Cardiovascular–renal axis disorders in the domestic dog and cat: a veterinary consensus statement


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OBJECTIVES: There is a growing understanding of the complexity of interplay between renal and cardiovascular systems in both health and disease. The medical profession has adopted the term “cardio-renal syndrome” (CRS) to describe the pathophysiological relationship between the kidney and heart in disease. CRS has yet to be formally defined and described by the veterinary profession and its existence and importance in dogs and cats warrant investigation. The CRS Consensus Group, comprising nine veterinary cardiologists and seven nephrologists from Europe and North America, sought to achieve consensus around the definition, pathophysiology, diagnosis and management of dogs and cats with “cardiovascular-renal disorders” (CvRD). To this end, the Delphi formal methodology for defining/building consensus and defining guidelines was utilised.

METHODS: Following a literature review, 13 candidate statements regarding CvRD in dogs and cats were tested for consensus, using a modified Delphi method. As a new area of interest, well-designed studies, specific to CRS/CvRD, are lacking, particularly in dogs and cats. Hence, while scientific justification of all the recommendations was sought and used when available, recommendations were largely reliant on theory, expert opinion, small clinical studies and extrapolation from data derived from other species.
**INTRODUCTION**

A complex interplay between the renal and cardiovascular systems exists in both health and disease. In humans, the pathological interactions between these two organ systems are increasingly deserving of further definition, classification and understanding. The term “cardiorenal syndrome (CRS)” defined as “disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other” (Ronco et al. 2010) has been adopted by physicians to describe this pathological interplay. CRS is subdivided into the following five types: type 1, involving acute worsening of heart function leading to kidney injury, such as that occurring in patients with acute congestive heart failure (CHF); type 2, involving chronic disease of the heart leading to kidney injury, such as that occurring in patients with chronic heart failure; type 3, involving acute worsening of kidney function leading to heart injury, such as that in patients with acute kidney injury (AKI); type 4, involving chronic kidney disease (CKD) leading to heart injury; and finally, type 5, involving systemic disease(s) leading to simultaneous injury of both the heart and kidney, such as that occurring in patients with sepsis, systemic hypertension or amyloidosis (Ronco et al. 2010).

Although the epidemiology, diagnosis, prevention and management of CRS in humans have been proposed (Ronco et al. 2010, McCullough et al. 2013, Braam et al. 2014, Ronco & Di Lullo 2014), the clinical relevance, time course of onset and pathophysiological mechanisms of CRS are incompletely understood (Braam et al. 2014). The only recognised facts are (i) blood volume, vasmotor tone and haemodynamic stability are dependent on the cardiovascular and renal systems and (ii) the interactions between the two systems (Bock & Gortlieb 2010). The concept of CRS combines the cardiovascular system and kidneys as part of a single homeostatic cardiorenal axis, which challenges cardiologists and nephrologists who treat heart and kidney failure, respectively, to consider this in a complete perspective.

Although kidney and heart diseases are commonly recognised in domestic dogs (Detweiler & Patterson 1965, Buchanan 1992, Beadow & Buchanan 1993, Polzin 2011, 2013) and cats (Buchanan 1992, Riesen et al. 2007, Chakraborti et al. 2013) as an important source of morbidity and mortality (Fleming et al. 2007, Chakrabarti et al. 2013), the interaction between the two systems has yet to be formally defined and described by the veterinary profession. The CRS Consensus Group, comprising 16 academic and clinical experts, including 9 veterinary cardiologists and 7 veterinary nephrologists from Europe and North America, was created with the goal of developing consensus definitions and recommendations for CRS in dogs and cats. The panelists were chosen based on expertise in the areas of cardiology, hypertension and nephrology and recognition as contributing experts in their respective fields. The group was intentionally selected as representative of academic veterinarians from Western Europe and North America, based on their ability and interest in participating in this project and diplomat status in one or more of the clinical specialties (American and European Colleges of Veterinary Internal Medicine [ACVIM, ECVIM, respectively, or the European College of Veterinary Clinical Pathology and Toxicology). Other criteria involved in this selection process included past participation in related consensus statement development (International Renal Interest Society [IRIS], ACVIM Hypertension Consensus Statement and ACVIM Consensus Statement on Diagnosis and Treatment of Canine Mitral Valve Disease). An advanced degree and/or research experience in nephrology/cardiology were also considered to be desirable attributes. All authors are board-certified and are currently involved in research in their area of specialty, and 10 of 16 have advanced degrees (3 MS, 6 PhD, 1 MD).

The objectives of the group were to 1) define CRS as it pertains to the dogs and cats as veterinary patients, 2) recommend diagnostic testing and evaluation of CRS, 3) provide general guidelines for the treatment of patients with CRS with an emphasis on the potential interplay between the two organ systems and 4) to increase awareness of CRS as an important disease entity in veterinary medicine deserving of further research. Early on, the CRS Consensus Group chose to refer to CRS in veterinary patients as “cardiovascular-renal disorders (CvRD)”, such that the vasculature as well as the heart was included, and because, based on

**RESULTS:** Of the 13 statements, 11 achieved consensus and 2 did not. The modified Delphi approach worked well to achieve consensus in an objective manner and to develop initial guidelines for CvRD.

**DISCUSSION:** The resultant manuscript describes consensus statements for the definition, classification, diagnosis and management strategies for veterinary patients with CvRD, with an emphasis on the pathological interplay between the two organ systems. By formulating consensus statements regarding CvRD in veterinary medicine, the authors hope to stimulate interest in and advancement of the understanding and management of CvRD in dogs and cats. The use of a formalised method for consensus and guideline development should be considered for other topics in veterinary medicine.
experience in cardiovascular and renal diseases, the clinical manifestations of CvRD in the dog and cat are expected to be widely varied among individuals and between species, precluding their description as a single clinical syndrome.

It is important to emphasise that the manifestations of cardiac and renal diseases differ between species, thereby limiting the validity of deriving information from human data for veterinary application, as well as comparisons between dogs and cats. Cardiac disease in humans is primarily related to hypertension and coronary artery disease, which is different from dogs (primary valvular disease, dilated cardiomyopathy and heartworm disease) and cats (hypertrophic cardiomyopathy, other myopathies and, to a lesser degree, systemic hypertension). Likewise, human renal diseases (glomerular disease, diabetic nephropathy, hypertensive nephropathy, nephrosclerosis, interstitial nephritis and polycystic kidney disease (Maschio et al. 1996, Hou et al. 2006)) do not correlate exactly to those seen in veterinary patients (dogs: glomerular disease, pyelonephritis, acute tubular necrosis, tubulointerstitial disease (Macdougall et al. 1986) and cats: idiopathic chronic end-stage kidney disease, most often characterised by tubulointerstitial fibrosis, typically of unknown origin (Chakrabarti et al. 2013)). Nevertheless, there are some aspects of the diseases and their pathophysiology that warrant interspecies comparison and application of human findings to veterinary medicine.

**METHODOLOGY**

The CRS Consensus Group included a 5-person steering and publication committee, comprising a chairman (JLP) and 4 additional steering members (CEA, CB, MAO, SLV), as well as an 11-member rating group. The chairman and steering group oversaw a PubMed search for relevant biomedical literature, published between 1995 and 2013. The committee then drafted a review of CvRD that included 13 summary statements. The 13 statements spanned four different subtopics, including definition, classification and pathophysiology (Subgroup 1 - 2 statements); epidemiology, clinical aspects and diagnosis (Subgroup 2 - 3 statements); biomarkers and imaging (Subgroup 3 - 5 statements); and management (Subgroup 4 - 3 statements) of CvRD. The literature review and statements were discussed during a 2-day meeting of the entire CRS Consensus Group in April 2013. During this meeting, the entire CRS Consensus Group revised the documents and summary statements to coalesce around points of agreement.

The ultimate goal of the CRS Consensus Group was to produce a consensus document describing CvRD in the dog and cat. A modified Delphi method, based on guidelines by the Haute Autorité de santé (HAS or French National Authority for Health) (Haute Autorité de Santé 2010), was utilised to evaluate whether or not each of the 13 draft summary statements achieved formal consensus. According to the method, each group member scored each statement from 1 to 9, depending on the strength of their agreement with the statement, with 1 being that the statement is totally inappropriate, 9 being the statement is totally appropriate and 5 being undecided. Among the 16 rating scores, the lowest and highest scores for each statement were discarded. This resulted in 14 scores, such that no score could be $<5$ and the median value must have been $\geq7$ in order for a statement to be described as having achieved consensus. Two rounds of consensus rating were performed. At the start of the 2-day meeting, group members were introduced to the rating method and they discussed and modified the statements. Following this discussion, the first round of rating was conducted and scores for each statement were reviewed. Then, the group broke out into four different subgroups, each of which were led by a steering committee member (Subgroup 1: CEA, VLF, JE; Subgroup 2: CB, VC, DJP, AMV; Subgroup 3: SLV, JDB, NVI, GFG; Subgroup 4: MAO, TF, LDC, NSM) with the task of revising the statements, based on the results and feedback from the first round of rating. Subsequently, the entire group reconvened for further discussion and revision, and by the end of the meeting, final wording for each of the 13 statements had been constructed. Over the next several weeks, members were able to further consider the statements, using a web-based platform accessible to all the 16 members. Eight weeks after conclusion of the meeting, a second and final round of rating was carried out, using the online platform, with identical rating instructions, scoring procedures and criteria for consensus. For those statements that achieved consensus, the strength of consensus was determined by the lowest value of the 14 individual rating scores, wherein strong consensus was defined as having a lowest individual score $\geq7$ and good consensus defined as a lowest individual score of either 5 or 6. The final rating results, statements and supporting information were compiled into a draft manuscript by the steering committee, which was then reviewed and edited by all group members before submission for publication.

**RESULTS**

Definition, classification and pathophysiology of CvRD

Statement 1: Cardiovascular-renal disorders (CvRD) are defined as disease, toxin or drug-induced structural and/or functional damage to the kidney and/or cardiovascular system, leading to disruption of the normal interactions between these systems, to the ongoing detriment of one or both. (Good consensus; median rating, 8; range 5–9)

Statement 2: CvRD includes subgroups CvRD$_{p}$ CvRD$_{v}$ and CvRD$_{e}$, to reflect renal disease/dysfunction emanating from a disease involving the cardiovascular system; cardiovascular disease/dysfunction secondary to renal disease and concurrent impairment of both systems caused by concurrent primary cardiovascular and kidney disease or “other” disease processes, drugs, toxins or toxicants that affect both systems, respectively. The three categories can be further subdivided into stable disease (S) or unstable disease (U) based on the patient’s clinical presentation. (Good consensus; median rating, 7; range, 6–9)

Each of these two statements achieved good consensus. A key concern of both CRS and CvRD is the way the kidney and cardiovascular systems interact, including the potential for harm along three different axes, from kidney to cardiovascular system, from cardiovascular system to kidney and from outside disease processes to both. In instances where disease coexists in both organ systems, it can be difficult to determine the directionality of CvRD or if concurrent primary disease coexists. The concept of CvRD emphasises the inter-related functions of the two organ systems and encourages a complete and early investigation of the function of the heart in instances of kidney disease and the function of the kidney in instances of heart disease. In human medicine, CRS is a relatively new, but evolving, field of medical study, while the understanding of the inter-relationship in animals (CvRD) is in its infancy. Therefore, it is expected that the proposed definition and classification scheme for CvRD in dogs and cats will require reassessment and modification as more veterinary research involving CvRD is performed.

Epidemiology, clinical aspects and diagnosis of CvRD

Statement 3: Despite the lack of specific data regarding the pathophysiology of CvRD in veterinary medicine, available literature suggests the likelihood that CvRD pathophysiology in animals shares some common patterns with human CRS, namely, the complex interplay of haemodynamic changes, neurohormonal activation and reactive oxygen species, to name a few. (Good consensus; median rating, 8; range, 5–9)

This statement achieved good consensus. The understanding of CRS in humans is incomplete (Ronco & Di Lullo 2014), and in veterinary medicine, the existence and exact nature of CvRD is largely speculative. Nevertheless, there are known disease aetiologies in the dog and cat that are characterised by detrimental interactions between the kidney and cardiovascular systems (Table 1).

The concept of CRS, which involves a bidirectional pathway of injury wherein disease of either organ directly or indirectly contributes to injury of the other (Fig 1), presents a broader view of fluid and haemodynamic homeostasis compared to a more traditional viewpoint, which considers kidney and cardiovascular impairment as separate pathophysiological entities. In the following section, the epidemiology and pathophysiology of each of the three classes of CvRD will be discussed.

Epidemiology and pathophysiology of CvRD

CvRD\textsubscript{a} refers to kidney injury or dysfunction emanating from a primary disease process involving the cardiovascular system. Potential mechanisms of CvRD\textsubscript{a} include decreased kidney perfusion secondary to decreased cardiac output; activation of neuroendocrine systems, namely, the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS); generation of reactive oxygen species by abnormal or injured endothelial tissue and passive venous congestion of the kidney (Table 1) (Haase et al. 2013, McCullough et al. 2013). Acute reduction in cardiac output can lead to decreased glomerular filtration rate (GFR), increased serum creatinine and blood urea nitrogen (BUN) and decreased urine output (Liang et al. 2008). In both humans and animals, increases in creatinine as little as 0·3 mg/dL (26·5 µmol/L) are regarded as indicative of AKI (Jose et al. 2006, Haase et al. 2013, McCullough et al. 2012, International Renal Interest Society 2014). The IRIS has proposed diagnostic criteria for AKI in dogs and cats (Table 2) (International Renal Interest Society 2014). This grading system encompasses a continuum of functional and parenchymal damage from its least to its most severe manifestations. The clinical presentation of AKI includes prerenal and postrenal conditions that may be independent or combined with intrinsic renal injury depending on the functional origin, extent and duration of the conditions inciting the disease. Mild AKI, defined as a serum creatinine concentration >1·6 mg/dL (1·7–2·5; >141 µmol/L;
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142–220), is detected in dogs or cats treated for heart failure (Goutal et al. 2010). These relatively modest values, even when they fail to exceed the relevant laboratory reference range, if sustained, have been shown to worsen outcome in humans with heart disease (Jose et al. 2006) and in dogs and cats with various underlying disease processes (Harison et al. 2012). Whether...
these changes indicate permanent structural renal damage remains to be determined in dogs and cats. The authors recommend that when treating animals with acute CHF, the lowest diuretic dosage required to resolve signs of congestion should be prescribed and renal values carefully assessed. However, there is no robust evidence that the development of a serum creatinine of ≥1·6 g/dL (≥141µmol/L) in cats and dogs with heart failure results in poor clinical outcomes. This would require an adequately powered prospective clinical trial that has not been undertaken. As such, a serum creatinine of ≥1·6 g/dL (≥141µmol/L) should not be used as an indicator to withhold necessary therapy in a patient with poorly controlled heart failure.

In humans, additional mechanisms beyond a decreased cardiac output and glomerular pressure are known to lead to kidney injury. The hydrostatic glomerular filtration gradient, defined as the difference between glomerular blood pressure and capillary hydrostatic pressure, is heavily influenced by systemic venous pressure. Congestion of kidney tissue, due to poor cardiac function and elevated systemic venous pressure, preferentially increases capillary pressure, decreases glomerular filtration pressure and rate and substantially decreases kidney function (Dupont et al. 2011). In humans with heart failure, incomplete resolution of venous congestion is a primary cause of worsening renal function (Testani et al. 2011, Guazzi et al. 2013) and is associated with poorer patient outcomes (Mullens et al. 2009). The reader can recognize the dilemma in trying to balance the negative effect of diuretic actions on arterial renal perfusion vs. the positive effect on venous renal congestion.

The RAAS, and in particular angiotensin II, precipitates and mediates oxidative and cytokine-mediated injury, inflammation and cell death (Mitani et al. 2013). The resulting endothelial dysfunction and reactive oxygen species (ROS) formation provides an important link between kidney and cardiac dysfunction (Fig 1) (Braam et al. 2014). CHF and accompanying elevated cytokine levels, reduced iron intake and absorption and suppression of angiotensin-converting enzyme (ACE) (angiotensin II is an erythropoietin secretagogue) contribute to anaemia in people (Pallazzuoli et al. 2008, Chalhoub et al. 2011). Chronic inflammation is also thought to decrease sensitivity to erythropoietin and, along with kidney injury and diminished erythropoietin production, contribute to anaemia (Chalhoub et al. 2011). Diminished or ineffective circulating erythropoietin reduces haemoglobin and its antioxidant properties and contributes to CvRD$_h$ through increased oxidative stress and apoptosis of kidney and cardiac cells (Silverberg et al. 2006). The importance of haemoglobin in CvRD$_h$ is a subject of debate, as erythropoietin therapy used to increase haemoglobin concentration in human patients with heart failure was not associated with improved patient outcome (Jackevicius et al. 2014).

The prevalence of CvRD$_h$ in dogs and cats is unknown; however, the incidence of primary kidney disease increases with age (Ross & Osborne 2006, Polzin 2011). Thus, older animals with cardiovascular disease are at additional risk of developing primary kidney disease and CvRD$_h$. Advances in medical therapy for CHF have resulted in improved life expectancy (Ettinger et al. 1998, Hagstrom et al. 2008, The BENCH Study Group 2008, Bernay et al. 2010), thereby increasing the potential for development of primary kidney disease over time as well as cumulative exposure to potentially nephrotoxic drugs, such as diuretics and ACE inhibitors (ACEIs). ACEIs, ubiquitous in managing heart failure and hypertension, are known to be nephrotoxic at very high (70×) dosages and when administered to volume-depleted dogs (MacDonald et al. 1987). Although not known to be directly nephrotoxic, potent loop diuretics, such as furosemide, at high dosages, are associated with volume contraction and worsening kidney function, suggesting their possible role in potentiation of ACEI-induced nephrotoxicity (Steimle et al. 1997, Schrier et al. 2004). Additionally, loop diuretics stimulate the RAAS system (Lantis et al. 2014), with well-documented pathological effects on the kidney (Francis et al. 1990). New evidence indicates that furosemide, by increasing sodium reaching the distal tubule, increases adenosine secretion, which, through vasoactive mechanisms, worsens renal function and contributes to diuretic resistance (Vallon et al. 2008, Lazzarini et al. 2012). In order to reduce worsening kidney function in people with heart failure, alternatives to diuresis are being explored (Costanzo et al. 2007, Givertz et al. 2007). However, there are contradictory studies, as well. A large retrospective study of human heart failure patients showed that the expected significant rise in serum creatinine with furosemide administration, although statistically significant, was very small (0.11 mg/dL; 9.7µmol/L [0.4%]) over 5 days of hospitalization and explained little of the variation in serum creatinine concentration and estimated GFR (El-Refai et al. 2011). Importantly, these results agree with a smaller prospective study on the effects of intravenous furosemide at varied dosages and administration methods (Felker et al. 2011). A timely review of this material details the conflicting evidence in virtually all aspects of CRS development, prevention and treatment in humans (Lazzarini et al. 2012). However, the authors were able to conclude from the data available that “… acute CRS prevention and treatment might be considered among the main targets of acute HF management” and that “… loop diuretics should be administered at the minimal dose sufficient to optimize volume status, and relieve signs and symptoms of congestion, without inducing an excessive reduction in intravascular volume, which could result in hypotension and/or renal dysfunction”. The dilemma of inconsistent results regarding the benefit vs. harm of loop diuretics has been recently addressed (Hanna & Deschamps 2014). Based on reviewing data at hand, these clinician scientists believe that a subset of CHF patients are worsened by aggressive diuresis. These authors conclude that “… congestion is at the center of acute (heart failure) syndromes. Aggressive decongestion greatly improves renal and myocardial flow and ventricular loading conditions. This allows renal function to improve enough to sustain diuresis with lower diuretic doses. This also allows the patient to tolerate lower systemic pressure without compromise of myocardial or renal perfusion. The combination of 2 particular factors predicts a poor renal tolerance of acute diuresis: (1) non-dilated left and right ventricles with a steep pressure-volume relationship (e.g. de novo acute [heart failure], diastolic [heart failure]) and (2) no or minimal peripheral edema. Patients with severe edema usually tolerate aggressive diuresis, especially if they have
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Epidemiology and pathophysiology of CvRD

CvRD refers to cardiovascular injury or dysfunction emanating from a primary disease process involving the kidney. There is little direct evidence for CvRD in dogs and cats (Carlos Sampedrano et al. 2006, Wilson et al. 2010). Likewise, in humans, there is more knowledge and clinical experience concerning CvRD than for CvRD in dogs and cats (Ronco et al. 2008). There are both known and suspected negative effects of kidney disease on the cardiovascular system (Bagshaw et al. 2013, Tumlin et al. 2013, Ronco & Di Lullo 2014). For example, electrolyte abnormalities, such as hyperkalaemia, can complicate both AKI and CKD and are associated with cardiac arrhythmias (Bagshaw et al. 2013). Various drugs used for the treatment of cardiac disease, such as digoxin, enalapril and atenolol, undergo renal excretion and cause primary kidney dysfunction, with reduced drug clearance, and can lead to signs of toxicity that include arrhythmias, hypotension and worsening myocardial function. Fluid volume and haemodynamic status are virtually always abnormal in patients with severe kidney disease (Much & Wilcox 1982, Polzin 2011). Uraemic patients who are anorexic and hypodipsic and vomiting are likely to be even further volume-depleted with a resultant reduction in cardiac output. Kidney injury can also lead to systemic volume overload that contributes to congestion, especially in those animals with coexisting cardiac diseases, such as valve disease, dilated cardiomyopathy, diastolic dysfunction (hypertrophic cardiomyopathy and hypertensive heart disease) and severe anaemia (Wilson et al. 2010). The anaemia of CKD unlikely plays a significant role here, as it is typically low-grade, unless there are other factors at work (chronic inflammation, neoplasia, etc) in addition to CKD. SHT is a common sequela to CKD and can result in myocardial hypertrophy and dysfunction in both cats (Chetboul et al. 2003, Henik et al. 2004, Carlos Sampedrano et al. 2006) and dogs (Mischak et al. 2011). Finally, azotaemia itself may have adverse effects on cardiac myocytes (Mall et al. 1990). 

Clinical staging and evaluation of CvRD

The diagnosis of either a kidney disease or a cardiovascular disease requires the integration of information obtained from multiple sources. The presenting complaint, medical history and physical examination can alert the clinician to the kidney, heart or vasculature as deserving of further diagnostic testing. Blood and urine testing, non-invasive blood pressure measurement and radiographic and ultrasonographic imaging are the diagnostic tools routinely available for both kidney and cardiovascular diseases. Accurate diagnosis and staging are essential to the detection of CvRD and in designing subsequent therapeutic plans.

Staging of Heart Disease in CvRD

Statement 4: When considering the potential involvement of the heart in CvRD, the most appropriate classification system is the International Small Animal Cardiac Health Council (ISACHC) system. (No consensus; median rating, 7; range, 2–9)
This statement achieved good consensus. In human and veterinary medicine, the term AKI reflects a broad spectrum of acute insults to the kidney. The IRIS systems for AKI (Table 2) and CKD (International Renal Interest Society 2014) were deemed useful in assessing potential kidney involvement in CvRD. The IRIS systems encompass a continuum of damage from mild to severe, including several key indices of kidney function. AKI is identified by an acute rise in serum creatinine concentration, the sudden appearance of glucosuria or cylindruria or the sudden decrease in urine concentrating ability. Each grade of AKI is further subdivided based on the current nature of urine production. Other biochemical abnormalities that often accompany AKI, including microalbuminuria and increased urine protein-to-creatinine ratio, are accounted for in the IRIS system. Based on the IRIS guidelines, relatively small changes in serum creatinine concentrations can signal AKI, and the severity of AKI can fluctuate as the patient improves, worsens or transitions to CKD. The IRIS system for CKD is based on markers of kidney function, including serum creatinine and proteinuria. The CKD guidelines also incorporate systemic arterial blood pressure, which is an important pathophysiological mechanism of CRS (Fig 1) (Ronco & Di Lullo 2014). Thus, as opposed to existing cardiovascular staging systems, the IRIS guidelines for kidney disease were considered sufficiently complete for description of kidney injury and disease in CvRD.

**Biomarkers and imaging of CvRD**

**Biomarkers of CvRD**

Biomarkers have been defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (Biomarkers Definitions Working Group 2001). Ideally, any particular biomarker not only reflects the severity of the pathological process but can also be used to assess the risk of adverse events, predict outcome and guide therapy. In veterinary medicine, biomarkers generally refer to substances that can be measured in either blood or urine. The consensus group deliberated as to whether or not existing biomarkers for kidney or cardiovascular disease can be used to specifically diagnose, predict outcome or guide therapy in CvRD.

This statement achieved good consensus. Biochemical and biomarker assays for assessment of kidney function are widely used and accepted (Table 3). For example, serum creatinine is...
used to assess GFR and serum and urine albumin and total protein concentrations are used to assess glomerular permselectivity. Urine glucose and amino acid concentrations are used to assess proximal tubular function, while serum electrolytes and bicarbonate concentrations reflect the kidney’s ability to maintain electrolyte and acid-base balance. Finally, urine specific gravity allows assessment of renal concentrating ability. The validity of these markers is well established in both primary acute and chronic kidney injury settings (Polzin 2011), and although their specificity to differentiate primary kidney injury vs. CvRD is untested, these traditional markers are likely adequately sensitive to detect kidney dysfunction due to CvRD. The search for novel biomarkers of kidney injury and markers specific to either CRS or CvRD is a topic of considerable interest in both human and veterinary patients (Maddens et al. 2011, Monti et al. 2012, Tvarijonaviciute et al. 2012, Cobrin et al. 2013, Daure et al. 2013, De Loor et al. 2013, Kai et al. 2013, Rossi et al. 2013, Segev et al. 2013). An abbreviated list of potential markers for various aspects of kidney function is presented in Table 3.

**Statement 7:** Currently, there are no specific biomarkers for CvRD. Consequences of kidney disease on the heart (CvRD<sub>K</sub>) should be evaluated with the cardiac biomarkers N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin-I (cTnI). Biomarkers of kidney function/damage are available but need to be evaluated further in the setting of cardiac disease. (No consensus; median rating, 7; range 3–8)

This statement did not achieve group consensus due to two individual scores that were <5. The most common biomarker tests used to assess cardiovascular disease are N-terminal pro-B-type natriuretic peptide (NT-proBNP), B-type natriuretic peptide (BNP), N-terminal pro-atrial natriuretic peptide (NT-proANP) and cardiac troponin I (cTnI). Although these biomarkers have been well studied in the setting of primary cardiovascular diseases such as cardiomyopathy and valve disease (DeFrancesco et al. 2007, Boswood et al. 2008, Connolly 2010, Oyama et al. 2013), their validity is less well established than that of the biomarkers used for assessment of kidney function, such as creatinine and urine specific gravity. Diagnostic guidelines involving the use of cardiac biomarkers are weakened by significant “grey-zones” that affect the ability to stratify patient populations on the basis of assay results alone (Oyama et al. 2013). The natriuretic peptides, including NT-proBNP, BNP and NT-proANP, are constitutively produced by the myocardium and help regulate plasma volume, sodium excretion and vasomotor tone in both health and disease (Potter et al. 2009). Thus, this system is inherently up- or down-regulated on a moment-to-moment basis and varies with stage of disease as well, potentially leading to erroneous conclusions. Additionally, clinically relevant individual and breed variation is recognised, both within and among healthy and diseased individuals (Kellihan et al. 2009, Sjostrand et al. 2014). Moreover, few studies on cardiac biomarkers have been performed in settings applicable to CvRD. In animals with apparently normal cardiac function, but with acute or chronic renal injury, serum or plasma concentrations of NT-proBNP, BNP and cTn are increased (Lalor et al. 2009, Schmidt et al. 2009, Sharkey et al. 2009, Miyagawa et al. 2013), as all three are at least partially dependent on kidney function for excretion. Therefore, it is difficult to know whether increased natriuretic peptide and cTnI concentrations reflect cardiac injury, normal variation or decreased excretion. Cardiac troponin is a part of the actin-myosin complex and, in healthy individuals, serum or plasma cTnI concentration should be very low. Studies reveal that cTnI concentrations are increased in dogs and cats with primary and secondary cardiac disease and predict clinical outcome (Oyama & Sisson 2004, Fonfara et al. 2010, Hezzell et al. 2012, Langhorn et al. 2013). This suggests that cTnI might be able to detect subclinical cardiac injury due to CvRD, however, interpretation of cTnI assay is clouded by lack of information regarding the time course and magnitude of cTnI release in many disease conditions.

**Imaging in CvRD**

**Statement 8:** Thoracic radiography is recommended to assess the presence or absence of congestive heart failure, and echocardiography is recommended to assess cardiac morphology, lesions, and to estimate relevant haemodynamic parameters. (Strong consensus; median rating, 8; range, 7–9)

This statement achieved strong consensus. Diagnostic imaging plays an important role in the assessment of cardiac function. Radiographic and ultrasound imaging modalities provide morphological expressions of the anatomy and function. These findings and complementary data are derived from history, physical examination, electrocardiography and laboratory analyses of blood and urine. Together, this combination of data allows determination of the presence, cause, severity and consequences of heart disease. Typically, the objective of cardiothoracic radiographic examination is to detect changes in the cardiac silhouette, vascular structures and lung parenchymal pattern, ultimately determining if there are signs of cardiac disease or CHF. Echocardiography is used to assess cardiac morphology and function. Doppler echocardiography, including spectral Doppler, color flow Doppler, tissue Doppler and more advanced modalities such as strain, strain rate and 2D speckle tracking, provides specific information about the velocity and direction of blood flow and myocardial motion (Chetboul 2010, Chetboul & Tissier 2012). Longitudinal changes in radiographic and echocardiographic indices help determine morbidity and predict mortality in dogs and cats with heart disease (Lord et al. 2011, Reynolds et al. 2012). Thus, radiographic and echocardiographic imaging modalities represent two cornerstones of cardiac diagnostic examination. The reader is referred to several excellent reviews of cardiothoracic radiographic and echocardiographic interpretation for more information (Thomas et al. 1993, Buchanan & Bucheler 1995, Litster & Buchanan 2000, Guglielmini et al. 2009, Chetboul 2010, Schober 2010, Chetboul & Tissier 2012).

**Statement 9:** Renal imaging is recommended to improve diagnosis, prognosis and guide potential therapies in CvRD. Conventional abdominal radiographs and ultrasound are recommended to help detect morphological abnormalities and determine underlying aetiology. (Good consensus; median rating, 8; range, 6–9)
This statement achieved good consensus. Various imaging modalities are available to assess the kidney and urinary system. Plain ventrodorsal radiographic examination, in particular, the ventrodorsal view, allows determination of kidney size and number and may provide evidence of unilateral or bilateral abnormalities or differences in kidney size, shape, and position, as well as detection of presence of radiodense uroliths (Rivers & Johnston 1996, Polzin 2011, Bartges 2012). Ultrasonographic examination of the kidneys and urinary tract allows visualisation of renal parenchymal abnormalities, renal pelvic and ureteral dilation, renal blood flow abnormalities, infarcts, cysts, mineralisation and uroliths and helps achieve a diagnosis of pyelonephritis, lymphoma or ethylene glycol toxicosis (Rivers & Johnston 1996, Lamb 1998, Debruyne et al. 2012). The biggest limitation to ultrasonic evaluation is its lack of sensitivity to minor alterations in the anatomy of renal pelvises and ureters (Lamb 1998). Contrast studies, such as the excretory urogram, or more advanced techniques, such as computed tomography or magnetic resonance imaging with contrast, may provide additional information regarding the patency of the urinary system and the presence of abnormalities (Ohlerth & O’Brien 2007, Chang et al. 2011, Fonseca-Matheus et al. 2011, Schmidt et al. 2012). The reader is referred to several excellent reviews of kidney and urinary tract imaging for additional information (Rivers & Johnston 1996, Lamb 1998, Debruyne et al. 2012).

**Systemic blood pressure measurement in CvRD**

**Statement 10:** As the kidney and heart are two organs at risk for damage due to systemic hypertension, and as kidney disease is often associated with systemic arterial hypertension, systemic arterial blood pressure should be systematically monitored in both kidney and cardiovascular diseases. (Good consensus; median rating, 8; range, 5–9)

This statement achieved good consensus. One of the best-described interactions between the kidney and cardiovascular system involves their intimate roles in regulation of arterial blood pressure. SHT represents the best example of a mechanism by which CvRD\textsubscript{SA}, CvRD\textsubscript{S}, and CvRD\textsubscript{A} may occur. Because hypertension negatively affects both organ systems, blood pressure measurement is routinely recommended in patients with kidney or cardiovascular disease, and the reader is referred to several excellent reviews regarding the measurement of blood pressure in dogs and cats (Brown et al. 2007, Syme 2011, Stepien 2014). SHT is also commonly associated with diseases other than kidney disease, such as hyperadrenocorticism, hyperaldosteronism, pheochromocytoma, hypertthyroidism, hypothyroidism, canine diabetes mellitus and canine acromegaly (Brown et al. 2007). SHT is likewise associated with certain therapeutic agents, such as glucocorticoids, mineralocorticoids, erythropoietin and phenylpropanolamine (Brown et al. 2007). SHT can also be stress-induced (i.e. white-coat hypertension) or may occur in the absence of other identifiable disease (i.e. idiopathic, primary or “essential” hypertension) (Belew et al. 1999, Marino et al. 2011). As in humans, SHT in dogs and cats is a potential cause of irreversible lesions in cardiac, vascular, renovascular, ocular and central nervous system tissues. Systolic pressure >160 mmHg indicates progressive risk of end- or target-organ damage (International Renal Interest Society 2014). With regard to the canine kidney, SHT can result in increased rate of renal injury, proteinuria, decreased GFR, increased incidence of uremic crisis and worsened mortality. (Jacobs et al. 2003) In the cat, the causal relationship between hypertension and kidney disease is less clear. It is known that hypertension is a risk factor for proteinuria, which, in turn, is a risk factor for worsening kidney disease (Syme et al. 2006, Jepson et al. 2007, Chakrabarti et al. 2012). In a correlative study of laboratory variables and pathological lesions in the kidneys of cats with CKD, proteinuria was associated with interstitial fibrosis and glomerular hypertrophy, whereas higher time-averaged systolic blood pressure was associated with glomerulosclerosis and hyperplastic arteriosclerosis (Chakrabarti et al. 2013). Cardiovascular injury secondary to SHT is well accepted in humans (Frohlich et al. 1992, Dzarn 2011) and includes left ventricular concentric hypertrophy, arrhythmia, haemorrhage, vascular and myocardial fibrosis and remodelling, development of aortic insufficiency, mainly diastolic but also systolic dysfunction, and heart failure. Controlled studies are lacking in dogs and cats, but observational studies have described several left ventricular hypertrophic patterns (Snyder et al. 2001, Chetboul et al. 2003, Henik et al. 2004, Carlos Sampedano et al. 2006), reversal of left ventricular hypertrophy with blood pressure control (Snyder et al. 2001), retinal vasculopathy (Maggio et al. 2000), aortic dissection and aortic insufficiency related to proximal aortic dilation (Wey & Atkins 2000, Mishbach et al. 2011) and heart failure (Wey & Atkins 2000, Chetboul et al. 2003). Additionally, two-dimensional tissue Doppler imaging studies have demonstrated that SHT in both cats and dogs is associated with diastolic and, to a lesser extent, systolic dysfunction, independent of the presence of myocardial hypertrophy (Carlos Sampedano et al. 2006, Mishbach et al. 2011).

The reported prevalence of SHT in dogs and cats with CKD varies considerably, depending on the population selected, the stage of kidney disease and the blood pressure measuring technique employed, but CKD is assuredly present in a considerable percentage of the population at risk for SHT (Brown et al. 2007). SHT is estimated to occur in 60–90% of dogs and 20–65% of cats with kidney disease (Stepien 2014). The relationship of SHT with mitral valve disease in dogs is incompletely understood, and heart failure. Controlled studies are lacking in dogs and cats, but observational studies have described several left ventricular hypertrophic patterns (Snyder et al. 2001, Chetboul et al. 2003, Henik et al. 2004, Carlos Sampedano et al. 2006), reversal of left ventricular hypertrophy with blood pressure control (Snyder et al. 2001), retinal vasculopathy (Maggio et al. 2000), aortic dissection and aortic insufficiency related to proximal aortic dilation (Wey & Atkins 2000, Mishbach et al. 2011) and heart failure (Wey & Atkins 2000, Chetboul et al. 2003). Additionally, two-dimensional tissue Doppler imaging studies have demonstrated that SHT in both cats and dogs is associated with diastolic and, to a lesser extent, systolic dysfunction, independent of the presence of myocardial hypertrophy (Carlos Sampedano et al. 2006, Mishbach et al. 2011).

The minimum database in animals with SHT should include a CBC, serum biochemistry panel, serum thyroxine concentration, urinalysis and abdominal ultrasound (Brown et al. 2007). Ruling out endocrine or other secondary causes of SHT may require additional disease-specific assays.

Disorders that cause systemic hypotension can also cause kidney and cardiovascular injury. Hypotension, due to severe volume depletion, low cardiac output or collapse of systemic vascular resistance, reduces tissue perfusion and GFR and activates maladaptive neurohormonal responses (Morales et al. 2002). Systemic hypotension, defined as systolic pressure <90 mmHg, has been associated with acute heart failure, occurring in 16%...
Management of CvRD

Treatment of CvRD is challenging, as the treatment for kidney disease often relies upon fluid therapy and close attention to the amount and quality of protein and phosphorous intake (Roudebush et al. 2010, Monaghan et al. 2012, Polzin 2013). In contrast, animals with heart failure typically undergo diuresis and receive protein supplementation, especially in those with signs of congestion (pulmonary oedema or third space effusions) and/or cardiac cachexia, respectively (Atkins et al. 2009, Borgarelli & Hagstrom 2010). Also important to the management of CvRD are an understanding of the tendency for azotaemia to develop in animals receiving diuretics, the benefits and risks of ACEI in the setting of concurrent kidney and cardiovascular disease and the potential influence of SHT on both organ systems (Nicolle et al. 2007, Atkins et al. 2009, Brewster et al. 2012). Thus, both the heart and kidney are affected by abnormal intravascular fluid volume, systemic blood pressure and commonly employed treatments such as diuretics, vasodilators and supplemental fluids used to correct these imbalances. These factors potentially affect the interaction between these two organ systems (DeFrancesco 2008).


Treatment of acute and chronic CHF involves the use of diuretics, including furosemide and hydrochlorothiazide (Atkins et al. 2009, Goutal et al. 2010, Atkins & Hagstrom 2012); vasodilators, including ACEI (Atkins et al. 2009, Goutal et al. 2010, Atkins & Hagstrom 2012), amloidipine (Quinones et al. 1996, Snyder et al. 2001), diltiazem (Gelz et al. 2009), nitroglycerin, hydralazine and nitroprusside (Atkins 2001, Atkins & Hagstrom 2012); neurohormonal blocking agents, including ACEI, spironolactone (Atkins et al. 2009) and beta blockers, such as atenolol and propranolol (Rush et al. 2002, Goutal et al. 2010); and positive inotropes such as digoxin, dobutamine and pimobendan (Atkins et al. 2009, Goutal et al. 2010, MacGregor et al. 2011, Atkins & Hagstrom 2012). AKI and CKD are conditions wherein the diseased kidney fails to adequately excrete waste products and to maintain fluid volume and electrolyte balance, resulting in volume and electrolyte abnormalities, azotemia and clinical signs of uremia, when severe.

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Management of CvRD<sub>k</sub>

**Statement 12:** Unstable CvRD<sub>k</sub>, such as in instances of acute kidney injury (AKI), typically requires hospitalisation to improve renal function and to restore fluid and electrolyte balance while simultaneously evaluating the risk of cardiac dysfunction. In addition to standard management of AKI, particular attention should be directed towards 1) appropriate fluid, diuretic and/or antihypertensive treatment based on hydration status; these therapies are aimed at restoration and maintenance of normal fluid balance and blood pressure while avoiding sodium and fluid overload and 2) re-evaluation of concurrent cardiac medications and possible dosage adjustment. (Strong consensus; median rating, 8; range, 7–9)

This statement achieved strong consensus. This agreement stems from the clinical experiences of the authors, in which diuretic use is recognised as a double-edged sword, saving lives by reducing congestion, but, conversely, being overused in coughing dogs or dyspneic cats with or at risk of developing AKI. Since the diagnosis of CHF can be elusive, these pets may undergo diuretic dosing inappropriately, when suffering from CHF, or inappropriately when not. The authors also note that potent loop diuretics, usually furosemide, are sometimes prescribed at inappropriately high dosages for extended periods, with harmful drying of airway secretions and/or worsening azotaemia.

In cases with clinically significant dehydration, parenteral fluid replacement is often provided in an effort to regain appropriate fluid balance and urine production in patients without frank heart failure. Even in the absence of clinical signs of heart failure, fluid supplementation should be closely monitored to avoid precipitation of congestion and discontinued if respiratory signs are noted or if weight gain becomes excessive. In instances where signs of over-hydration and congestion occur, fluid administration should be discontinued and the addition of diuretics considered.

Patients with CvRD<sub>k</sub> might necessitate a cautious and stepwise approach to fluid replacement or maintenance with a selection of a fluid type relatively low in sodium, along with careful monitoring of body weight, respiratory rate and effort, arterial blood pressure and for development of jugular venous distension or ascites. Resting (i.e. non-panting) respiratory rates >40 breaths per minute have been shown to be a sensitive indicator of early pulmonary congestion (oedema) (Schober et al. 2010, Ohad et al. 2013, Ljungvall et al. 2014). Inadvertent fluid overloading puts additional stress on the cardiovascular system and increases the risk of congestion. With the exception of cases of systemic hypertension, dopamine is not indicated for management of AKI due to lack of proven efficacy and potential for adverse side effects, such as worsening of renal function, arrhythmias and sinus tachycardia. (Chertow et al. 1996, Lauchske et al. 2006, Wohl et al. 2007)

The use of renal replacement therapies (such as haemodialysis and ultrafiltration) that enable fine control over intravascular volume in CvRD<sub>k</sub> is intriguing (Acierno 2011, Cowgill 2011, Eatroff et al. 2012), but requires additional study.

**Important aspects of managing all forms of CvRD**

**Statement 13:** In addition to specific management strategies for CvRD<sub>d</sub> or CvRD<sub>k</sub>, particular attention should be directed towards the following when managing any form of CvRD: 1) identification and treatment of elevated blood pressure as per IRIS recommendations; 2) stepwise titration of dosages of diuretics, ACEI, inotropes and/or fluids with frequent monitoring of renal function, body weight, hydration, electrolyte status, and systemic blood pressure (i.e. performed and rechecked within 3–5 days following initiation or dose adjustment of these drugs); 3) proper nutrition, with respect to reduced dietary sodium and phosphate and appropriate protein and caloric intake. (Strong consensus; median rating, 8; range, 8–9)

This statement achieved strong consensus. In dogs and cats with CvRD, the goal is to maintain systolic blood pressure <160 mmHg in an attempt to prevent or minimise target-organ damage (International Renal Interest Society 2014). As blood pressure increases to above 160 mmHg, the risk to target organs increases and treatment is recommended, with or without evidence of target-organ damage. In both dogs and cats, expert opinion advocates for dietary sodium restriction with concurrent pharmacological therapy (Brown et al. 2007, International Renal Interest Society 2014). In dogs, the first choice therapy is an ACEI, which is titrated to effect while monitoring renal function. In cats, the first choice therapy is the calcium channel blocker amiodipine (International Renal Interest Society 2014).
In cases of refractory SHT, combination therapy with ACEI and amlopidine is useful in both species. Measuring systemic blood pressure accurately in dogs and cats requires careful attention to the equipment and technique. This and a more detailed description of therapy is the subject of several excellent reviews (Brown et al. 2007, Syme 2011, Stepien 2014).

In animals with any form of CvRD, stepwise changes in diuretics or fluids are performed with care and with concurrent monitoring of hydration, renal function and resting respiratory rate. Veterinarians usually administer intravenous or subcutaneous fluids to dogs and cats with anorexia, with urinary tract disease and during anaesthesia in an attempt to maintain hydration and renal perfusion. While potentially useful, fluid administration should be performed with caution, using low-sodium parenteral fluids or sodium-free enteral hydration via feeding tube, especially in the face of underlying heart disease or SHT. Any fluid type can precipitate CHF or hypertensive crisis if administered too rapidly or in excessive volumes. During treatment, veterinarians and, when possible, owners, should monitor the animal’s renal function, respiratory rate and effort, food and water intake, body weight and urine output. Changes in these parameters often signal significant changes in hydration status, worsening of disease or need for medication adjustments. In instances of severe CvRD, in which treatment balance is difficult to achieve, referral to a secondary or tertiary hospital should be considered.

Another important consequence of CvRD is the alteration of drug pharmacokinetics and pharmacodynamics due to impaired heart or kidney function. For example, furosemide requires active secretion across proximal renal tubular cells in order to reach the lumen and its site of co-transporter binding, so that decreased renal perfusion or tubular injury decreases the expected diuretic response (Rose et al. 1976). Cardiac drugs primarily excreted by the kidneys, such as digoxin, enalapril and atenolol, may require dosage adjustments in animals with AKI or CKD (Fleet et al. 2014, Kitagawa et al. 2000, Merrett 2000, Quinones 1996, Toutain 2000). In patients with CvRD and metabolic acidosis or hypoproteinaemia, dosages of drugs that are highly protein bound, such as pimobendan or digoxin, may need to be adjusted. Finally, drug dosages may change for a variety of other reasons. Cardiac cachexia can result in a reduction in dosage requirements as the volume of distribution or drug protein binding is altered necessitating careful modification of the drug dosage with disease progression (Freeman 2012). Likewise, abnormal protein catabolism in cachectic patients may increase serum BUN concentrations, worsening azotaemia. In animals with persistent congestion, the presence of ascites or pleural effusion alters the volume of drug distribution and dosing on lean body weight is preferred.

Ensuring proper nutrition is an important component of managing CvRD. Moderately sodium-restricted diets are appropriate for both kidney and cardiovascular diseases and reduced phosphorus diets are important in kidney disease (Rush et al. 2000, Atkins et al. 2009, Polzin 2011). As previously mentioned, dogs with chronic heart disease may lose muscle mass and body condition, thus confirming that adequate protein and caloric intake is an important goal. In animals with CvRD, this need is counterbalanced by the detrimental effect of high protein intake on azotaemia; therefore, careful dietary planning with the support of a veterinary nutritionist or internist might be helpful. Dietary supplements, such as omega-3 fatty acids, are occasionally used in animals with CvRD (Freeman et al. 1998, Smith et al. 2007, Roudebush et al. 2010, Polzin 2011), both as antioxidants and appetite stimulants, but their safety and efficacy have not been rigorously demonstrated (Lenox & Bauer 2013).

CONCLUSION

Although still very early, there is growing evidence indicating that the pathological states, CRS and CvRD, respectively, may be important in both humans and animals. While some aspects of CvRD clearly exist in dogs and cats, the existence of others is merely speculative. There is clearly much to do in identifying, proving and understanding this subject. This consensus statement is meant to increase the awareness of and codify the definition, classification and means of identification and provide provisional information on management of CvRD. Additionally, this manuscript aims to stimulate and provide a framework for research and communication on CvRD and to encourage collaborative studies involving cardiologists and nephrologists.

The CRS Consensus Group is made up of a diverse group of experts in veterinary cardiology and nephrology, whose efforts resulted in 11 (of 13 proposed) CvRD consensus statements for dogs and cats. The authors recommend that this consensus document be modified, as new information regarding CvRD is available. During their discussions and deliberations, the authors were continuously reminded that the heart, vessels and kidney are inexorably linked, not only anatomically but also by principles at the foundations of physiology, pathology and medicine, and that consideration of a single cardiovascular-renal axis has great merit. The authors hope that this manuscript stimulates interest; advances knowledge of CvRD, its existence and importance; and ultimately contributes to the ability of veterinarians to successfully manage dogs and cats with, or at risk for, this condition.

The modified Delphi methodology, used to build the consensus and develop guidelines for CvRD, provided a formal, predictable and objective scaffold for this project. This method or others like it warrant consideration for developing future consensus statements for veterinary medicine.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could appropriately influence or bias the content of the paper. However, the project was sponsored by Vétoquinol and authors received compensation for their efforts.

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