴⁸ Conivaptan is a dual V1 and V2 receptor blocker that not only reduces aquaresis but also may reduce systemic vascular resistance and improve systolic function.⁴⁹

Studies have demonstrated consistently an association between worsening renal function in ADHF, along with the associated adverse outcomes. The placebo-controlled randomized study of the selective A1 adenosine receptor

antagonist rolofylline for patients hospitalized with ADHF and volume overload to assess treatment effect on congestion and renal function (PROTECT) clinical trial revealed that rolofylline was no better than placebo for patients with ADHF.⁵⁰ Although the participants in the trial who were given rolofylline did show some improvement in shortness of breath, the drug did not prevent kidney damage or have any significant effect on overall treatment success.

CONCLUSION

CRS-1 complicating ADHF is common and leads to more challenging management and higher mortality. CRS-1 is an important clinical phenomenon that occurs either de novo or in the setting of preexisting CKD in which the development of ADHF is complicated by multiple pathophysiologic mechanisms. Passive congestion of the kidneys, reduced renal perfusion, and neurohormonal activation combine to initiate this syndrome. Acute cardiac and renal congestion, neurohormonal activation, dysregulation of immune cell and cytokine signaling, superimposed infection and anemia, and a failure of normal counterregulatory systems lead to progressive and combined cardiac and renal dysfunction. This scenario leads to multiorgan system failure, drug resistance, and death in a considerable proportion of patients. New diagnostic and therapeutic targets should be considered to reduce the incidence and severity of this syndrome.

Key Points

1. Cardiorenal syndrome type 1 (CRS-1) is characterized by the development of acute kidney injury (AKI) and dysfunction in patients with acute cardiac illness, most commonly acute decompensated heart failure (ADHF).
2. Multiple pathophysiologic mechanisms operating simultaneously and sequentially are involved in the clinical syndrome.
3. Chronic kidney disease and associated factors such as obesity, cachexia, hypertension, diabetes, pro-

teinuria, uremic solute retention, anemia, and repeated subclinical AKI events produce and increase susceptibility of the patient to develop CRS in the setting of ADHF.

4. In the hospitalized patient, hemodynamic changes lead to venous renal congestion, neurohormonal activation, hypothalamic-pituitary stress reaction, inflammation and immune cell signaling, systemic endotoxemic exposure from the gut, superimposed infection, and iatrogenesis contribute to CRS-1.
5. The final common pathways of bidirectional organ injury appear to be humoral and cellular with specific signals operating at local and systemic levels.
6. Treatment approaches include neurohormonal blockade, less aggressive diuresis when feasible, and extracorporeal forms of fluid removal that provide a more gentle correction of renal congestion without worsened neurohormonal activation.

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