STATE-OF-THE-ART PAPER

Cardiorenal Syndrome Type 1

Pathophysiological Crosstalk Leading to Combined Heart and Kidney Dysfunction in the Setting of Acutely Decompensated Heart Failure

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Cardiorenal syndrome (CRS) type 1 is characterized as the development of acute kidney injury (AKI) and dysfunction in the patient with acute cardiac illness, most commonly acute decompensated heart failure (ADHF). There is evidence in the literature supporting multiple pathophysiological mechanisms operating simultaneously and sequentially to result in the clinical syndrome characterized by a rise in serum creatinine, oliguria, diuretic resistance, and in many cases, worsening of ADHF symptoms. The milieu of chronic kidney disease has associated factors including obesity, cachexia, hypertension, diabetes, proteinuria, uremic solute retention, anemia, and repeated subclinical AKI events all work to escalate individual risk of CRS in the setting of ADHF. All of these conditions have been linked to cardiac and renal fibrosis. 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 all contribute to CRS type 1. The final common pathway of bidirectional organ injury appears to be cellular, tissue, and systemic oxidative stress that exacerbate organ function. This review explores in detail the pathophysiological pathways that put a patient at risk and then effectuate the vicious cycle now recognized as CRS type 1. (J Am Coll Cardiol 2012;60:1031–42) © 2012 by the American College of Cardiology Foundation

Combined disorders of heart and kidney are today classified as cardiorenal syndromes (CRS) (1). The most recent definition includes a variety of conditions, either acute or chronic, where the primary failing organ can be either the heart or the kidney. CRS are thus disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. The current definition has been expanded into 5 subtypes whose etymology reflects the primary and secondary pathology, the time frame, and simultaneous cardiac and renal co-dysfunction secondary to systemic disease. Such advances in the recognition and classification of CRS provide a platform to examine complex organ crosstalk and introduce the possibilities of new prevention, treatment, and recovery strategies (2). It should be mentioned that the temporal sequence of organ dysfunction largely distinguishes type 1 (cardiac first) from type 3 (renal 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 presents with acute decompensated HF (ADHF)

and a mild elevation in serum creatinine or cystatin C at baseline and then develops acute kidney injury (AKI) with the temporary need for dialysis would be classified as type 1 CRS since the HF was the initial, predominant problem and the renal failure ensued.

Type 1 CRS (acute CRS) occurs in approximately 25% to 33% of patients admitted with ADHF, depending on the criteria used, 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. Factors beyond the classic hemodynamic mechanisms appear to play a role in the pathogenesis of renal injury. 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 all been implicated. The complexity of this syndrome presents a key challenge for singular diagnostic or treatment approaches. Considering the possibilities for any given patient, there are 4 subtypes of type 1 CRS: 1) de novo cardiac injury leads to de novo kidney injury; 2) de novo cardiac injury leads to acute-on-chronic kidney injury; 3) acute-on-chronic cardiac decompensation leads to de novo kidney injury; and 4) acute-on-chronic cardiac decompensation leads to acute-on-chronic kidney injury. In this review, we characterize in detail the nature of CRS type 1; we

focus on the various pathophysiological pathways and reconcile mechanistic aspects of organ damage into a comprehensive and holistic approach to understanding this syndrome.

Type 1 CRS is characterized by an acute heart disorder leading to AKI (Fig. 1) and occurs in ~25% of unselected patients admitted with ADHF (5,6). Among these patients, pre-morbid chronic kidney disease (CKD) is common and predisposes to AKI in approximately 60% of cases. AKI is an independent risk factor for 1-year mortality in ADHF patients, including patients with ST-segment elevation myocardial infarction who develop signs and symptoms of HF or have a reduced left ventricular ejection fraction (7). This independent effect

might be due to an associated acceleration in cardiovascular pathobiology due to 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 largely regulated by neurohormonal systems. Specific regulatory and counter-regulatory mechanisms are activated with variable effects, depending on the duration and the intensity of the insult.

Predisposition for Cardiorenal Syndromes

Obesity and cardiometabolic changes. There are a host of predisposing factors that create baseline risk for CRS type 1,
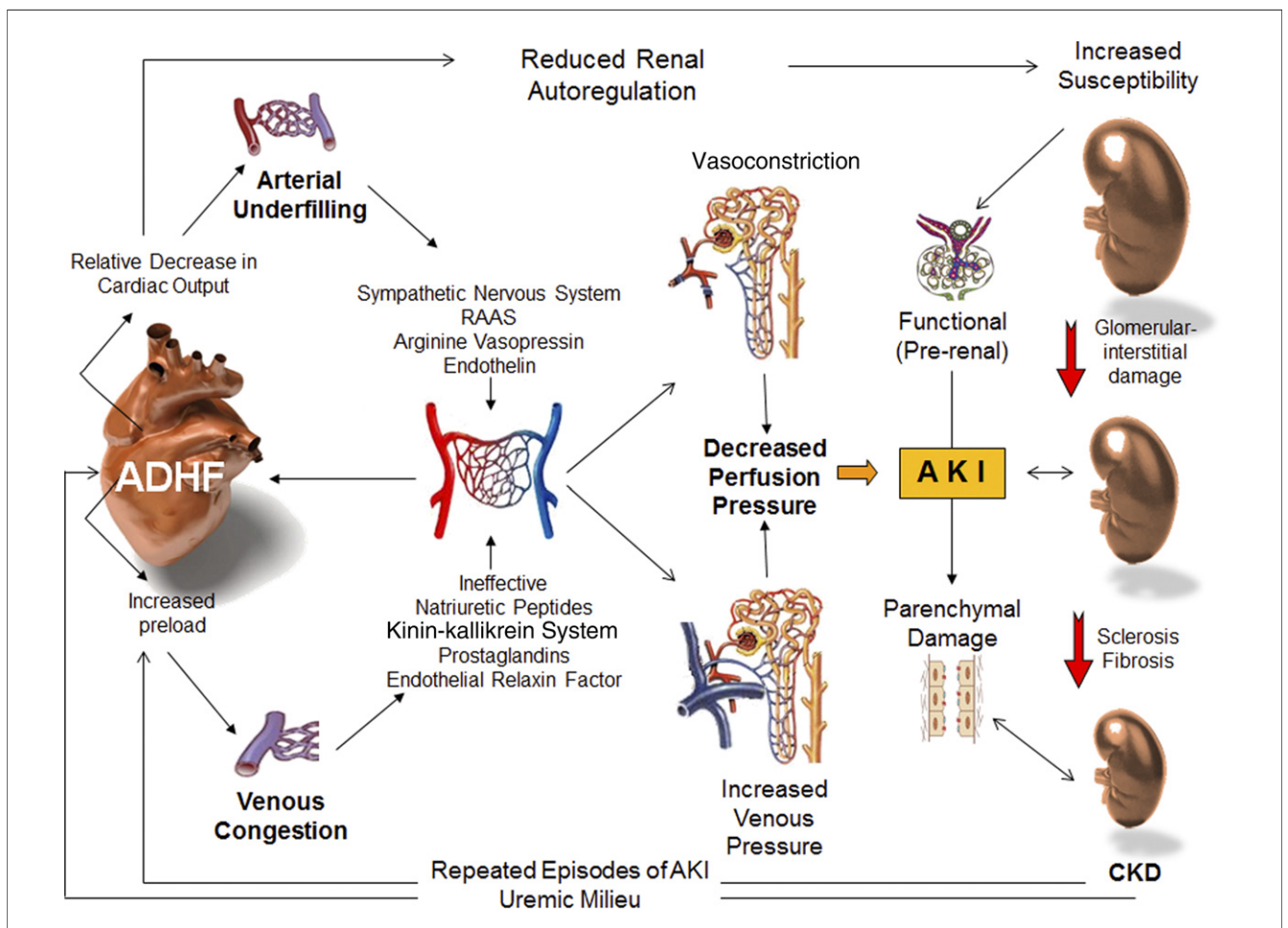
**Figure 1   Pathogenesis of Type 1 CRS**

Acute decompensated heart failure (ADHF) via arterial underfilling and venous congestion sets off a series of changes in neurohormonal and hemodynamic factors that culminate in acute kidney injury (AKI). CKD = chronic kidney disease; CRS = cardiorenal syndrome; RAAS = renin-angiotensin-aldosterone system.

which commonly occurs as an acute-on-chronic disorder as shown in Figure 2. Thus, there are developing obesity-associated epidemics of at least 26 chronic diseases, including type 2 diabetes mellitus (DM), hypertension, obstructive sleep apnea, atrial fibrillation, HF, hyperuricemia, and CKD, all directly or indirectly related to excess adiposity. It has been shown that the number of adipocytes in the human body can increase 10-fold both in number and in size. The adipocytes secrete cytokines, and as a result, these cytokines may cause cardiac and renal injury, as for example interleukin (IL)-6 and tumor necrosis-factor alpha, which are both secreted by adipocytes have been implicated in both heart and kidney disease. 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. Thus, high-sensitivity C-reactive protein levels are highest in obese individuals and fall to a greater extent with weight loss than any other intervention (9,10).

Body mass index, a global measure of excess adiposity, is associated with abnormalities on echocardiography, including left atrial dilation, left ventricular hypertrophy and dilation, and impaired relaxation (11). These findings suggest that changes in the lipid content within cardiomyocytes themselves are playing a role in these pathological 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 type 1 (12,13). In addition, the cardiometabolic syndrome in the absence of frank DM has been associated with 3- to 7-fold increased risk of CRS type 1 in a variety of clinical settings (14).

Cachexia. Opposite to obesity and metabolic syndromes, combined disorders of the heart and kidney are also likely to develop in the presence of some degree of cachexia and sarcopenia and are associated with organ crosstalk via tumor necrosis factor-alpha and other pro-inflammatory cytokines
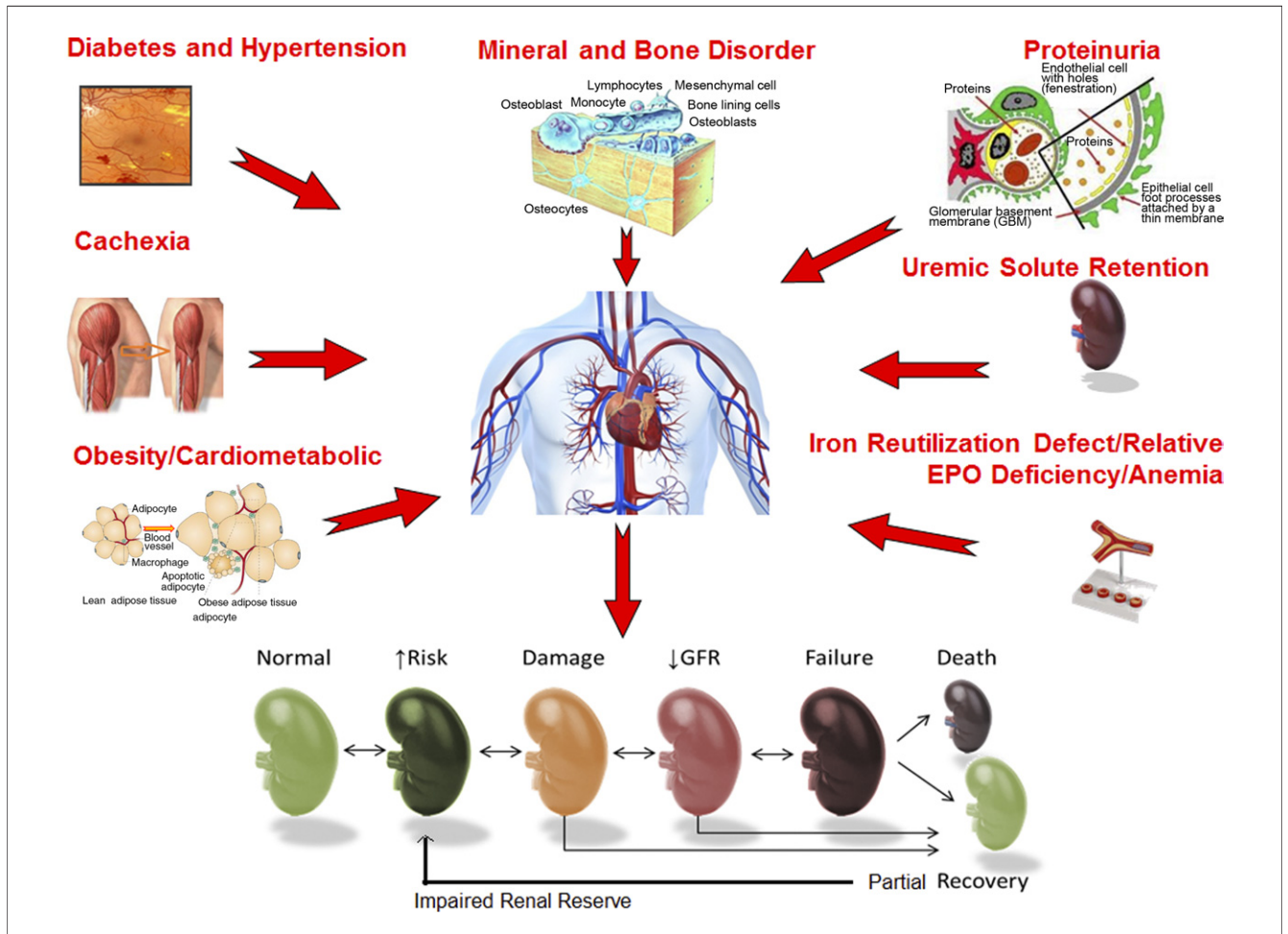
Figure 2   Predisposing Factors for CRS

Obesity and cardiometabolic changes in the cardiovascular system, including diabetes and hypertension, and later in the course of disease, cachexia, biochemical, and hormonal changes due to bone and mineral disorder, proteinuria, uremic solute retention, and anemia, all contribute to the risk for developing cardiorenal syndrome (CRS) type 1. The course of this syndrome can lead to permanent renal failure and need for dialysis or partial renal recovery. EPO = erythropoietin; GFR = glomerular filtration rate.

(15). In these circumstances, a vicious circle could arise, in which cachexia and nutritional deficiencies associated with either HF or CKD may contribute to further damage and fibrosis of the other organ (16,17). Thus, we speculate that the occurrence of chronic CRS and cachexia could be a harbinger of serious complications such as infection or death.

Hypertension and diabetes. Hypertension and type 2 DM account for the majority of CKD and end-stage renal disease in developed countries (18). Lack of blood pressure control is directly related to accelerated loss of nephrons and reductions in glomerular filtration rate (19). 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 and sodium retention, in patients with ADHF has been consistently associated with CRS type 1 (20). 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 <2% of type 1 CRS.

Proteinuria. Endothelial, mesangial, and podocyte injury in the presence of hypertension and DM results in excess quantities of albumin in Bowman's space; thus, 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 has been consistently associated with the risk of AKI in a variety of settings (21). Albuminuria in the general population is predictive of the development of HF, and in those with established HF, it is present in ~30% and associated with hospitalization and mortality (22,23). Microalbuminuria, thus, is a risk marker for cardiovascular disease 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 (24). In addition, uremia directly contributes to accelerated fibrosis and adverse cardiac remodeling after myocardial infarction (25). 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 (26,27). Observational studies of patients with gout and HF have shown that allopurinol is associated with improved outcomes (28). Small randomized trials suggest that lowering uric acid may influence the natural history and symptoms of both CKD and cardiovascular disease (29,30). 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 worsening renal function (31). The pathogenesis of anemia in HF is multifactorial, encompassing hemodilution due to water retention, blockade of normal iron transport, inflammation/cytokine-induced erythropoietin deficiency, and tissue resistance, malnutrition, cachexia, vitamin deficiency, all amplified in the presence of pre-existing CKD (32,33). 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 throughout the body (34). 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 (35). Thus, attempts to control anemia in HF will have to take into consideration blockade of iron transport in the body, and attempts to overcome this problem with supplemental iron, as well as erythropoiesis-stimulating agents such as erythropoietin and darbepoetin. Many studies of anemia in HF with these agents and/or enteric or intravenous iron have shown a positive effect on hospitalization rates, New York Heart Association functional class, cardiac and renal function, quality of life, exercise capacity, and reduced B-type natriuretic peptide levels (36,37). However, long-term exposure of higher-dose erythropoiesis-stimulating agents has been associated 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 (38).

Repeated episodes of subclinical AKI. 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 kidney's ability to alter both 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 ADHF.

Cardiac and Renal Fibrosis

Increased stress or injury to the myocardium, glomeruli, and renal tubular cells, due to uncontrolled hypertension, DM,

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 crosslinked to collagen-generating cardiac and renal fibrosis (41).

Galectin-3 (aka MAC-2 Ag), a regulator of cardiac fibrosis, is one of 14 mammalian galectins and is an ~30-kDa glycoprotein that has a carbohydrate-recognition binding domain of ~130 amino acids that enables the binding of beta-galactosides (42–44). 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 (45). Galectin-3 as a paracrine signal is involved in cell adhesion, activation, chemoattraction, growth and differentiation, cell cycle regulation, and apoptosis in multiple diseases including cancer, liver disease, rheumatological conditions, and CRS (46). In the myocardium and the kidney, angiotensin II and aldosterone are major stimuli 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 (TGFβ) to increase cell cycle (cyclin D1) and direct both the proliferation of pericytes and fibroblasts, and the deposition of procollagen 1 (47). These observations strongly suggest that fibrosis is a critical participant in the pathogenesis and progression of CKD and HF (48). 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 CRS.

The Acute Pathways of CRS Type 1

Hemodynamics and congestion. Registry data have shown that it is the pulmonary congestion that brings the patients to the hospital. In the ADHERE (Acute Decompensated Heart Failure National Registry) registry, 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 of <90 mm Hg (49). The increase in blood pressure is likely a reflection of sodium retention and sympathetic activation. A dysfunctioning left ventricle is particularly sensitive to afterload variations, and therefore, an increase in blood pressure can abruptly worsen 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 (50). 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 (51). 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 ADHF (52). 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 (53). It is commonly observed that coexisting renal dysfunction may complicate the treatment course of HF and that the use of intravenous loop diuretics often alleviate congestion at the cost of worsening renal function within days of hospitalization and is a strong, independent predictor of adverse outcomes (54). Although loop diuretics provide prompt diuresis and relief of congestive symptoms, they provoke a marked activation of the sympathetic and RAAS, resulting 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 Figure 3.

Neurohormonal activation. The RAAS has an important role in the initiation and maintenance of vascular, myocardial, and renal dysfunction leading to edema in HF (55). Increased renin secretion occurs early in biventricular failure, which leads to stimulation of angiotensin II. This 8–amino acid oligopeptide has many physiological 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 promotes cellular hypertrophy, apoptosis, and fibrosis (56). 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 usually occurs 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 (57,58). Aldosterone stimulates macrophages in heart and kidney tissue to secrete galectin-3, which in turn stimulates fibroblasts to secrete procollagen I and III that is crosslinked to collagen, resulting in fibrosis (59). Moreover, patients with biventricular failure may also have poor hepatic perfusion and decreased clearance of aldosterone, thereby contributing to an elevation in the plasma aldosterone concentration (60).
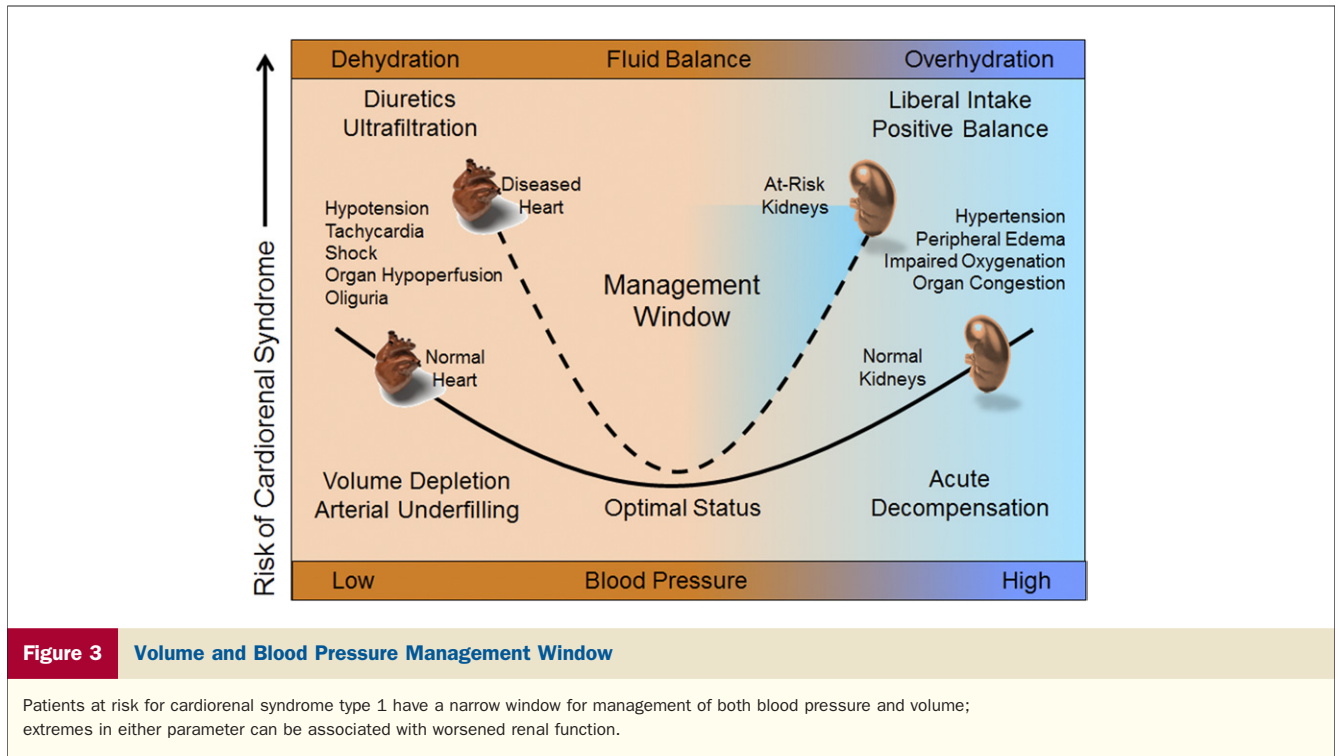
Figure 3   **Volume and Blood Pressure Management Window**

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

As a result of sympathetic activation, catecholamines play a vital role in the pathogenesis and progression of HF (61). It is well known that elevated plasma norepinephrine 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 (62).

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 non-osmotic 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 rapidly cleared from plasma. Arginine vasopressin is derived from a larger precursor peptide (preprovasopressin) 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 levels. 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, while 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 occurs both 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 4 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. (63) showed that in patients with

severe HF, circulating levels of tumor necrosis factor-alpha were much higher than normal. Numerous studies showed activation of inflammation at various levels in HF patients. Further support for the inflammatory etiology of HF came from the demonstration that inflammatory cytokines may also be produced by cardiomyocytes, following ischemic or mechanical stimuli, but also by the innate immune response, represented by Toll-like receptors, pentraxin-like C-reactive protein, and pentraxin 3 (64–69). These findings suggest that in HF, an immune dysregulation may exist; cytokines not only could produce distant organ damage such as AKI, but they 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, tumor necrosis factor-alpha, IL-1, and IL-6 (70–74).

Excessive elevations of cytokines and markers of inflammation have been consistently documented in ADHF (75). Inflammatory activation may have a role in HF by contributing to both vascular dysfunction and fluid overload in the extravascular space (76). The amount of fluid in the pulmonary interstitium and alveoli is tightly controlled 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 (77,78). This mechanism could be a cause for inadequate renal perfusion pressures, peritubular edema, pathological reduction of glomerular filtration, and finally, mixed inflammatory and ischemic tubular damage.

The role of the gut and endotoxemia. Underperfusion of the intestine and the hematogenous release of endotoxin in patients with HF has been proposed as a mechanism for progression of HF and CRS type 1, particularly in patients with cachexia (79). In HF, blood flow is presumably 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 (tumor necrosis factor-alpha, IL-1, and IL-6) can exacerbate myocyte dysfunction (80). They exert their cardiosuppressive effects primarily by altering myocardial intracellular calcium, reducing mitochondrial activity, causing imbalance of autonomic nerve activity, thus affecting many other organs, including the kidneys (81,82). When cardiomyocytes are exposed to lipopolysaccharides, 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, for example, 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 pathological 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 (83). An inflammatory pathogenesis can be a common key feature for both the kidneys and cardiovascular system during sepsis, leading to cell ultrastructural alterations and organ dysfunction. Murugan et al. (84) recently demonstrated that AKI is associated with pneumonia via an inflammatory pathogenesis. In their paper, the outcomes of AKI were adversely associated with IL-6 plasma concentration. Proinflammatory cytokines, such as tumor necrosis factor-alpha, IL-1, and IL-6, induce myocardial dysfunction, cause microcirculatory damage, and contribute to altered tissue perfusion and oxygen delivery/consumption, thus contributing to both heart and kidney failure. Enhanced endothelial expression of leukocyte adhesion molecules and alteration of endothelial cell 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 to 1.2 μm) molecular structure that lies beneath capillary endothelial cells and regulates capillary flow, leukocyte adhesion and migration, platelet adhesion, and coagulation. Glycocalyx disruption due to sepsis and cytokines contributes to increased permeability, both in systemic and renal microcirculation, increasing leukostasis, microthrombosis, fluid shift, and interstitial edema.

Iatrogenesis. Among the mechanisms involved in organ crosstalk between the heart and kidney, we must consider iatrogenesis (Fig. 4). In several clinical conditions, drugs required to treat DM, oncological diseases, infections, HF itself, 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 worsening heart function due to 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, may also be induced by diuretic therapy. Uric acid, as discussed in the preceding text, 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 RAAS (89). Iodinated contrast causes a much different form of AKI characterized by transient vasoconstriction and
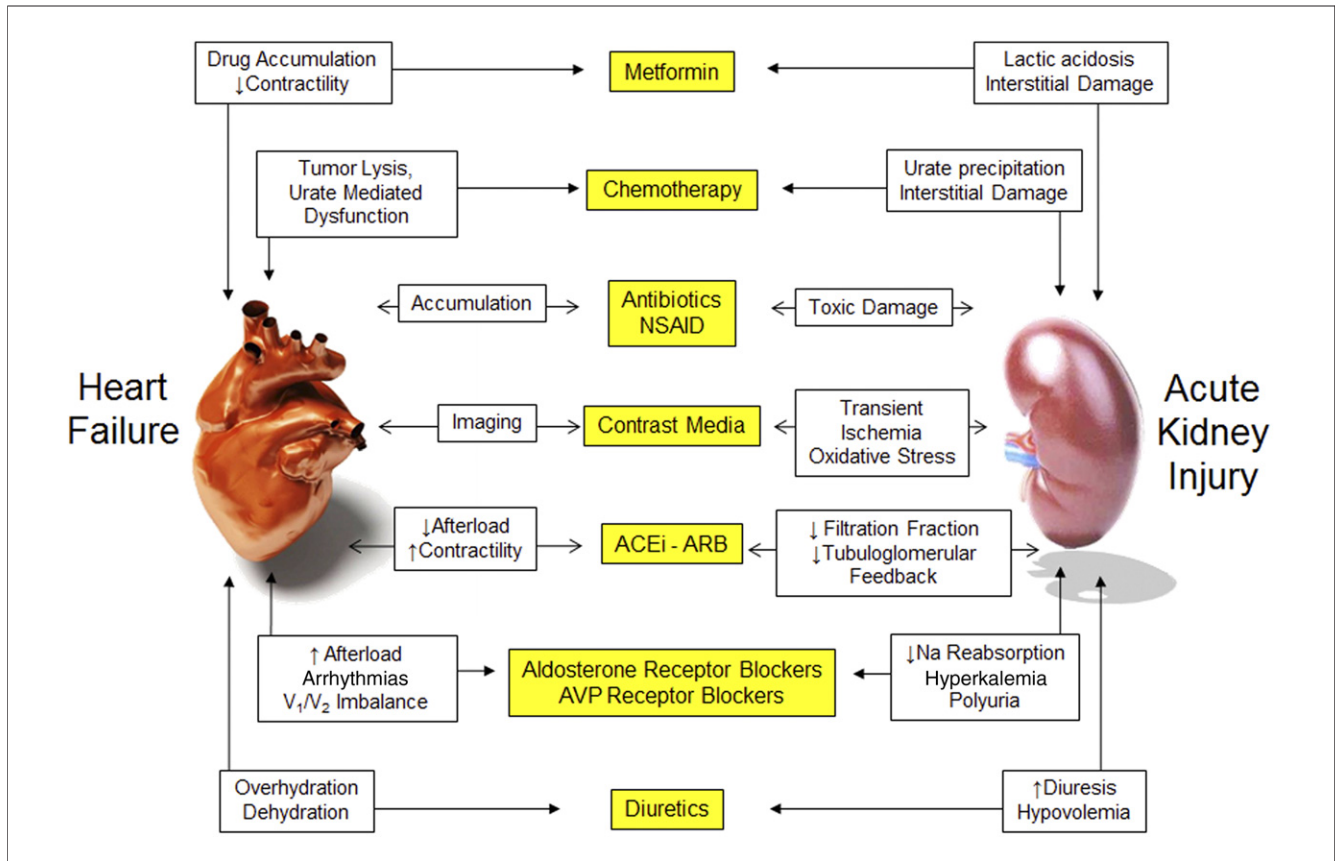
Figure 4   Iatrogenesis and Type 1 CRS

Multiple sources of iatrogenic injury, some of which may be unavoidable, can result in either cardiac, renal, or cardiorenal impairment and kidney damage in patients with acutely decompensated heart failure (ADHF). ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AVP = arginine vasopressin; NSAID = nonsteroidal anti-inflammatory drug.

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 due to 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 [KIM]-1, L-type fatty acid binding protein [LFABP], *N*-acetyl-β-D-glucosaminidase [NAG], and others) serve as both 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 physiological 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 impact tubuloglomerular feedback (95). However, holding these agents, while temporarily causing less creatinine re-

tention 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 glomerular filtration rate is reduced below 45 ml/min, may lead to secondary hyperkalemia. Nonsteroidal inflammatory agents reversibly inhibit cyclooxygenases 1 and 2, impair prostaglandin synthesis, and result in sodium and fluid retention, as well as 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 may then contribute to progressive organ dysfunction (98).

The cornerstone of treatment for ADHF is the use of oral and intravenous loop diuretics. These agents represent a double-edged sword as they 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 ADHF, there is an

overall relationship between increased loop diuretic dosing and mortality (100). Felker et al. (101), in a small randomized trial of ADHF, demonstrated that higher doses and continuous infusions of furosemide resulted in more patients developing AKI (rise in creatine >0.3 mg/dl) with no improvement in hospitalization or death. 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 levels 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: Final Common Pathway of Injury

Oxidative stress is a final common pathway for cellular dysfunction, tissue injury, and organ failure. The mechanisms discussed in the previous text all render both 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 iron, copper, and so on. Since 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 that remains unbound in a fraction has been implicated in both acute ischemic cardiac models 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 both 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 Counter-Regulatory Mechanisms

The regulatory and counter-regulatory 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 (107). Ischemia is also recognized as a stimulus for natriuretic peptide production. Natriuretic peptides, working via natriuretic peptide receptors in the glomerulus and the renal tubules, activate cCMP and reduce sodium reabsorption. When given in supraphysiological doses, B-type natriuretic peptide reduces levels of catecholamines, angiotensin II, and aldosterone (108). However, this counter-regulatory 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 counter-regulatory 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 earlier in the text. 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 counter-regulatory protein has been shown to be a useful diagnostic tool for AKI and is elevated in patients with CRS type 1 (112).

Conclusions

CRS type 1 is an important clinical phenomenon that occurs either de novo or in the setting of pre-existing CKD in which the development of ADHF is complicated by multiple pathophysiological mechanisms. Acute cardiac and renal congestion, neurohormonal activation, dysregulation of immune cell and cytokine signaling, superimposed infection and anemia, and a failure of normal counter-regulatory 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. Future research exploring the mechanisms discussed in this paper, in particular, strategies to distinguish which organ is the primary initiator (type 1 versus type 3 CRS) will likely lead to new diagnostic and therapeutic targets aimed to reduce the incidence and severity of this syndrome.

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Key Words: acute kidney injury ■ cardiorenal syndrome ■ fluid overload ■ heart failure ■ hemodialysis ■ hemofiltration ■ refractory edema ■ oliguria ■ ultrafiltration.