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STATE-OF-THE-ART PAPER

Cardiorenal Syndrome

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The term cardiorenal syndrome (CRS) increasingly has been used without a consistent or well-accepted definition. To include the vast array of interrelated derangements, and to stress the bidirectional nature of heart-kidney interactions, we present a new classification of the CRS with 5 subtypes that reflect the pathophysiology, the time-frame, and the nature of concomitant cardiac and renal dysfunction. CRS can be generally defined as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other. Type 1 CRS reflects an abrupt worsening of cardiac function (e.g., acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury. Type 2 CRS comprises chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive chronic kidney disease. Type 3 CRS consists of an abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac dysfunction (e.g., heart failure, arrhythmia, ischemia). Type 4 CRS describes a state of chronic kidney disease (e.g., chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events. Type 5 CRS reflects a systemic condition (e.g., sepsis) causing both cardiac and renal dysfunction. Biomarkers can contribute to an early diagnosis of CRS and to a timely therapeutic intervention. The use of this classification can help physicians characterize groups of patients, provides the rationale for specific management strategies, and allows the design of future clinical trials with more accurate selection and stratification of the population under investigation. (J Am Coll Cardiol 2008;52:1527–39) © 2008 by the American College of Cardiology Foundation

A large proportion of patients admitted to hospital have various degrees of heart and kidney dysfunction (1). Primary disorders of 1 of these 2 organs often result in secondary dysfunction or injury to the other (2). Such interactions represent the pathophysiological basis for a clinical entity called cardiorenal syndrome (CRS) (3). Although generally defined as a condition characterized by the initiation and/or progression of renal insufficiency secondary to heart failure (4), the term CRS is also used to describe the negative effects of reduced renal function on the heart and circulation (5). The absence of a clear definition and the complexity of this cluster of conditions contribute to lack of clarity with regard to diagnosis and management (6). This is unfortunate, because recent advances in basic and clinical sciences have improved our understanding of organ crosstalk and have demonstrated the efficacy of some therapies in attenuating both cardiac and renal injury (7). Thus, a more articulated definition in terms of clinical presentation, pathophysiology, diagnosis, and management is needed to explore the complex nature of CRS and its different clinical subtypes.

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CRS: A Definition

The simplistic view of CRS is that a relatively normal kidney is dysfunctional because of a diseased heart, with the assumption that, in the presence of a healthy heart, the same kidney would perform normally (8). This concept has been recently challenged, and a more articulated definition of the CRS has been advocated (5). The CRS includes a variety of acute or chronic conditions, where the primary failing organ can be either the heart or the kidney (9).

Previous terminology did not allow physicians to identify and fully characterize the chronology of the pathophysiological interactions that characterize a specific type of combined heart/kidney disorder. A diseased heart has numerous negative effects on kidney function but, at the same time, renal insufficiency can significantly impair cardiac function (9). Thus, direct and indirect effects of each organ that is dysfunctional can initiate and perpetuate the combined disorder of the 2 organs through a complex combination of neurohormonal feedback mechanisms. For this reason, a subdivision of CRS into 5 different subtypes seems to provide a more concise and logically correct approach.

CRS type 1 (acute CRS). Type 1 CRS is characterized by a rapid worsening of cardiac function, leading to acute kidney injury (AKI) (Fig. 1). Acute heart failure (HF) may be divided into 4 subtypes: hypertensive pulmonary edema with preserved left ventricular (LV) systolic function,

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AKI = acute kidney injury
ARB = angiotensin receptor blocker
BNP = B-type natriuretic peptide
CKD = chronic kidney disease
CRS = cardiorenal syndrome
GFR = glomerular filtration rate
HF = heart failure
ICU = intensive care unit
IL = interleukin
LV = left ventricular
NGAL = neutrophil gelatinase-associated lipocalin
TNF = tumor necrosis factor

acutely decompensated chronic HF, cardiogenic shock, and predominant right ventricular failure (10). Type 1 CRS is a common occurrence. More than 1 million patients in the U.S. are admitted to the hospital every year with either de novo acute HF or acutely decompensated chronic HF (11). Among these patients, pre-morbid chronic renal dysfunction is a common occurrence and predisposes them to AKI (12,13). The mechanisms by which the onset of acute HF or acutely decompensated chronic HF leads to AKI are multiple and complex (4) (Fig. 1). The clinical importance of each mechanism is likely to vary from patient to patient (e.g., acute cardiogenic shock vs. hypertensive pulmonary edema) and situation to situation (acute HF secondary to perforation of a mitral valve leaflet from endocarditis vs. worsening right HF secondary to noncompliance with diuretic therapy). In acute HF, AKI appears to be more severe in patients with impaired LV ejection fraction compared with those with preserved LV function, achieving an incidence >70% in patients with cardiogenic shock (14). Furthermore, impaired renal function is consistently found as an independent risk factor for 1-year mortality in acute HF patients, including patients with ST-segment elevation myocardial infarction (15). A plausible reason for this independent effect might be that an acute decline in renal function does not simply act as a marker of illness severity but also carries an associated acceleration in cardiovascular pathobiology through activation of inflammatory pathways (9,16).

In CRS type 1, a salient clinical issue is how the onset of AKI impacts on prognosis and treatment of acute HF. The first clinical principle is that the onset of AKI in this setting implies inadequate renal perfusion until proven otherwise, which should prompt clinicians to consider the diagnosis of a low cardiac output state and/or marked increase in venous pressure leading to kidney congestion through the use of physical examination, ancillary signs, imaging, and laboratory findings.

The second important consequence of type 1 CRS is decreased diuretic responsiveness. In a congestive state, decreased response to diuretics may result from the physiological phenomena of diuretic braking (diminished diuretic effectiveness secondary to postdiuretic sodium retention) (17) and post-diuretic sodium retention (18). In addition, concerns of aggravating AKI by the administration of diuretics at greater doses or in combination also can act as an additional, iatrogenic mechanism. Diuretics are best provided to HF patients with evidence of systemic fluid overload with the goal of achieving a gradual diuresis. Loop diuretics may be titrated according to renal function, systolic blood pressure, and history of chronic diuretic use. High doses may cause tinnitus, and a continuous low-dose diuretic infusion might be more efficient (19).

Measurement of cardiac output (arterial pressure monitoring combined with pulse contour analysis or by Doppler ultrasound) and venous pressure may help ensure adequate and targeted diuretic therapy (20–22) and allow safer navigation through the precarious situation of combined HF and AKI. If diuretic-resistant fluid overload exists despite an optimized cardiac output, removal of isotonic fluid can be achieved by the use of extracorporeal ultrafiltration (23,24).

The presence of AKI with or without concomitant hyperkalemia may also affect patient outcome by inhibiting the prescription of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone inhibitors (drugs that have been shown in large randomized controlled trials to increase survival in the setting of heart failure and myocardial infarction) (25). However, provided there is close monitoring of renal function and potassium levels, the potential benefits of these interventions often outweigh their risks, even in these patients.

The acute administration of beta-blockers in the setting of type 1 CRS generally is not advised. Such therapy should wait until the patient has stabilized physiologically and until concerns about a low output syndrome have been resolved. In some patients, stroke volume cannot be increased, and relative or absolute tachycardia sustains the adequacy of cardiac output. Blockade of such compensatory tachycardia and sympathetic system-dependent inotropic compensation can precipitate cardiogenic shock with associated high mortality (26). Particular concern applies to beta-blockers excreted by the kidney, such as atenolol or sotalol, alone or in combination with calcium antagonists (27). This should not inhibit the slow, careful, titrated administration of beta-blockers later on, once patients are hemodynamically stable.

In patients with kidney dysfunction, undertreatment after myocardial infarction is common (28). Attention should be paid to preserving renal function, perhaps with the same vigor as we attempt to salvage and protect cardiac muscle. Worsening of renal function during admission for ST-segment elevation myocardial infarction is a powerful and independent predictor of in-hospital and 1-year mortality (14,15). In patients who receive percutaneous coronary intervention or cardiac surgery, even a small increase in serum creatinine (>0.3 mg/dl) is associated with increased hospital stay and mortality (29,30). In this context, an increase in creatinine is not simply a marker of illness severity but, rather, it represents the onset of AKI acting as a causative factor for cardiovascular injury acceleration through the activation of neurohormonal, immunological and inflammatory pathways (9,16). No specific kidney-

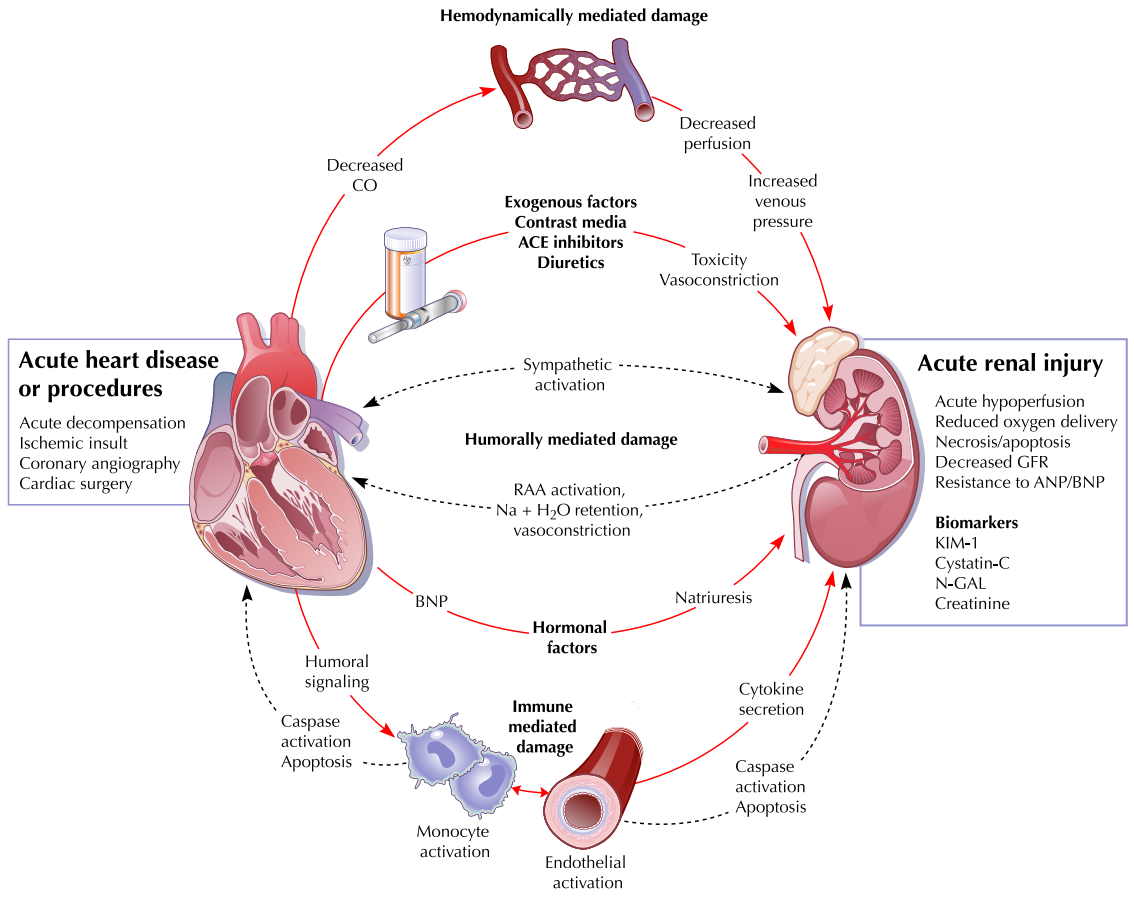

Figure 1 **CRS Type 1**

Pathophysiological interactions between heart and kidney in type 1 cardiorenal syndrome (CRS) or "acute CRS" (abrupt worsening of cardiac function, e.g., acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury. ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CO = cardiac output; GFR = glomerular filtration rate; KIM = kidney injury molecule; N-GAL = neutrophil gelatinase-associated lipocalin; RAA = renin angiotensin aldosterone. Figure illustration by Rob Flewell.

protective treatments have yet emerged for this condition. Despite some initial promising results, the use of nesiritide remains controversial, and a recent negative randomized controlled trial in these very patients (31) suggests that this agent is unlikely to have significant clinical benefit.

A very specific and common threat to kidney function in the setting of acute cardiac disease relates to the administration of radiocontrast for heart imaging procedures. This topic, recently reviewed in the *Journal* (32), would require separate detailed discussion and is beyond the scope of this article. Suffice it to say that this high-risk group requires appropriate prophylaxis to avoid radiocontrast nephropathy. Given that the presence of type 1 CRS defines a population with high mortality, a prompt, careful, systematic, multidisciplinary approach involving cardiologists, nephrologists, critical care physicians, and cardiac surgeons is both logical and desirable.

In CRS type 1, the early diagnosis of AKI remains a challenge (33). This is also true in CRS type 3, where AKI is believed to be the primary inciting factor leading to cardiac dysfunction. In both cases, classic markers such as creatinine increase when AKI is already established and very little can be done to prevent it or to protect the kidney. An interesting evolution in the early diagnosis of CRS has been the discovery of novel AKI biomarkers. With the use of a complementary deoxyribonucleic acid microarray as a screening technique, a subset of genes whose expression is up-regulated within the first few hours after renal injury has been discovered (34,35).

Neutrophil gelatinase-associated lipocalin (NGAL) appears to be one of the earliest markers detected in the blood and urine of humans with AKI (36–39). Urine and serum NGAL are early predictors of AKI both in adult and children either in cardiac surgery or patients in the intensive care unit (ICU) (40,41). In these patients, an increase in creatinine is observed only 48 to 72 h later (42). NGAL is also a biomarker of delayed graft function in kidney transplantation (43), AKI caused by contrast-media (44), and AKI in critically ill patients admitted to intensive care (45).

Cystatin C appears to be a better predictor of glomerular function than serum creatinine in patients with chronic kidney disease (CKD) because its blood levels are not affected by age, gender, race, or muscle mass (46). Cystatin C predicts AKI and the requirement for renal replacement therapy earlier than creatinine (47). Serum cystatin C has been compared with NGAL in cardiac surgery-mediated AKI (48). Both biomarkers predicted AKI at 12 h, although NGAL outperformed cystatin C at earlier time points. Considering them together, they may represent a combination of structural and functional damage of the kidney.

Kidney injury molecule 1 is a protein detectable in the urine after ischemic or nephrotoxic insults to proximal tubular cells (49–51) and seems to be highly specific for ischemic AKI. Combined with NGAL which is highly sensitive, it may represent an important marker in the early phases of AKI.

Biomarkers such as *N*-acetyl-β-(D)glucosaminidase (52), interleukin (IL)-18 (53) and others reported in Table 1 have been proposed as an interesting and promising contribution to diagnosis of AKI and progression of CKD. The most likely evolution will be a "panel" of biomarkers that include several molecules both in serum and urine that combine their best characteristics in terms of specificity and sensitivity of each marker molecule.

CRS type 2 (chronic CRS). Type 2 CRS is characterized by chronic abnormalities in cardiac function (e.g., chronic congestive HF) causing progressive CKD (Fig. 2). Worsening renal function in the context of HF is associated with adverse outcomes and prolonged hospitalizations (32). The prevalence of renal dysfunction in chronic HF has been reported to be approximately 25% (54). Even slight decreases in estimated glomerular filtration rate (GFR) significantly increase mortality risk (54) and are considered a marker of severity of vascular disease (55). Independent predictors of worsening function include old age, hypertension, diabetes mellitus, and acute coronary syndromes.

The mechanisms underlying worsening renal function likely differs based on acute versus chronic HF. Chronic HF is likely to be characterized by a long-term situation of reduced renal perfusion, often predisposed by microvascular and macrovascular disease. Although a greater proportion of patients with low estimated GFR have a worse New York Heart Association functional class, no evidence of association between LV ejection fraction and estimated GFR can be consistently demonstrated. Thus, patients with chronic HF and preserved LV function appear to have similar estimated GFR than patients with impaired LV (ejection fraction <45%) (55).

Table 1 Protein Biomarkers for the Early Detection of Acute Kidney Injury

Biomarker	Associated Injury
Cystatin C	Proximal tubule injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, pre-renal, post-renal AKI
Cytokines (IL-6, IL-8, IL-18)	Toxic, delayed graft function
Actin-actin depolymerizing F	Ischemia and delayed graft function
α-GST	Proximal T injury, acute rejection
π-GST	Distal tubule injury, acute rejection
L-FABP	Ischemia and nephrotoxins
Netrin-1	Ischemia and nephrotoxins, sepsis
Keratin-derived chemokine	Ischemia and delayed graft function

GST = glutathione S-transferase; IL = interleukin; KIM = kidney injury molecule; L-FABP = L-type fatty acid binding protein; NGAL = neutrophil gelatinase-associated lipocalin; NHE = sodium-hydrogen exchanger.

There is very limited understanding of the pathophysiology of renal dysfunction in the setting of even advanced cardiac failure. In this setting, where one would intuitively consider hemodynamic issues to be dominant, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Catheterization Effectiveness) trial (56) found no link between any pulmonary artery catheter-measured hemodynamic variables and serum creatinine in 194 patients. The only link was with right atrial pressure, suggesting that renal congestion may be more important than appreciated. Clearly, hypoperfusion alone cannot explain renal dysfunction in this setting. More work needs to be performed to understand the mechanisms at play to develop targeted and physiologically sound approaches to treatment.

Neurohormonal abnormalities are present with excessive production of vasoconstrictive mediators (epinephrine, angiotensin, endothelin) and altered sensitivity and/or release of endogenous vasodilatory factors (natriuretic peptides, nitric oxide). Pharmacotherapies used in the management of HF may worsen renal function. Diuresis-associated hypovolemia, early introduction of renin-angiotensin-aldosterone system blockade, and drug-induced hypotension have all been suggested as contributing factors (4).

More recently, there has been increasing interest in the pathogenic role of relative or absolute erythropoietin deficiency contributing to a more pronounced anemia in these patients than might be expected for renal failure alone (57). Erythropoietin receptor activation in the heart may protect it from apoptosis, fibrosis, and inflammation (58,59). Preliminary clinical studies show that erythropoiesis-stimulating agents in patients with chronic HF, CKD, and anemia lead to improved cardiac function, reduction in LV size, and the lowering of B-type natriuretic peptide (BNP) (60). Patients with type 2 CRS are more likely to receive loop diuretics and vasodilators and also to receive greater doses of such drugs compared with those patients with stable renal function (61). Treatment with these drugs may participate in the development and progression of renal injury. However, such therapies may simply identify patients with severe hemodynamic compromise and, thus, a predisposition to renal dysfunction rather than being responsible for worsening function.

Renal insufficiency is highly prevalent among patients with HF and is an independent negative prognostic factor in both diastolic and systolic ventricular dysfunction and severe HF (62). The logical practical implications of the plethora

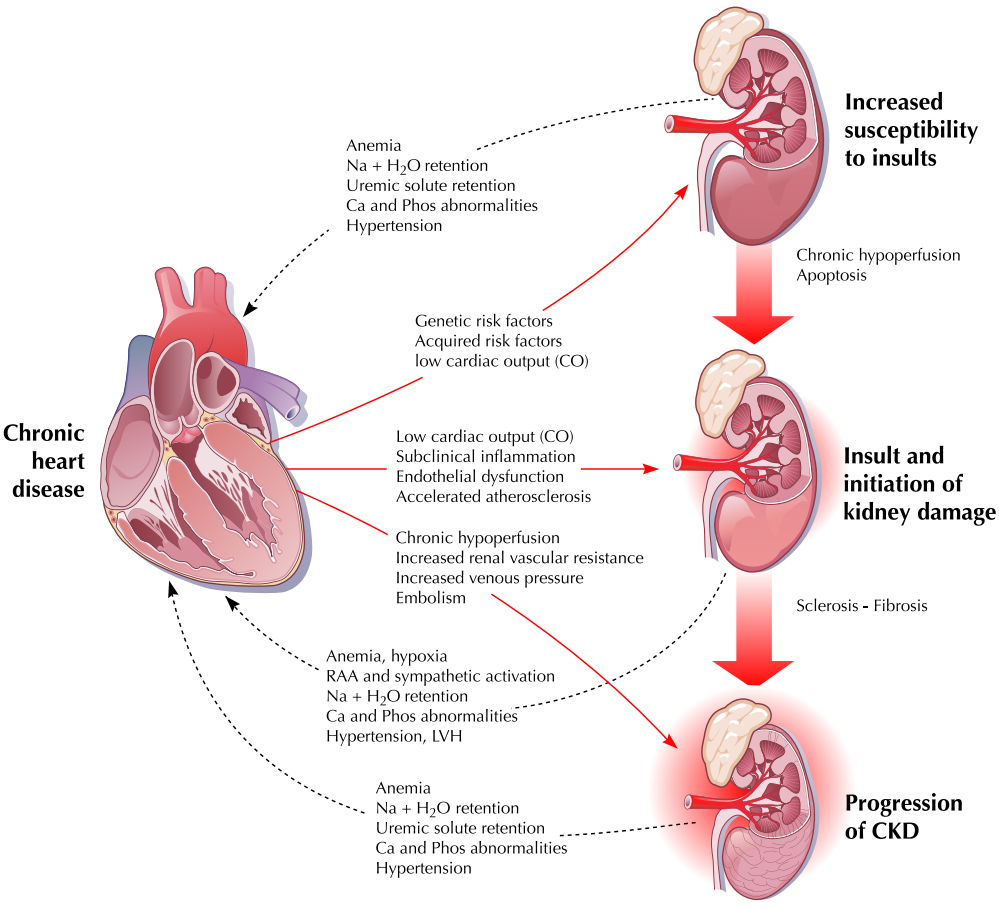

Figure 2 **CRS Type 2**

Pathophysiological interactions between heart and kidney in type 2 cardiorenal syndrome (CRS) or "chronic CRS" (chronic abnormalities in cardiac function, e.g., chronic heart failure) causing progressive chronic kidney disease (CKD). Figure illustration by Rob Flewell. LVH = left ventricular hypertrophy; RAA = renin angiotensin aldosterone.

of data linking CKD with cardiovascular disease are that more attention needs to be paid to reducing risk factors and optimizing medications in these patients and that undertreatment due to concerns about pharmacodynamics in this setting may have lethal consequences at an individual level and huge potential adverse consequences at a public health level. Nonetheless, it is equally important to acknowledge that clinicians looking after these patients often are faced with competing therapeutic choices and that, with the exception of MERIT-HF (Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure) (63), large randomized controlled trials that have shaped the treatment of chronic HF in the last 2 decades have consistently excluded patients with significant renal disease. More on the use of specific agents is covered in the sections on type 3 and 4 CRS.

CRS type 3 (acute renocardiac syndrome). Type 3 CRS is characterized by an abrupt and primary worsening of kidney function (e.g., AKI, ischemia, or glomerulonephritis), leading to acute cardiac dysfunction (e.g., HF, arrhythmia, ischemia). Type 3 CRS appears less common than type 1 CRS, but this may only be due to the fact that, unlike type 1 CRS, it has not been systematically studied. AKI is a growing disorder in hospital and ICU patients. When the RIFLE (risk, injury, and failure; loss; and end-stage kidney disease) consensus definition is used, AKI has been identified in close to 9% of hospital patients (64). In a large ICU database, AKI was observed in more than 35% of patients (65). Acute kidney injury can affect the heart through several pathways (Fig. 3), whose hierarchy is not yet established. Fluid overload can contribute to the development of pulmonary edema. Hyperkalemia can contribute to arrhythmias and may cause cardiac arrest. Untreated uremia affects myocardial contractility through the accumulation of myocardial depressant factors (66) and pericarditis (67). Acidemia produces pulmonary vasoconstriction (68), which can significantly contribute to right-sided HF. Acidemia appears to have a negative inotropic effect (69) and might, together with electrolyte imbalances, contribute to an increased risk of arrhythmias (70). Finally, renal ischemia

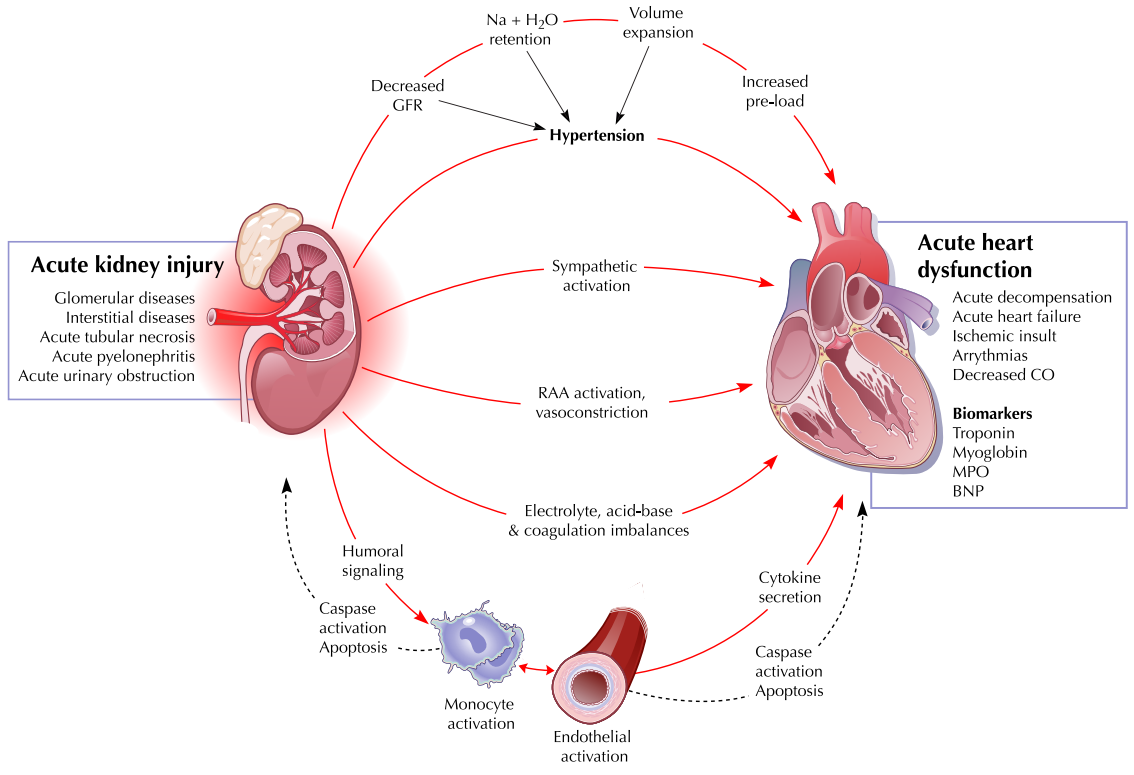

Figure 3 **CRS Type 3**

Pathophysiological interactions between heart and kidney in type 3 CRS or "acute renocardiac syndrome" (abrupt worsening of renal function, e.g., acute kidney failure or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, pulmonary edema). MPO = myeloperoxidase; other abbreviations as in Figure 1. Figure illustration by Rob Flewell.

itself may precipitate activation of inflammation and apoptosis at cardiac level (9).

A unique situation leading to type 3 CRS is bilateral renal artery stenosis (or unilateral stenosis in a solitary kidney). Patients with this condition may be prone to acute or decompensated HF because of diastolic dysfunction related to chronic increase of blood pressure from excessive activation of the renin-angiotensin-aldosterone axis, renal dysfunction with sodium and water retention, and acute myocardial ischemia from an increase in myocardial oxygen demand related to intense peripheral vasoconstriction (71,72). In these patients, angiotensin blockade is generally required to manage the hypertension and HF. However, the GFR is highly dependent upon angiotensin and significant decompensation of kidney function may ensue. Although the management of these unusual patients has not been subject to scrutiny in large randomized trials, those exhibiting renal decompensation with ACE inhibition or ARB are likely candidates for renal revascularization (72).

Sensitive and specific biomarkers of cardiac injury may help physicians to diagnose and treat type 3 CRS earlier and perhaps more effectively (73). Cardiac troponins are biomarkers for ischemic myocardial injury (74,75), and they correlate with outcomes in the general population and specifically in renal patients (76–78). A marker of myocyte stress is BNP and allows the diagnosis of acute and acutely decompensated chronic HF (79). It also is an independent predictor of cardiovascular events and overall mortality in the general population (80,81) and also in patients with renal insufficiency (82–84). In HF, despite high levels of serum BNP, its physiological effects (vasodilatory, diuretic, and natriuretic) do not appear sufficient to prevent the disease progression and CRS. Recent findings suggest a resistance to BNP (85) and/or a relative preponderance of the biologically inactive precursor of BNP (86). In CRS type 4 (discussed in the following text), an association between increased levels of BNP and the accelerated progression of nondiabetic CKD to end-stage kidney disease has been observed (87).

Myeloperoxidase is a marker of altered myocyte metabolism, oxidative stress, and inflammation, especially in acute coronary syndrome (88). Oxidative stress may cause myocyte apoptosis and necrosis, and it is associated with arrhythmias and endothelial dysfunction with a potential role in the pathogenesis of CRS (89). Cytokines such as tumor necrosis factor (TNF), IL-1, and IL-6 may have a diagnostic role as early biomarkers of CRS, but also a pathogenic role causing myocardial cell

injury and apoptosis (90,91) and mediating myocardial damage in ischemic AKI (92).

The development of AKI can affect the use of medications normally prescribed in patients with chronic HF. For example, an increase in serum creatinine from 1.5 mg/dl (130 μmol/l) to 2 mg/dl (177 μmol/l), with diuretic therapy and ACE inhibitors, may provoke some clinicians to decrease or even stop diuretic prescription; they may also decrease or even temporarily stop ACE inhibitors. This may, in some cases, lead to acute decompensation of HF. It should be remembered that ACE inhibitors do not damage the kidney but rather modify intrarenal hemodynamics and reduce filtration fraction. They protect the kidney by reducing pathological hyperfiltration. Unless renal function fails to stabilize, or other dangerous situations arise (i.e., hypotension, hyperkalemia) continued treatment with ACE inhibitors and ARBs may be feasible.

Finally, if AKI is severe and renal replacement therapy is necessary, cardiovascular instability generated by rapid fluid and electrolyte shifts secondary to conventional dialysis can induce hypotension, arrhythmias, and myocardial ischemia (93). Continuous techniques of renal replacement, which minimize such cardiovascular instability, appear physiologically safer and more logical in this setting (94).

CRS type 4 (chronic renocardiac syndrome). Type 4 CRS is characterized by a condition of primary CKD (e.g., chronic glomerular disease) contributing to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events (Fig. 4). Today, CKD is divided into 5 stages based on a combination of severity of kidney damage and GFR (95). When these criteria are used, current estimates of CKD account for at least 11% of the U.S. adult population (96), thus becoming a major public health problem. In fact CKD today includes individuals with serum creatinine levels previously dismissed as not representative of significant renal dysfunction.

Individuals with CKD are at extremely high cardiovascular risk (97). More than 50% of deaths in CKD stage 5 cohorts are attributed to cardiovascular disease. The 2-year mortality rate after myocardial infarction in patients with CKD stage 5 is estimated to be 50% (98). In comparison, the 10-year mortality rate post-infarct for the general population is 25%. Patients with CKD have between a 10- and 20-fold increased risk of cardiac death compared with age-/gender-matched control subjects without CKD (98–100). Part of this problem may be related to the fact that such individuals are also less likely to receive risk-modifying interventions compared to their non-CKD counterparts (101).

Less severe forms of CKD also may be associated with significant cardiovascular risk. Evidence for increasing cardiovascular disease morbidity and mortality tracking with mild-to-moderate renal dysfunction (stages 1 to 3) has mainly stemmed from community-based studies (102–105). These studies documented an inverse relationship between renal function and adverse cardiovascular outcomes (consistently occurring at estimated GFR levels <60 ml/min/1.73 m^2).

Among high-risk cohorts, baseline creatinine clearance is a significant and independent predictor of short-term outcomes, namely death and myocardial infarction (99). Similar findings also were noted among patients presenting with ST-segment elevation myocardial infarction (106), an effect independent of the Thrombolysis In Myocardial Infarction risk score (107).

In large-scale studies (e.g., SOLVD [Studies Of Left Ventricular Dysfunction], TRACE [Trandolapril Cardiac Evaluation], SAVE [Survival And Ventricular Enlargement], and VALIANT [Valsartan in Acute Myocardial Infarction]) in which the authors excluded individuals with baseline serum creatinine of ≥ 2.5 mg/dl, reduced renal function was associated with significantly greater mortality and adverse cardiovascular event rates (108–111).

Adverse cardiovascular outcomes in renal patients are associated with plasma levels of specific biomarkers (112–114). Troponins, asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, natriuretic peptides, C-reactive protein, serum amyloid A protein, hemoglobin, and ischemia-modified albumin are biomarkers whose levels correlate with cardiovascular outcomes in patients with CKD (115–117). These observations provide a mechanistic link between chronic inflammation (118), subclinical infections (119), accelerated atherosclerosis, heart–kidney interactions, and negative cardiovascular and renal outcomes.

The proportion of individuals with CKD receiving appropriate cardiovascular risk modification treatment is lower than in the general population. This "therapeutic nihilism" (120) is based on the concern of worsening kidney function (121,122) and leads to treating $<50\%$ of patients with CKD with the combination of aspirin, beta-blockers, ACE inhibitors, and statins (123). In a cohort involving $>140{,}000$ patients, 1,025 with documented CKD were less likely to receive aspirin, beta-blockade, or ACE inhibition after infarction than patients without CKD. Yet CKD patients had 30-day mortality risk reductions similar to non-CKD patients when receiving the drug combination (123).

Potential reasons for this subtherapeutic performance include concerns about further worsening of renal function, and/or therapy-related toxic effects due to low clearance rates (124,125). Many medications necessary for management of complications of advanced CKD generally are considered safe with concomitant cardiac disease. These include regimens for calcium-phosphate balance and hyperparathyroidism, vitamins, and erythropoiesis-stimulating agents (126–129). The same appears to hold true for novel regimens, for instance, endothelin system antagonists, adenosine and vasopressin receptor antagonists, and inflammation suppressors (130–133). For immunosuppressive drugs, controversy exists regarding the effects of certain agents on the heart, indicating a need for more research in the area (134).

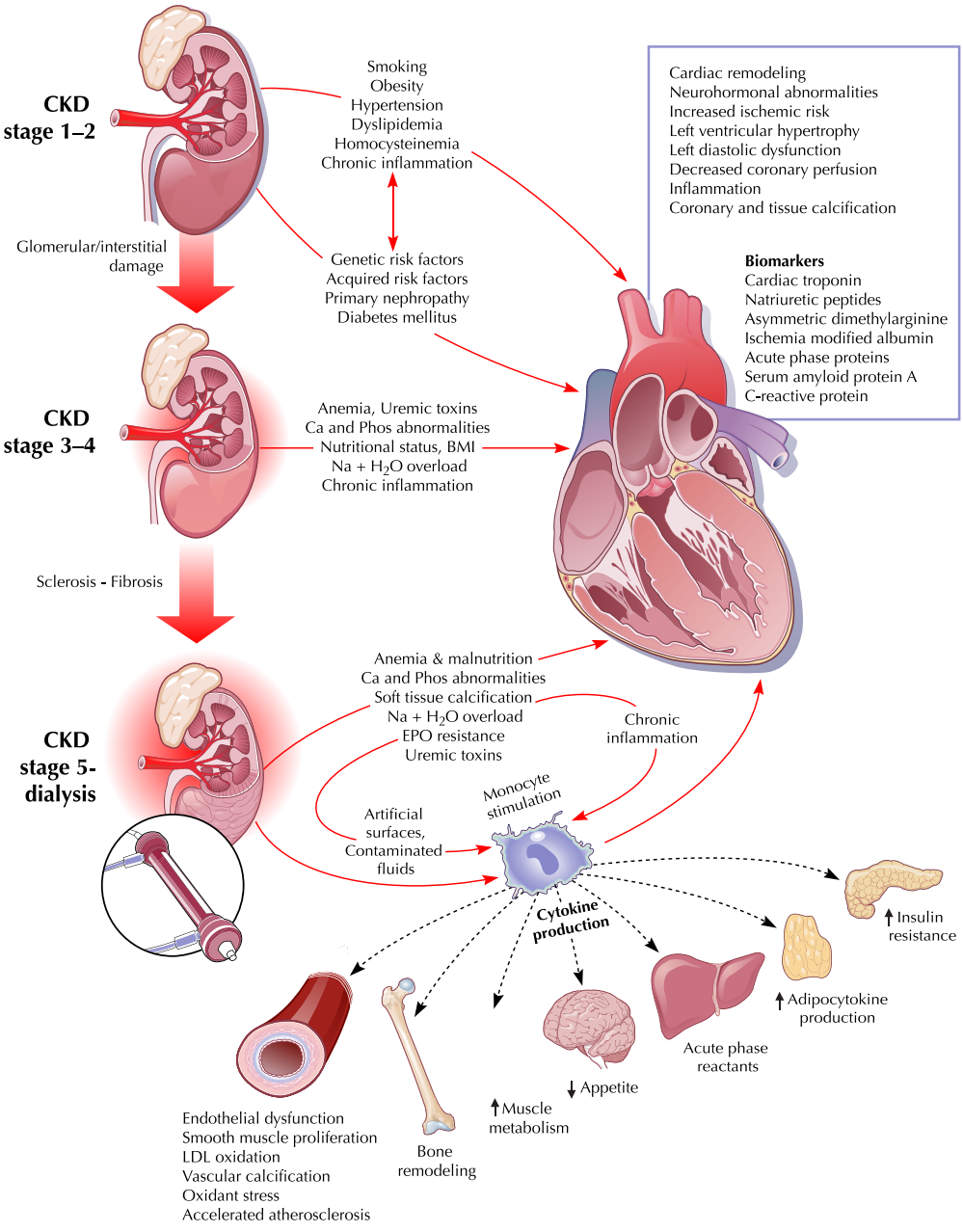

Figure 4 **CRS Type 4**

Pathophysiological interactions between heart and kidney in type 4 cardiorenal syndrome (CRS) or "chronic renocardiac syndrome" (chronic kidney disease [CKD], e.g., chronic glomerular disease, contributing to decreased cardiac function, cardiac hypertrophy, or increased risk of adverse cardiovascular events). BMI = body mass index; EPO = erythropoietin; LDL = low-density lipoprotein. Figure illustration by Rob Flewell.

Bleeding concerns contribute to the decreased likelihood of patients with severe CKD receiving aspirin and/or clopidogrel despite the minor bleeding risk and benefits that are sustained in these patients (135). Other medications requiring thorough considerations of pros and cons include diuretics, digitalis, calcium-channel blockers, and nesiritide (136–141). Nevertheless, when appropriately titrated and monitored, cardiovascular medications can be safely administered to CKD patients with benefits similar to the general population (142).

Lack of CKD population-specific treatment effect data makes therapeutic choices particularly challenging. In particular, in patients with advanced CKD, the initiation or increased dosage of ACE inhibitors or ARBs can precipitate clinically significant worsening of renal function or marked hyperkalemia. The latter may be dangerously exacerbated by the use of

aldosterone antagonists. Such patients, if aggressively treated, become exposed to a significant risk of developing dialysis dependence or life-threatening hyperkalemic arrhythmias. Yet, if too cautiously treated, they may develop equally life-threatening cardiovascular complications.

It is comforting to note that up to a 30% increase in creatinine that stabilizes within 2 months was actually associated with long-term nephroprotection in a systematic review of 12 randomized controlled studies (143). This result leads to the practical advice that ACE inhibitors and ARBs can be cautiously used in patients with CKD, provided the serum creatinine does not increase beyond this amount and potassium remains consistently <5.6 mmol/l. Regarding patients with end-stage renal disease, and in particular those with anuria and a tendency to hyperkalemia interdialytically, the administration of ACE inhibitors or ARBs may be problematic; however, even the combination of these medications has been used safely in select populations (144). At present, most end-stage kidney disease patients with LV dysfunction seem to be undertreated with ACE inhibitors or ARBs (145).

With respect to aldosterone blockade, drugs such as spironolactone have been widely used for severe HF patients with evidence of beneficial effects on morbidity and mortality (146). Concerns have been raised, however, about the use of aldosterone blockade, particularly in conjunction with angiotensin blockade, since after publication of RALES (Randomized Aldactone Evaluation Study) (146), prescriptions for spironolactone and rates of hospitalizations and mortality related to hyperkalemia increased sharply (147). Proper patient selection, including patients with diminished LV ejection fraction and excluding ones with moderate CKD (creatinine level ≥2.5 mg/dl) or hyperkalemia >5 mmol/l, would help minimize potential life-threatening hyperkalemia (140).

CRS type 5 (secondary CRS). Type 5 CRS is characterized by the presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders (Fig. 5). There is limited systematic information on type 5 CRS, although there is an appreciation that as more organs fail in this setting, mortality increases. There is limited insight into how combined renal and cardiovascular failure may differentially affect such an outcome com-

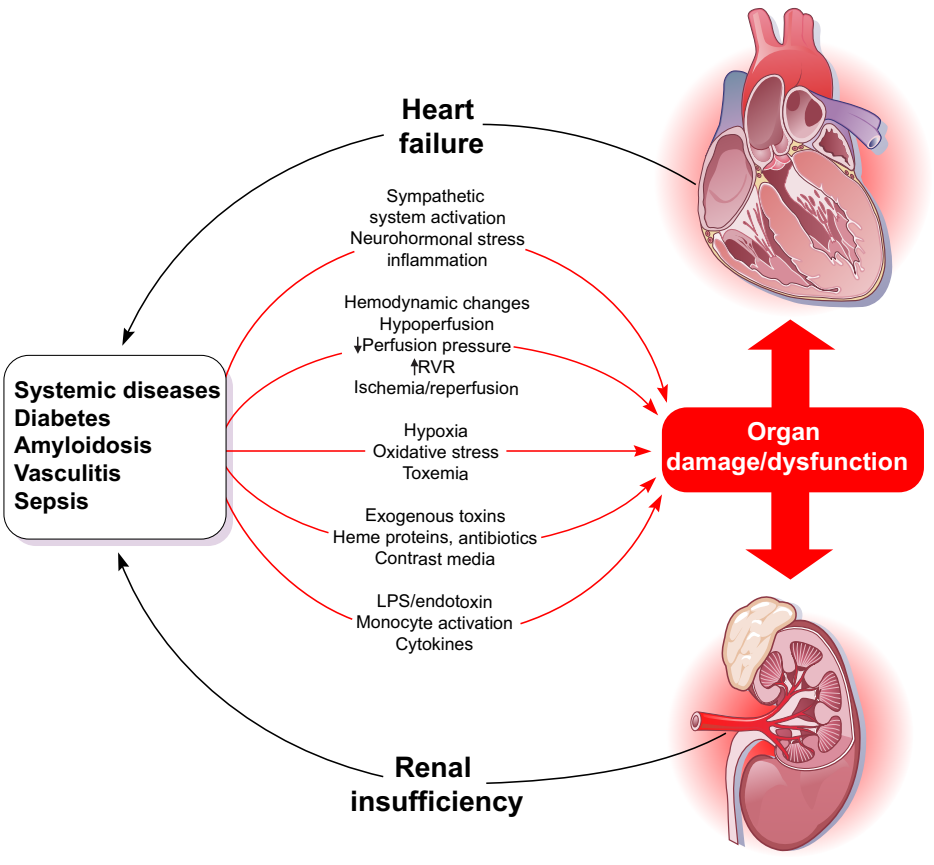

Figure 5 CRS Type 5

Pathophysiological interactions between heart and kidney in type 5 cardiorenal syndrome (CRS) or "secondary CRS" (systemic condition, e.g., diabetes mellitus, sepsis, causing both cardiac and renal dysfunction). LPS = lipopolysaccharide (endotoxin); RVR = renal vascular resistance. Figure illustration by Rob Flewell.

pared to, for example, combined pulmonary and renal failure. Nonetheless, it is clear that several acute and chronic diseases can affect both organs simultaneously and that the disease induced in one can affect the other and vice versa. Examples include sepsis, diabetes, amyloidosis, systemic lupus erythematosus, and sarcoidosis. Several chronic conditions such as diabetes and hypertension may contribute to type 2 and 4 CRS.

In the acute setting, severe sepsis represents the most common and serious condition which can affect both organs. It can induce AKI while leading to profound myocardial depression. The mechanisms responsible for such changes are poorly understood but may involve the effect of TNF and other mediators on both organs (148,149). The onset of myocardial functional depression and a state of inadequate cardiac output can further decrease renal function as discussed in type 1 CRS, and the development of AKI can affect cardiac function as described in type 3 CRS. Renal ischemia may then induce further myocardial injury (9) in a vicious cycle, which is injurious to both organs. Treatment is directed at the prompt identification, eradication, and treatment of the source of infection while supporting organ function with invasively guided fluid resuscitation in addition to inotropic and vasopressor drug support.

In this setting, all the principles discussed for type 1 and 3 CRS apply. In these septic patients, preliminary data derived from the use of more intensive renal replacement technology suggest that blood purification may have a role in improving myocardial performance while providing optimal small solute clearance (150). Despite the emergence of consensus definitions (151) and many studies (152,153), no therapies have yet emerged to prevent or attenuate AKI in critically ill patients. However, evidence of the injurious effects of pentastarch fluid resuscitation in septic AKI recently has emerged (154). Such therapy should, therefore, be avoided in septic patients.

Conclusions

In both chronic and acute situations, an appreciation of the interaction between heart and kidney during dysfunction of each or both organs has practical clinical implications. The depth of knowledge and complexity of care necessary to offer best therapy to these patients demands a multidisciplinary approach, combining the expertise of cardiology, nephrology, and critical care. In addition, achievement of a consensus definition for each type of cardiorenal syndrome will allow physicians to describe treatments and interventions that are focused and pathophysiologically sound. It will also help to conduct and compare epidemiological studies in different countries and more easily identify aspects of each syndrome. This is a priority for improvement and further research. Randomized controlled trials can then be designed to target interventions aimed at decreasing morbidity and mortality in these increasingly common conditions. Developing awareness, the ability to identify and define, and physiological understanding will help improve the outcome of these complex patients.

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