SECTION 18

Interaction of the Heart and the Kidney

CHAPTER 109

Heart-Kidney Cross-Talk

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OBJECTIVES

This chapter will:

1. Review the epidemiology and classification system applied to cardiorenal syndromes.
2. Understand the predisposing factors that increase the risk for acute and chronic cardiorenal syndromes.
3. Explore the wide range of systems and mediators involved in organ cross-talk in the setting of critical illness.

Combined disorders of heart and kidney are classified as cardiorenal syndromes (CRS) and include a variety of conditions, either acute or chronic, in which the primary failing organ can be either the heart or the kidney.[1] Classification of CRS provides a platform to examine complex organ cross-talk and introduce the possibilities of new prevention, treatment, and recovery strategies.[2] The temporal sequence of organ dysfunction largely distinguishes type 1 (i.e., cardiac first). However, it is not only the timing but also the predominance of the problem that allows the correct determination. For instance, in a patient with known heart failure (HF) who has acute heart failure (AHF) and a mild elevation in serum creatinine or cystatin C at baseline and then develops acute kidney injury (AKI) confirmed by a urinary marker of AKI followed by the temporary need for dialysis would be classified as type 1 CRS because the HF was the initial, predominant problem and the renal failure ensued.

Type 1 CRS (acute cardiorenal syndrome) occurs in approximately 25% to 33% of patients admitted with AHF and represents an important consequence of hospitalization with a myriad of implications for diagnosis, prognosis, and management.[3,4] There are direct and indirect effects of HF that can be identified as the primers for AKI and dysfunction. Venous congestion, sympathetic nervous system dysfunction, anemia, activation of the renin-angiotensin-aldosterone system (RAAS), disruption of the hypothalamic-pituitary axis, and a marked alteration of immune and somatic cell signaling have been implicated (Fig. 109.1). The complexity of this syndrome presents a key challenge for singular diagnostic or treatment approaches.

Risk factors for type 1 CRS include premorbid chronic kidney disease (CKD), which is common and predisposes to AKI in approximately 60% of cases.[5,6] AKI is an independent risk factor for 1-year mortality in AHF patients, including patients with ST-elevation myocardial infarction who develop signs and symptoms of HF or have a reduced left ventricular ejection fraction.[7] This independent effect may be due to an associated acceleration in cardiovascular pathobiology resulting from kidney dysfunction through the activation of neurohormonal, cell signaling, oxidative stress, or exuberant repair (fibrosis) pathways. Upon initial recognition, AKI induced by primary cardiac dysfunction implies inadequate renal perfusion until proven otherwise.[8] This should prompt clinicians to consider the diagnosis of a low cardiac output state and/or marked increase in venous pressure leading to kidney congestion. It is important to remember that central venous pressure translated to the renal veins is a product of right heart function, blood volume, and venous capacitance, which is regulated largely by neurohormonal systems acting on the venous vasculature. Specific regulatory and counterregulatory mechanisms are activated with variable effects depending on the duration and the intensity of the insult.

PREDISPOSING FACTORS

It is beyond the scope of this chapter to review the broad field of CKD. However, it is important to recognize that the vast majority of heart-kidney cross-talk is believed to occur in the setting of predisposing CKD. In this setting there are a variety of elevated and dysregulated cytokines,[9–14] in some cases cachexia or obesity,[15–17] diabetes mellitus and hypertension,[18–20] proteinuria,[21–23] uremia,[24–30] and anemia.[31–38] There are numerous studies and publications supporting the concept that all of these conditions are probably independently related to the progression of CKD, the development of HF, and the risk of AKI in the setting of AHF.

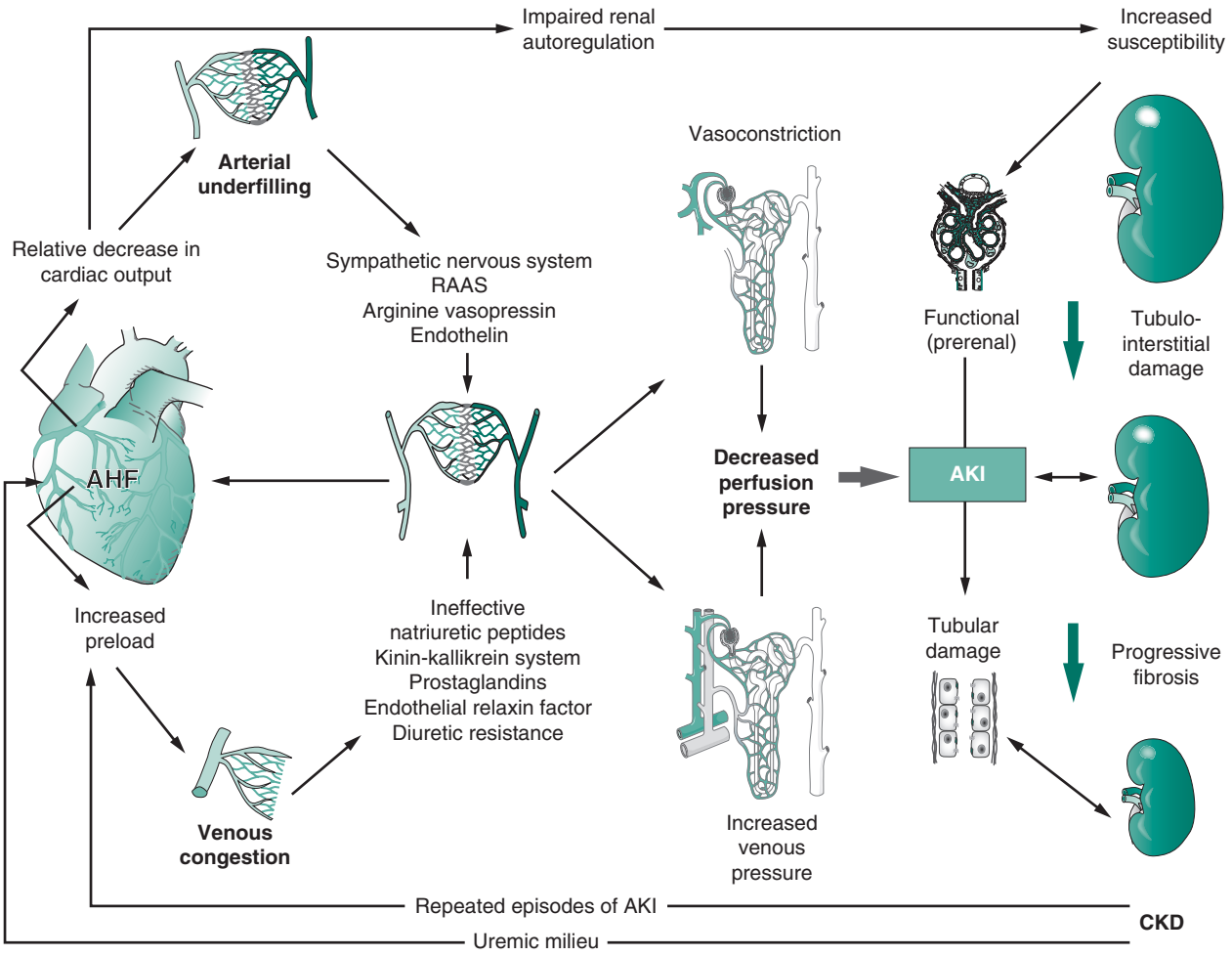

FIGURE 109.1 Pathogenesis of type 1 cardiorenal syndrome. Acute heart failure (AHF) via arterial underfilling and venous congestion sets off a series of changes in neurohormonal and hemodynamic factors that culminate in acute kidney injury (AKI).

SUBCLINICAL ACUTE KIDNEY INJURY

It is likely that 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 kidney's ability to alter blood flow and filtration, the clinician would not be able to detect these events with the measurement of serum creatinine.[39] 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.[40] 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 AHF.

CARDIAC AND RENAL FIBROSIS

Increased stress or injury to the myocardium, glomeruli, and renal tubular cells because of uncontrolled hypertension, diabetes mellitus, and other factors discussed in this section have 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.[41]

Galectin-3 (also known as MAC-2 Ag), a regulator of cardiac fibrosis, is one of 14 mammalian galectins and is an approximately 30 kDa glycoprotein that has a carbohydrate-recognition-binding domain of approximately 130 amino acids that enables the binding of β-galactosides.[42–45] 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.[46] 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 cardiorenal syndromes.[47] In the myocardium and the kidney, angiotensin II and aldosterone is 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.[48] These observations

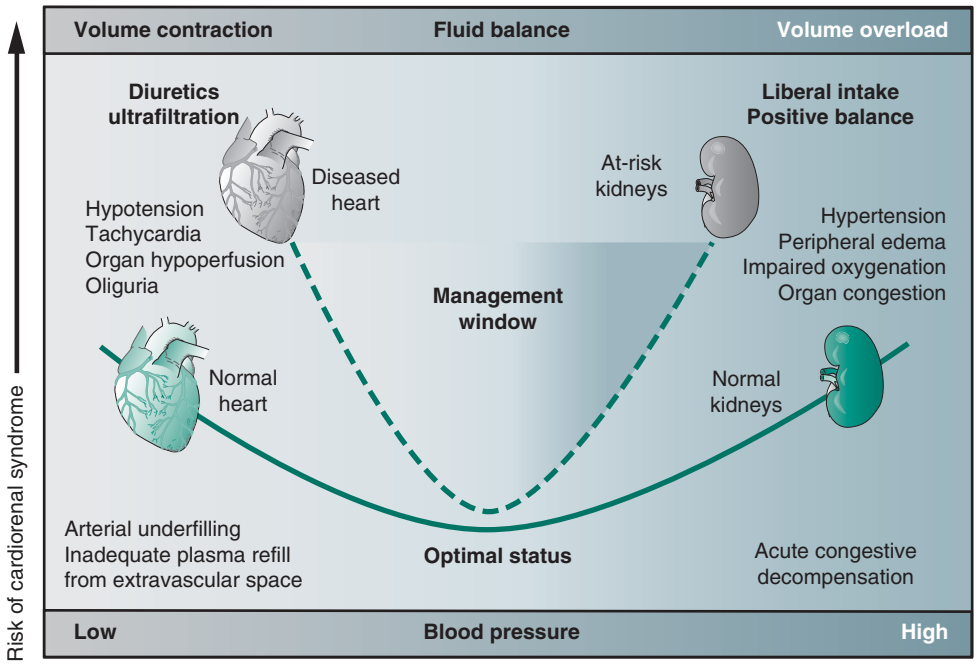

FIGURE 109.2 Volume and blood pressure management window. Patients at risk for cardiorenal syndrome type 1 have a narrow window for management of blood pressure and volume; extremes in either parameter can be associated with worsened renal function.

strongly suggest that fibrosis is a critical participant in the pathogenesis and progression of CKD and HF.[49] 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.

HEMODYNAMICS AND CONGESTION

In the ADHERE (Acute Decompensated Heart Failure National Registry) registry, 50% of patients who were admitted to the hospital with symptomatic AHF had a systolic blood pressure (BP) of 140 mm Hg or higher, and only 2% had a systolic BP of less than 90 mm Hg.[50] The increase in BP is likely a reflection of sodium retention and sympathetic activation. A dysfunctioning 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.[51] 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.[52]

Chronic passive congestion of the kidneys results in attenuated vascular reflexes over time. 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 AHF.[53] However, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial found no relationship with baseline or changes in hemodynamics on renal outcomes.[54] It is observed commonly that coexisting renal dysfunction may complicate the treatment course of HF and that the use of intravenous loop diuretics often alleviates congestion at the cost of worsening renal function within days of hospitalization and is a strong independent predictor of adverse outcomes.[55] Although loop diuretics provide prompt diuresis and relief of congestive symptoms, they provoke a marked activation of the sympathetic and RAAS result in renovascular reflexes and sodium retention and thus are considered a primary precipitant of CRS. This places the patient with AHF at risk for CRS in a narrow therapeutic management window with respect to fluid balance and blood pressure as shown in Fig. 109.2.

NEUROHORMONAL ACTIVATION

The RAAS system has an important role in the initiation and maintenance of vascular, myocardial, and renal dysfunction leading to edema in HF.[56] Increased renin secretion occurs early in biventricular failure, which leads to stimulation of angiotensin II. This eight amino acid oligopeptide has 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 at the same time increasing contractility. Angiotensin II is also known to be a potent stimulator of the sympathetic nervous system, which increases systemic vascular resistance, venous tone, and congestion. Angiotensin II has direct trophic effects on cardiomyocytes and renal tubular cells that promote cellular hypertrophy, apoptosis, and fibrosis.[57] 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.[58,59] Aldosterone stimulates macrophages in heart and kidney tissue to secrete galectin-3, which in turn stimulates fibroblasts to secrete procollagen I and III, which is cross-linked to collagen resulting in fibrosis.[60] 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.[61]

As a result of sympathetic activation, catecholamines play a vital role in the pathogenesis and progression of HF.[62] It is well known that elevated plasma NE levels in patients with HF correlate with increased mortality. Meanwhile, renal effects occur secondary to sympathetic activation. Stimulation of adrenergic receptors on proximal tubular cells enhances the reabsorption of sodium, whereas adrenergic receptors in the juxtaglomerular apparatus stimulate the RAAS.[63]

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 (e.g., AHF). 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. Measurement of circulating arginine vasopressin levels has been challenging because it is released in a pulsatile pattern, unstable, and is cleared rapidly from plasma. Arginine vasopressin is derived from a larger precursor peptide (pre-provasopressin) along with copeptin, which is released from the posterior pituitary in an equimolar ratio to arginine vasopressin and is more stable in the circulation and closely reflects arginine vasopressin. Copeptin levels have been found to closely mirror the production of arginine vasopressin 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. Arginine vasopressin 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. Arginine vasopressin 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 occur in low-output and high-output cardiac failure. It is important to recognize that hyponatremia is a relatively late sign of arginine vasopressin 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 sympathetic and RAAS. 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 tumor necrosis factor-alpha (TNF-α) were much higher than normal.[64] 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, after ischemic or mechanical stimuli, but also the innate immune response, represented by Toll-like receptors, pentraxin such as C-reactive protein and pentraxin 3.[65–70] 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, interleukin-1 (IL-1), and IL-6.[71–75]

Excessive elevations of cytokines and markers of inflammation have been documented consistently in AHF.[76] Inflammatory activation may have a role in HF by contributing to vascular dysfunction and fluid overload in the extravascular space.[77] 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.[78,79] 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.

SUBCLINICAL ENDOTOXEMIA

Underperfusion of the intestine and the hematogenous release of endotoxin in patients with HF is a possible mechanism for progression of HF and CRS type 1.[80] In HF, blood flow presumably is shunted away from the splanchnic region, and ischemia is particularly pronounced 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.[81] They exert their cardiosuppressive 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.[81,82] 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, such as 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.

CONCURRENT INFECTION

Pneumonia is the most common concurrent infection in AHF.[83] 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.[84] In this paper, the outcomes of AKI were adversely associated 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 μm) 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.

COMPLICATIONS OF MEDICAL THERAPY

Multiple medications can play a role in adverse heart-kidney cross-talk (Fig. 109.3). Metformin is an antidiabetic drug that can result in lactic acid accumulation and worsen heart function because of a negative inotropic effect.[85,86] Chemotherapeutic agents used in solid tumor treatments may induce a tumor lysis syndrome with a sudden increase in circulating uric acid levels.[87] Such an effect, although less dramatic, also may be induced by diuretic therapy. Uric acid as discussed earlier is potentially toxic to the myocardium as well as for the tubulointerstitial component of the kidney.[88] Antibiotics may cause interstitial nephritis and tubular dysfunction and contribution to progressive renal insufficiency, especially when glomerular filtration is stressed by a low cardiac output and activation of the

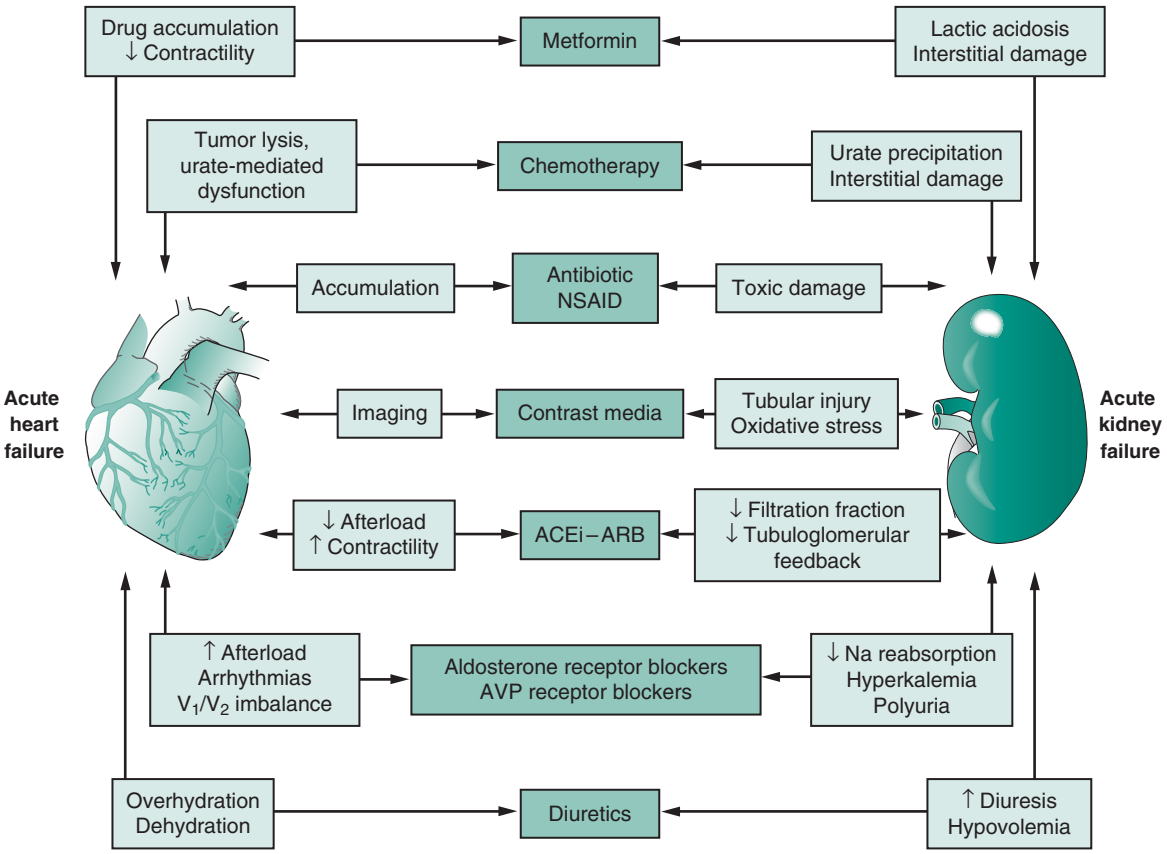

FIGURE 109.3 Iatrogenesis and type 1 cardiorenal syndrome. Multiple sources of iatrogenic injury, some of which may be unavoidable, can result in cardiac, renal, or cardiorenal impairment and kidney damage in patients with acute decompensated heart failure (AHF).

RAAS.[89] 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.[90] Contrast-induced nephropathy can be an important cause of negative feedback on the heart with progressive worsening of cardiac disease resulting from uremic complications.[91] 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 (neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 [KIM-1], L-type fatty acid binding protein [L-FABP], N-acetyl-β-D-glucosaminidase [NAG], and others) serve as baseline risk predictors and diagnostic indicators of kidney damage after cardiac surgery.[92,93]

Progressive salt and water retention alter intraglomerular hemodynamics and thereby influence physiologic tubular-glomerular feedback.[94] Patients may already be undergoing treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, direct renin inhibitors, and or aldosterone blockers, all of which may negatively affect tubuloglomerular feedback.[95] 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.[96] Combinations of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, and especially aldosterone blockers when GFR is reduced below 45 mL/min, may lead to secondary hyperkalemia. Nonsteroidal anti-inflammatory 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.[97] 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.[98]

The cornerstone of treatment for AHF is the use of oral and intravenous loop diuretics. These agents may resolve congestion but worsen renal perfusion by arterial underfilling and heightened activation of the sympathetic and RAAS leading to type 1 CRS.[99]

Although registry data have demonstrated that earlier diuretic use decreases mortality in severe AHF, there is an overall relationship between increased loop diuretic dosing and mortality.[100] Felker et al., in a small randomized trial of AHF 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.[101] These arguments suggest the clinician needs better guidance on the use of loop diuretics in AHF. Two such sources of guidance include the use of bioimpedance to estimate body water as well as novel biomarkers of AKI such as neutrophil gelatinase-associated lipocalin, which rises in the setting of diuretic-induced AKI.[102]

OXIDATIVE STRESS AS RESULT OF HEART KIDNEY CROSS-TALK

Oxidative stress is a final common pathway for cellular dysfunction, tissue injury, and organ failure. The mechanisms discussed earlier 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 forms such as iron or 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.[102] 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.[103–105] Importantly, labile iron transitioning from Fe^{2+} to Fe^{3+} facilitates the production of hydrogen peroxide and the dangerous hydroxyl radical, which overwhelm the homeostatic antioxidant defense mechanisms in cells.[106] Attempts to slow these reactions may have benefit, particularly for the kidney, and include alkalinization, 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.

COUNTERREGULATORY MECHANISMS

In response to wall tension, the cardiomyocyte produces large quantities of natriuretic peptides, which work to reduce wall tension, vasodilate, and promote natriuresis and diuresis.[107] 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 cCMP and reduce sodium reabsorption. When given in supraphysiologic doses, B-type natriuretic peptide reduces levels of catecholamines, angiotensin II, and aldosterone.[108] However, this counterregulatory set of functions appears to be overwhelmed in CRS type 1, and thus the patient worsens clinically and develops oliguria in the setting of markedly elevated levels of natriuretic peptides.

The kidney also produces counterregulatory proteins that work to reduce cellular injury. The most notable protein is neutrophil gelatinase-associated lipocalin, or siderocalin.[109] 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. Siderocalin works to mop up this poorly liganded iron and reduce oxidative stress.[110,111] 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 type 1.[112]

CONCLUSION

Heart-kidney cross-talk is a critical component of type 1 CRS and occurs most commonly in the setting of preexisting CKD, where the development of AHF is complicated by multiple pathophysiologic mechanisms.[113] 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.[114] This scenario leads to multiorgan system failure, drug resistance, and death in a considerable proportion of patients. Future research exploring the mechanisms discussed in this paper likely will lead to new diagnostic and therapeutic targets aimed to reduce the incidence and severity of this syndrome.

Key Points

1. It is likely that 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 kidney's ability to alter blood flow and filtration, the clinician would not be able to detect these events with the measurement of serum creatinine.
2. In the ambulatory patient, increased stress or injury to the myocardium, glomeruli, and renal tubular cells resulting from uncontrolled hypertension, diabetes mellitus, and other factors 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 cross-linked irreversibly to collagen generating cardiac and renal fibrosis.
3. In the hospitalized patient, hemodynamic changes leading 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 acute cardiorenal syndromes. The final common pathway of bidirectional organ injury appears to be cellular, tissue, and systemic oxidative stress, which worsen cellular and tissue function.

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A complete reference list can be found online at ExpertConsult.com.

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