INTRODUCTION

The definition of cardiorenal syndrome (CRS) includes a variety of acute or chronic conditions, in which the primary failing organ can be the heart, the kidney, or both (due to an independent systemic condition), and how dysfunction of one organ system affects injury to or function of the other organ system.¹⁻³ The Cardiovascular-Renal Axis Disorders (CvRDs) Consensus Group proposed that CvRDs are defined as

KEY POINTS

- An increased ability to identify and understand the pathophysiological characteristics of the kidney and the cardiovascular system and their interactions is needed.
- Novel cardiac and renal biomarkers and advanced imaging are crucial for early detection and premature diagnosis and therapy.
- Worsening renal function in the context of a clinical maneuvers (eg, starting diuretic therapy) may not be detrimental in the long-term, and treatment of the congestion/patient is associated with better outcomes.
- A cardiorenal panel that includes more sensitive renal and cardiac biomarkers and requires a blood and urine sample may substitute the current laboratorial assessment of the kidney and heart.
- A multidisciplinary evaluation including the expertise of cardiologists and nephrologists may benefit the management of cardiorenal patients.

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disease-induced, toxin-induced, or drug-induced structural and/or functional damage to the kidney or to the cardiovascular system leading to disruption of the normal interactions between these systems, to the ongoing detriment of one or both.  

CLASSIFICATION

The human CRS classification and the cardiovascular renal-axis disorders consensus classification are conceptually similar and overlap in many respects, because they both describe the primary insult, sequence of events, and chronicity of the process; but they disregard the pathophysiology and therapeutic management.

For the human CRS classification, 5 subtypes have been suggested to simplify the identification in the clinical setting. An equivalent 5 subtypes are suggested for the veterinary CvRD classification by the consensus group, and both are described in the following sections and summarized in Table 1.

**Type 1 Cardiorenal Syndrome (Acute Cardiorenal Syndrome) or Cardiovascular-Renal Axis Disorder**

Type 1 CRS (Acute Cardiorenal Syndrome) or CvRD$_H$ (U: unstable disease) is characterized by a rapid impairment of the cardiac function leading to acute kidney injury/dysfunction. There are multiple and complex mechanisms by which acute heart failure or an acute onset of chronic heart failure leads to acute kidney injury (AKI). Acute kidney injury can result from reduced renal perfusion secondary to decreased left systolic function, neuroendocrine and sympathetic systems activation, and passive congestion of the kidney. The congestive state can induce decreased diuretic responsiveness, which can lead to excessive use of diuretics and further kidney injury. Early recognition of AKI remains a challenge due to the lack of biomarkers for early International Renal Interest Society (IRIS) AKI Grades. Serum creatinine and blood urea nitrogen (BUN) have been the classic markers for AKI, but when the concentrations of these markers are detectably elevated, the injury process typically is well established.

<table>
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<tr>
<th>Type of Cardiorenal Syndrome (Human Classification)</th>
<th>CvRD Consensus</th>
<th>Brief Definition</th>
<th>Conditions</th>
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<tr>
<td>Type 1: Acute cardiorenal syndrome</td>
<td>CvRD$_H$ unstable</td>
<td>Acute impairment of the cardiac function leading to acute kidney injury (AKI)</td>
<td>Acute heart failure, Cardiogenic shock</td>
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<td>Type 2: Chronic cardiorenal syndrome</td>
<td>CvRD$_H$ stable</td>
<td>Chronic cardiovascular disease causing progressive chronic kidney disease (CKD)</td>
<td>Chronic heart failure “Congestive nephropathy”</td>
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<tr>
<td>Type 3: Acute renocardiac syndrome</td>
<td>CvRD$_K$ unstable</td>
<td>Acute primary worsening of kidney function that leads to cardiac dysfunction</td>
<td>AKI, Hyperkalemia, uremia</td>
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<td>Type 4: Chronic renocardiac syndrome</td>
<td>CvRD$_K$ stable</td>
<td>Primary CKD that contributes to cardiac dysfunction</td>
<td>Chronic glomerular disease, anemia, systemic hypertension</td>
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<tr>
<td>Type 5: Secondary cardiorenal syndrome</td>
<td>CvRD$_O$</td>
<td>Cardiac and renal dysfunction secondary to an acute or chronic systemic condition</td>
<td>Diabetes mellitus, Sepsis</td>
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Abbreviation: CvRD, cardiovascular-renal axis disorders.
and it is often too late to protect the kidneys or prevent progressive damage. The discovery and validation of novel biomarkers of kidney injury or dysfunction, such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C and B, symmetric dimethylarginine (SDMA), serum inosine, serum and urinary clusterin, and others, may allow an earlier recognition of AKI and CRS.\textsuperscript{10,11}

**Type 2 Cardiorenal Syndrome (Chronic Cardiorenal Syndrome) or Cardiovascular-Renal Axis Disorder\textsubscript{H} (Stable Disease)**

Type 2 CRS (Chronic Cardiorenal Syndrome) or CvRD\textsubscript{H} (S: stable disease) consists of chronic cardiovascular disease causing progressive chronic kidney disease (CKD).\textsuperscript{2–5} Chronic heart failure is likely to cause persistently reduced renal perfusion, chronic renal congestion (“congestive kidney failure” or “congestive nephropathy”), and neurohormonal changes associated with chronic sympathetic stimulation (production of epinephrine, angiotensin, endothelin, and release of natriuretic peptides and nitric oxide).\textsuperscript{12,13} Therapy for congestive heart failure (CHF) using diuretics and renin-angiotensin-aldosterone system (RAAS) blocking agents can cause drug-induced hypovolemia and hypotension, and changes in intrarenal hemodynamics.\textsuperscript{6} In humans, the prevalence of renal dysfunction in CHF is high and constitutes an independent predictor of outcomes and mortality; therefore, it is of the upmost importance to preserve the renal function in these patients.\textsuperscript{14}

**Type 3 Cardiorenal Syndrome (Acute Renocardiac Syndrome) or Cardiovascular-Renal Axis Disorder\textsubscript{K} (U)**

Type 3 CRS (Acute Renocardiac Syndrome) or CvRD\textsubscript{K} (U) is characterized by an acute primary worsening of kidney function that leads to acute cardiac dysfunction. AKI can affect cardiac function through multiple mechanisms, such as fluid overload, electrolyte disturbances, neurohormonal activation, and myocardial depressant factors, potentially contributing to the development of arrhythmias, pericarditis, and acute heart failure.\textsuperscript{15,16} Diagnosis of AKI in patients concurrently treated for heart failure may force clinicians to reduce the dose or discontinue heart failure medications, further decompensating the cardiovascular system to prevent additional kidney injury.

**Type 4 Cardiorenal Syndrome (Chronic Renocardiac Syndrome) or Cardiovascular-Renal Axis Disorder\textsubscript{K} (S)**

Type 4 CRS (Chronic Renocardiac Syndrome) or CvRD\textsubscript{K} (S) reflects primary CKD that contributes to secondary cardiac dysfunction. Decreased systolic function, left ventricular hypertrophy, and a high output state (secondary to anemia) are some of the potential long-term cardiac sequelae of CKD.\textsuperscript{5} The medical management of CKD and concurrent CHF is not as problematic as the acute forms of these conditions, but some forms of CHF are likely undertreated, due to concerns of further worsening kidney function and creating a vicious cycle of bidirectional damage secondary to the specific pathophysiology and pharmacotherapy of both conditions.

**Type 5 Cardiorenal Syndrome (Secondary Cardiorenal Syndrome) or Cardiovascular-Renal Axis Disorder\textsubscript{O}**

Type 5 CRS (Secondary Cardiorenal Syndrome) or CvRD\textsubscript{O} is characterized by cardiac and kidney dysfunction secondary to an independent acute or chronic systemic condition. Sepsis is the most common acute condition that affects both the heart and the kidney.\textsuperscript{4,17,18} Pancreatitis and hyperadrenocorticism are typical chronic diseases in dogs that have a similar effect on the urinary and cardiovascular systems.\textsuperscript{19–21}
To appropriately characterize patients with CRS, they have to be staged independently accordingly their cardiac and kidney disease severity. The American College of Veterinary Internal Medicine cardiac disease severity classification (for dogs)\(^22\) and the International Small Animal Cardiac Health Council classification (dogs and cats)\(^23\) have been proposed to recognize the different stages of heart disease, but there is no current consensus on the best method of classification. The IRIS AKI grading and CKD staging classification are widely accepted to stage acute and chronic kidney disease, respectively.\(^24–26\) Although these staging schemes are important to characterize and classify cardiac and kidney disease, they, along with clinical features, current practice patterns, and conventional diagnostic criteria, may be too insensitive to predict the early onset of cardiorenal interactions that could influence therapeutic interventions and clinical outcomes.

**HYPOTHESIS**

Novel cardiac-specific and kidney-specific biomarkers have potential to identify the comorbid development of cardiac and kidney injury and dysfunction in a more timely manner than conventional clinical assessments. Novel kidney biomarkers can facilitate therapeutic targets and disease surveillance to minimize the establishment of CRSs.

**CARDIAC AND KIDNEY BIOMARKERS**

To date, worsening renal function (WRF) has been inferred from measurements of serum creatinine or calculated estimates of glomerular filtration rate (GFR). The ideal marker of kidney dysfunction secondary to cardiac disease should be a sensitive and specific early marker of renal injury as well as disease severity, morbidity, and mortality. It should detect changes in renal impairment and renal function and allow guidance of therapy. A singular biomarker is unlikely able to distinguish all processes associated with induction of the kidney injury and also events associated with repair of the injury. More realistically, a panel of biomarkers predictive of differing phases of induction, maintenance, and repair of active kidney injury might serve these ideal goals.

Currently there is no ideal biomarker, but some of the currently described blood markers of glomerular filtration are BUN, creatinine, cystatin C, and SDMA. To evaluate glomerular damage, proteinuria can be used; and for tubular injury, urinary NGAL has shown promising results in dogs.

**Cardiac Biomarkers**

N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) are the most commonly used biomarkers for cardiovascular disease.\(^{27–31}\) NT-proBNP is released by the myocardium, and its main function is to help regulate plasma volume and promote natriuresis. It is loosely correlated with left ventricular filling pressures and reflects ventricular wall stress, revealing congestion at the cellular level.\(^{32–34}\) Cardiac troponin I is a well-established indicator of cardiac disease or injury. Both NT-proBNP and cTnI are partially excreted by the kidneys; therefore, their values are dependent on kidney function, which should be remembered when evaluating patients with concurrent cardiac and kidney dysfunction. The combined interpretation of these biomarkers in the context of a specific clinical condition may help guide therapy.

**Biomarkers of Kidney Function/Damage**

Recognition of the onset or progressive worsening of kidney function in the context of cardiovascular disease or its management constitutes an important setback to
successful outcome of heart disease. Early recognition of kidney involvement could provide greater opportunities to tailor therapeutic intervention of both the cardiac and kidney components to promote the mutual benefit to both organs.

The recognition of kidney involvement currently is documented and stratified by use of function markers, including urine specific gravity, proteinuria, serum creatinine, and SDMA that may reflect progressive states of transition or relatively steady-state conditions that may not reveal kidney involvement until it is well established. In addition, conventional practice pattern for the management of heart disease may not be sufficiently timely to detect the early compromise of kidney function. Despite familiarity with serum creatinine as a predictor of kidney disease, its utility may be constrained or blinded to early and subclinical kidney dysfunction and its excessively broad reference range for dogs and cats. IRIS CKD Staging or AKI Grading for early kidney disease (stage 1 and grade I, respectively) encompasses the reference range for creatinine, which creates ambiguity in recognizing early kidney injury or compromise. Once documented, kidney involvement often is advanced at the time of diagnosis, and the kidney fate may be determined. The advent of IDEXX SDMA has provided a new diagnostic assessment that predicts the onset of CKD at an earlier time than serum creatinine, but it remains a function test that may not discriminate subclinical or subtle kidney injury. A functional diagnostic marker like serum creatinine and SDMA may fail to detect underlying active injury imposed by the cardiac disease or its management if offset by renal reserve, decreased generation rate with progressive muscle loss, or if it is matched by compensatory adaptation of the residual kidney mass. Only when active injury outpaces repair, the influences of generation rate, or compensatory adaptation will the presence of kidney involvement become evident.

The risks and patterns for progression from occult active kidney injury to progressive CKD with the development of cardiac disease or failure require further clarification. When in the course or management of cardiac disease the kidney injury is triggered, and which factors sustain the progression of the kidney injury are largely unknown. The injury could be acute in onset and of finite duration. Alternatively, kidney involvement can be progressive to end-stage kidney disease over time driven by forces associated with the cardiac disease or its management. Episodic acute injuries from progression or intermittent decompensation of cardiac function could promote cumulative kidney damage, resulting in chronic dysfunction and concurrent reduction of GFR and GFR markers (Fig. 1).

The underlying mechanisms participating in the intrinsic progression of CKD have been hypothesized widely and could represent mechanisms associated with cardiorenal disease. What appears common to many forms of progressive kidney disease are common features of active hemodynamic or metabolic stresses or injury to the residual structures of the kidney-activating altered tubular epithelial metabolism and often self-perpetuating inflammatory and fibrotic events. Accumulating evidence from a variety of models of AKI proposes a sequence of effective adaptive or maladaptive events in cellular repair that likely influence the prevention or predisposition to ongoing and progressive kidney injury. From these lines of evidence, cardiac disease could initiate an acute insult to the kidney in which the injured tubular cells either become fatally injured and undergo terminal necrosis or apoptosis, regenerate and repair the cellular damage, or undergo failed regeneration but survive cell death in a state of cell cycle G2/M arrest. Arrested cells repleted from apoptosis, however, fail to participate in regenerative repair and upregulate maladaptive signaling pathways for myofibroblast proliferation and fibrosis in the interstitium predisposing to ongoing kidney injury in the presence or absence of ongoing cardiac dysfunction. Tubular epithelia subjected to more severe or repeated injury, sustained or ongoing
injury, or epithelia that are more senescent also are more susceptible to cell cycle arrest.43,45–48

These observations from ischemic and metabolic insults to the kidney provide a speculative foundation for the associated sudden and/or progression injury to the kidney associated with cardiac dysfunction or its management. Independent of the nature of the insult to the kidney, a common theme for episodic or progressive injury appears to be active and ongoing stress, metabolic dysregulation, and loss of morphologic and functional integrity of the tubular epithelium leading to interstitial inflammation and fibrosis. The tubular epithelial focus prevails, regardless of the nature or intrarenal target of the prevailing insult.40,43,46

Despite its high metabolic activity and oxygen requirements, the inner cortex and outer medullary segments of the kidney exist in a state of tenuous oxygenation, which is highly regulated in health but subject to profound inadequacy with vascular compromise, hypoperfusion, and relative hypoxia. With either subtle or profound tubulointerstitial injury, this tenuous vasculature can be further compromised, disrupting oxygen delivery and the balance between tubular energy demands and oxygen availability. Tubular epithelial injury subsequent to oxidative stress activates vasoconstrictive signals, promoting a vicious cycle of heightened ischemia, progressive vascular rarefaction, and stimulation of growth factors that signal interstitial fibrosis and progressive hypoxia.40,43,45–48 Cardiac disease and its management may precipitate a sudden-onset AKI or remain clinically occult and undetected until there is a sufficient decrement in functional renal mass to be detectable by traditional clinical markers. As can be seen, the kidney responds to many overt stresses and injuries with a series of adaptive reactions fundamentally intended to reestablish cellular integrity and promote cell survival. However, when the stress or injury is sustained or insurmountable (as may be the case in progressive cardiac dysfunction), these same cellular responses may become maladaptive or the tubular cell becomes programmed to die.38,45 These latter responses are expressed clinically as AKI with variable

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**Fig. 1.** Hypothetical schematic illustration of chronic progressive worsening of functional kidney mass (predicted by GFR or GFR markers) over time in response to stepwise insults to the kidney imposed by episodic cardiac events (upper panel) or subsequent to sustained active kidney injury resulting from persistent cardiac dysfunction promoting intrinsic stress or disordered metabolism in the kidneys (lower panel). (Reproduced from Cowgill LD, Polzin DJ, Elliott J, et al. Is progressive chronic kidney disease a slow acute kidney injury? Vet Clin North Am Small Anim Pract 2016;46(6):995–1013.)
recovery, kidney death, or more subtly as progressive CKD. If the kidney recovers, many of these adaptive cellular responses may become pathways for the transition of overt AKI (including “pre-renal” etiologies) to progressive CKD.38,41–50

CANDIDATE BIOMARKERS FOR ACTIVE KIDNEY INJURY IN CARDIOVASCULAR-RENAL AXIS DISORDERS

Kidney-specific biomarkers that localize to functional renal tubular epithelia (or other kidney-specific loci) and respond to diverse stresses or disruption of normal cellular functions have potential to signal the early, specific, and sensitive development of kidney injury subsequent to prevailing heart disease. An active kidney injury biomarker could expose ongoing or progressive kidney injury subsequent to cardiac dysfunction in advance of conventional diagnostic methods. Documented increases of serum creatinine and/or SDMA are the current standards identifying kidney involvement in cardiac disease, but these changes can be relatively slow to develop and reflect injury after it has compromised kidney function substantially. Novel biomarkers have potential to predict cardiac-induced “active” kidney injury in a timelier manner to facilitate redirected therapy of either the cardiac or kidney dysfunction.

Many candidate serum and urinary biomarkers have been assessed in human medicine,48,51–54 and many of the promising markers are now being evaluated and validated in animals.10,55,56 Some of the most promising candidates include urinary proteins that reflect functions or cellular processes specific to the kidney that are disrupted by pathophysiologic events secondary to ischemia, injury, or cellular stress. Retinol binding protein, cystatin C, cystatin B, kidney injury molecule-1, NGAL, interleukin-18, liver-type fatty acid–binding protein, tissue inhibitor metalloproteinase-2, and insulinlike growth factor–binding protein 7 are among the most actively pursued.10,44,47,48,51,52,54–56

The authors have been prospectively evaluating urinary clusterin, serum and urinary cystatin B, serum inosine, and urinary NGAL as promising early predictors of kidney involvement in a variety of cardiac diseases. Although our current experience is preliminary, we are encouraged by the potential clinical value of the combined assessment of cardiac-specific and novel active kidney injury biomarkers to provided new insights and understanding of cardiorenal disorders in the dog. It remains tenable that different kidney markers would be selectively sensitive to cardiac-induced kidney stress versus therapy-induced renal toxicity.

NGAL is a 24-kDa protein initially identified bound to gelatinase in specific granules of neutrophils. Subsequently, NGAL expression has been demonstrated by a variety of epithelia and specifically is upregulated more than 10-fold in renal tubular epithelia within the first few hours following ischemic, obstructive, and toxic kidney injuries in human patients with AKI, naturally acquired kidney disease in dogs, and experimental models of AKI in dogs.40,42,51–54 Although urinary NGAL is promising and commercially available, it lacks unique specificity for kidney injury, and it can be influenced by co-morbid diseases.

Serum inosine, urinary clusterin, and urinary cystatin B have only recently gained attention as canine acute injury biomarkers, but are attractive for their exclusive origins to renal tubular epithelia, integral association with cellular stress or damage pathways, and their highly specific analytical evaluation.56 As such, these markers offer the potential sensitivity and specificity to better forecast comorbid kidney involvement in cardiac dysfunction than conventional kidney diagnostics. These novel biomarkers reflect active and ongoing injury in the kidney before detection by conventional diagnostics of
kidney function. Importantly, they may provide the tools to establish a new understanding of cardiorenal disorders beyond our current views, as well as renewed paradigms for the diagnostic evaluation and treatment of cardiac disease in dogs and cats.

**Biomarker-Predicted Patterns for Kidney Involvement in Cardiovascular-Renal Axis Disorders**

Active kidney injury biomarkers may facilitate recognition of the incipient kidney damage. The identification of early kidney injury would permit more conscientious management of the cardiac disease and proactive preservation of kidney function and protection from kidney injury with its management. Preliminary assessments of the patterns of responsiveness of conventional and novel kidney biomarkers in response to cardiac disease has provided new insights about cardiac and kidney interactions in response to heart disease.

First, and likely of no surprise to cardiologists, kidney function appears to remain stable and well preserved despite documented and persisting cardiac disease when cardiac function is well preserved (Fig. 2). The preservation of kidney function is documented by stability of conventional function markers and absence of active kidney injury predicted by novel active injury biomarkers. The opposite extreme is demonstrated in animals with persistent or progressive deterioration of cardiac function. In these patients, as illustrated in Fig. 3, there is a progressive erosion of kidney function (predicted by serum creatinine and IDEXX SDMA) coexistent with sustained active injury (documented with the novel biomarkers), which likely predisposed the loss of function. Resolution of the heart failure would be expected to abate the active injury and promote stabilization or repair of the kidney injury/function. If the kidney markers were activated primarily by events associated with failure of the heart, they could serve as therapeutic benchmarks to direct cardiac therapeutics in combination with the cardiac-specific biomarkers. If the early markers were predictive of renal toxicity to the cardiac therapy, they could serve as early management targets to prevent progressive renal comorbidity (Fig. 4).

The sensitivity and responsiveness of these novel active kidney markers to predict cardiorenal events is demonstrated in Fig. 5 in a dog with right heart failure and abdominal effusion promoting congestive nephropathy. Following abdominocentesis and relief of the intra-abdominal hypertension, there is rapid resolution of the existing kidney stress/injury predicted by the rapid decline in urinary clusterin and increase in serum inosine. At this stage of disease, serum creatinine failed to predict kidney involvement and IDEXX SDMA is just above the reference threshold. These early findings are consistent with the hypothesis that heart failure induces active kidney injury, which, if sustained, promotes progressive nephron loss or functional compromise that is ultimately detectable with conventional markers. If the heart failure were corrected, active cardiac-induced kidney injury has potential to resolve and kidney function the potential to stabilize.

These clinical examples suggest active kidney injury biomarkers offer the potential to identify cardiorenal interactions that may be subclinical and could modify therapeutic decisions in the management of cardiac disease.

These markers are equally responsive and predictive of kidney involvement in settings associated with acute and precipitous worsening of cardiac function. This is illustrated in a dog with progressive but stable degenerative valve disease manifesting acute decompensated heart failure associated with a ruptured *chorda tendinea* (Fig. 6).
In patients with cardiovascular disease, the renal hemodynamics are significantly affected and considered the main contributor to secondary kidney disease. A low cardiac output stage triggers neurohormonal activation through the sympathetic nervous system (SNS) and the RAAS. This process leads to initial preservation of renal function. Note in the presence of stable and compensated heart disease (normal NT-proBNP and cTnI - not shown), there is relatively no biomarker-predicted active kidney injury and remarkable stability of kidney function.

**Fig. 2.** Changes in conventional and novel markers of kidney function in a dog with compensated chronic degenerative valve disease. (Upper panel) Changes in serum creatinine (upper reference range, <1.5 mg/dL; solid circles, broken line) and IDEXX SDMA (reference range <14 μg/dL; solid squares and line) over time. (Lower panel) Associative changes in the “active kidney injury” biomarkers, urine clusterin (reference range <350 ng/dL; solid circles and line) and serum inosine (reference range, >200 μg/dL; open triangles and dashed line).
Fig. 3. Progressive CKD in a dog with chronic degenerative valve disease and right heart failure, ascites, and increased intra-abdominal pressure. Both NT-proBNP and cTroponin I (not shown) were markedly elevated, consistent with heart failure. (Upper panel) Changes in serum creatinine (solid squares) and IDEXX SDMA (open circles) over time illustrating progressive worsening of kidney function. The solid and dotted horizontal lines represent the upper reference range for creatinine and IDEXX SDMA, respectively. (Lower panel) Associative changes in the “active kidney injury” biomarkers, urine clusterin (open triangles) and serum inosine (closed circles), throughout the course of the disease as managed with intermittent abdominocentesis for the congestion and drug escalation for the worsening heart disease. The mixed dashed and dotted horizontal lines represent the upper reference ranges for serum inosine and urine clusterin, respectively. Note the temporary improvement in both urinary clusterin and serum inosine subsequent to abdominocentesis (on day 0). Although improved, both markers demonstrate only transient resolution of the ongoing kidney injury that progresses between abdominocentesis procedures as the congestion progresses. The biomarker-predicted active injury is further associated with the progressive CKD. (Reproduced from Cowgill LD, Polzin DJ, Elliott J, et al. Is progressive chronic kidney disease a slow acute kidney injury? Vet Clin North Am Small Anim Pract 2016;46(6):995–1013.)
the GFR, but likely at the expense of active and ongoing subclinical kidney stress that subsequently promotes loss of kidney mass and function. These systems also promote water and sodium retention, elevating central venous pressure and organ congestion. Congestion of the kidneys in turn also stimulates the SNS and RAAS, and likely increases in renal parenchymal pressure contributing to progressive reductions of GFR and tubular fluid flow and induction of active kidney injury (see Fig. 5). 12,57–59

Fig. 4. Changes in conventional and novel markers of kidney function in a dog with compensated chronic degenerative valve disease. (Upper panel) Changes in serum creatinine (upper reverence reference range, <1.5 mg/dL; solid circles, broken line) and IDEXX SDMA (reference range <14 μg/dL; solid squares and line) over time. (Lower panel) Associative changes in the “active kidney injury” biomarkers, urine clusterin (reference range <350 ng/dL; solid circles and line) and serum inosine (reference range, >200 μg/dL; open triangles and dashed line). Despite initial clinical stability of the heart disease (normal NT-proBNP and cTnI; not shown) and serum creatinine and SDMA, serum inosine, and urinary clusterin predict persistent active kidney stress or injury with the onset of therapy (on day 0). The novel kidney biomarkers predicted the immediate and persistence of kidney involvement within days of starting therapy.
Research should focus on clinically useful knowledge to understand the hemodynamic drivers of cardiorenal interactions and how renal function should influence therapeutic decisions. In human medicine, low forward flow or decreased cardiac output do not appear consistently associated with WRF, and central venous pressure is not a good way to access congestion-induced renal dysfunction. The best marker for congestion-induced renal dysfunction appears to be intra-abdominal pressure, which may represent a useful diagnostic and therapeutic target pending further investigation.

Fig. 5. Acute responses in conventional and novel kidney biomarkers following abdominocentesis (arrow) and decreased intra-abdominal pressure. (Upper panel) Changes in serum creatinine (upper reference range, <1.5 mg/dL; solid circles, broken line) and IDEXX SDMA (reference range <14 μg/dL; solid squares and line). (Lower panel) Associative changes in the “active kidney injury” biomarkers, urine clusterin (reference range <350 ng/dL; solid circles and line) and serum inosine (reference range, >200 μg/dL; open triangles and dashed line). Following abdominocentesis, urinary clusterin decreased and serum inosine increased within 2 days predicting relief of the active injury associated with the congestion. With re-occurrence of the abdominal effusion, the biomarker-predicted kidney injury redeveloped (see Fig. 3), concurrent with worsening of kidney function.
Fig. 6. Changes in conventional and novel kidney biomarkers and cardiac biomarkers in a dog with chronic degenerative valve disease and an acute onset of CHF secondary to a ruptured chorda tendinea. (Upper panel) Changes in serum creatinine (upper reverence reference range, <1.5 mg/dL; solid circles, broken line) and IDEXX SDMA (reference range <14 μg/dL; solid squares and line) over time. (Middle panel) Associative changes in urine clusterin (reference
validation of this marker. Worsening renal function also is correlated strongly with changes in systemic blood pressure, and a reduction in blood pressure appears to be the strongest hemodynamic driver for worsening of renal function in humans.\(^{60}\) A small pilot study (performed by the authors) in dogs with ascites due to right heart failure secondary to chronic degenerative valve disease or cardiomyopathy, showed that an acute decrease in the intra-abdominal pressure following abdominocentesis led to an increase in serum inosine (favorable response) within a 24-hour to 48-hour period in a subset of patients who had initial values below the normal limits, without changes in the therapeutic protocol (Fig. 7). These results illustrate improvement in kidney injury or stress promoted by decreasing the intra-abdominal pressure and likely also renal capsule pressure.

These very dramatic effects of CHF to promote active injury in the kidney and its reversal with abdominocentesis to relieve the abdominal congestion illustrate the potential of these markers to more rapidly reflect the status of the disease and management. These data are consistent with comparable observations in human patients.\(^{61}\)

Abnormal kidney function may lead to metabolic and functional disturbances in multiple organs, which include the cardiovascular system. These processes may directly affect the heart, such as systemic hypertension causing decreased systolic function, left ventricular hypertrophy, and diastolic dysfunction, or indirectly by reducing the production of erythropoietin leading to anemia.\(^{62–64}\) Therefore, routine monitoring of systemic blood pressure is advised to identify hypertension or hypotension.

Cardiologists treat a significant number of patients with AKI and CKD, but there is no established protocol for the treatment or monitoring of cardiovascular disorders in these patients. AKI appears to be associated with cardiac injury and arrhythmias in dogs.\(^{65}\) Additionally, chronic mitral valve disease is associated with increased prevalence of CKD and anemia in dogs. The severity of heart disease seems to be directly correlated with the IRIS classification, and dogs with cardiovascular-renal disorders have a decreased survival time.\(^{66,67}\)

Patients with kidney dysfunction may receive suboptimal treatment for concurrent cardiovascular conditions, even though they may benefit from the standard therapies. This may account in part for the worsening prognosis attributed to patients with renal disease. In human medicine, early referral to a nephrologist is associated with a delayed progression of CKD. Patients with CRS may benefit from comanagement by cardiologists and nephrologists.\(^{68}\)

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are beneficial in cardiovascular and renal diseases, but patients with renal dysfunction are less likely to receive these types of drugs due to the concern of WRF.\(^{69–72}\) A better understanding of the relative risk of using these and other drugs may be very important in patients with CRS. Mineralocorticoid receptor antagonists (aldosterone blockers) have the potential for renal and cardiac protection; therefore, the use of spironolactone in this subset of patients may be beneficial.\(^{22,73}\)

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**Figure 7**

Changes in NT-proBNP (normal range, \(\leq 1800\) pmol/L; open squares and dashed line) and cardiac troponin I (normal range, \(\leq 0.2\) ng/mL; open triangles and dashed line). With the onset of the acute decompensated heart failure (arrow) there is a rapid increase in cTnI and subsequent rapid change in urinary clusterin, serum inosine, and SDMA predicting the active injury and functional compromise associated with the heart failure. Although there was an increasing trend for creatinine, it failed to predict the AKI.
A large meta-analysis in human patients showed that RAAS inhibition is particularly beneficial in patients with WRF. Therefore, maintaining patients with CRS on these drugs may be beneficial despite a mild increase in the renal function markers.\textsuperscript{74}

Loop diuretics may have conflicting effects on renal function. By reducing renal congestion, they may improve GFR and delay the progression of CKD, but on the other hand, excessive doses of diuretics may also decrease renal perfusion and

Fig. 7. Acute responses in conventional and novel kidney biomarkers, and intra-abdominal pressure following abdominocentesis. (Upper panel) Intra-abdominal pressures before (pre-tap) and after abdominocentesis (post-tap). (Middle panel) Associative changes in the “active kidney injury” biomarker, serum inosine (reference range, >200 μg/dL). (Lower panel) Changes in IDEXX SDMA (reference range <14 μg/dL). The solid lines correspond to the dogs that had initial inosine values below the normal limits and the dotted lines represent the dogs with initial inosine values within normal limits. Following abdominocentesis, the intra-abdominal pressure decreased in all dogs, and the biomarker-predicted active injury was relieved, as shown by the increase in serum inosine within 2 days in all the patients with low initial serum inosine values. IDEXX SDMA was not sensitive to these acute changes.

A large meta-analysis in human patients showed that RAAS inhibition is particularly beneficial in patients with WRF. Therefore, maintaining patients with CRS on these drugs may be beneficial despite a mild increase in the renal function markers.\textsuperscript{74}

Loop diuretics may have conflicting effects on renal function. By reducing renal congestion, they may improve GFR and delay the progression of CKD, but on the other hand, excessive doses of diuretics may also decrease renal perfusion and
consequently GFR. In human medicine, appropriate decongestion of the patient is associated with significantly longer survival times, regardless of the presence of WRF.\(^7\) WRF that occurs in the context of a therapeutic maneuver may not represent an adverse prognosis. The patient should be treated, and if a mild to moderate increase in serum creatinine occurs, that should be expected and may be tolerated within limits. Kidney biomarker targets may document when more aggressive management of the heart failure ultimately relieves the ongoing injury to the kidney or, alternatively, predict when more aggressive management is ultimately harmful.

The combination of loop diuretics and thiazide diuretics has a synergistic effect that may cause excessive volume depletion and electrolyte disturbances, therefore they should be used with caution in the patient with CRS.

Pimobendan improves systolic function, which may increase GFR. Pimobendan does not enhance or suppress furosemide-induced RAAS activation.\(^76\) Digoxin and other drugs with predominant renal excretion may require closer monitoring and potential reduction of the dose.

Omega-3 fatty acids are a recommended oral supplement that has been used as an antioxidant and appetite stimulant in patients with heart and kidney disease.\(^21,77,78\)

Advanced imaging of the kidneys and heart, such as digital radiography of the thorax and abdomen, echocardiography, and abdominal ultrasonography, is crucial for a premature and accurate diagnosis of patients with CRS.\(^21,79,80\)

A cardiorenal panel that includes more sensitive predictors of renal function, such as SDMA, novel kidney biomarkers for ongoing kidney injury, or stress, such as urinary NGAL, serum inosine, urinary clusterin, serum or urinary cystatin B, cardiac biomarkers (NT-proBNP and cTnI) and electrolytes, which require blood and urine sampling may substitute the current laboratorial assessment of the kidney and cardiac function. The effective use of these more sensitive predictors of cardiorenal interactions will require modification of current practice patterns and more timely assessment and monitoring of patients following therapeutic interventions or adjustments.

**SUMMARY**

An accurate appreciation of the kidney and the cardiovascular system and their interactions may have practical clinical implications. A multidisciplinary evaluation, including the expertise of cardiologists and nephrologists, may be the most appropriate approach for patients with concurrent cardiac and kidney disease or predisposed to CRS.\(^81\) The outcome of patients with CRS is likely to improve with the increasing awareness and ability to identify and understand the pathophysiological characteristics of CRS. The greater utilization of existing and emerging organ-specific biomarkers with greater sensitivities than conventional diagnostics forecast new opportunities to diagnose and manage cardiac disease.

**REFERENCES**


