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Cardiorenal Syndrome: the bidirectional heart-kidney axis

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Abstract: Cardiorenal syndrome is configured as a set of disorders that affect the heart and/or kidneys, and induce a series of events that alter the entire pre-existing axis between the two systems. Accurate diagnosis and adequate monitoring of patients with cardiovascular and renal diseases have become increasingly frequent. Systems are increasingly interconnected, and paying attention to changes has become fundamental. The objective of this article is to characterize cardiorenal syndrome, highlighting its clinical, pathophysiological, diagnostic, and therapeutic management aspects. Dogs and cats are susceptible to kidney changes that alter blood flow, which can interfere with cardiac function, and the reverse may also occur, particularly if dogs/cats already have the organ affected by other diseases. Furthermore, a series of systemic events can end up interfering even more with the communication between the two systems. The monitoring and follow-up of cardiac and/or nephropathic patients are of fundamental importance in determining the best therapeutic management to be instituted, thereby avoiding complications and injuries to other organs, preventing aggravations to the patient's clinical condition, and reducing their life expectancy.
Keywords: heart-kidney axis, cardiac injuries, kidney injuries

1. Introduction

Domestic animals, such as dogs and cats, are susceptible to various pathophysiological conditions, among which renal and cardiovascular disorders are particularly significant due to the interdependence of these systems in maintaining overall homeostasis. The bidirectional heart-kidney axis ensures an adequate blood supply to the kidneys, allowing for proper kidney function. As a result, any changes in renal blood flow are closely linked to cardiac output (CO). Additionally, kidney diseases such as chronic kidney disease (CKD) often lead to hypertension and the progressive, harmful activation of the renin-angiotensin system (RAS), which can impact cardiovascular function. When an animal with heart disease develops some degree of kidney dysfunction as the disease progresses, or when a patient with kidney disease exhibits signs of heart failure, this condition is recognized as cardiorenal syndrome (CRS). CRS is considered a complex disorder affecting both the heart and kidneys, triggering a series of compensatory mechanisms aimed at correcting the dysfunctions present. These mechanisms result in alterations in blood flow, kidney filtration, and systemic blood pressure regulation (Lopes, 2016).

Because CRS involves two organ systems connected by the bidirectional axis, diagnosing the condition is challenging, and its therapeutic management is equally complex. Treating one system can have a direct impact on the function of the other. Among canine heart diseases, myxomatous valve degeneration, especially mitral valve disease, and acquired conditions like dilated cardiomyopathy are the most notable. In feline cardiology, hypertrophic cardiomyopathy (HCM) is the most prevalent form of heart disease (Luis Fuentes et al., 2020; Sousa et al., 2025). Regarding kidney disorders, CKD stands out as a major concern, regardless of its underlying cause. It leads to a decline in glomerular filtration rate and is recognized as the leading cause of death in cats over five years old (O'Neill et al., 2016). This article aims to provide an overview of CRS, highlighting its characteristics, the recognized subtypes of the disease, and current diagnostic and therapeutic strategies.

2. Cardiorenal syndrome (CRS)

According to Ronco et al. (2010), CRS is defined as a pathophysiological disorder affecting both the heart and kidneys, where acute or chronic dysfunction in one organ can lead to acute or chronic changes in the other. In veterinary medicine, discussions have expanded this concept to include not just the heart but the entire cardiovascular system. As a result, the term "cardiovascular-renal disorder" (C_VRD) has been proposed (Pouchelon et al., 2015). Regardless of whether it is referred to as CRS or C_VRD, both terms recognize that the process is triggered by a primary condition that may originate from the cardiovascular system, the kidneys, or even a systemic disorder such as sepsis. This primary dysfunction is sufficient to cause significant effects on both the heart and kidneys. According to Aronson (2012) and Orvalho & Cowgill (2017), cardiac and renal dysfunctions can co-occur, as these systems are interdependent. Thus, heart conditions can impact kidney function, and vice versa.

Even in humans, where CRS is better understood, uncertainties persist regarding its mechanisms, clinical presentations, and progression (Ronco & Di Lullo, 2014). Rangaswami et al. (2019) note that identifying the initial cause and the subsequent effects leading to either acute or chronic CRS remains a challenging task. Orvalho & Cowgill (2017) state that CRS in both humans and animals shares many similarities, particularly concerning the initial triggering event, its consequences, and the process of progressive

disease progression. Challenges remain in understanding its pathophysiology and developing effective therapies. In cases of inadequate CO (whether due to increased afterload or reduced myocardial contractility) or congestion (caused by increased preload), the entire body is affected, including the kidneys, which typically receive 20-25% of the total blood pumped by the heart (Guyton & Hall, 2021). As heart disease progresses, renal blood flow gradually decreases, leading to impaired glomerular filtration, renal excretion and reabsorption processes, and blood pressure regulation (Lopes, 2016). Similarly, the progression of CKD can also cause cardiac changes, particularly affecting blood pressure and fluid balance.

3. Pathophysiology of SCR

Although the exact pathophysiology of CRS is not yet fully understood, some of the mechanisms observed in animals resemble those seen in human cases (Pouchelon et al., 2015). These mechanisms primarily involve compensatory strategies in response to chronic heart failure CHF or kidney disease, typically activating the RAS and the sympathetic nervous system (SNS) (Langhorn et al., 2018; Wrzesniewska et al., 2024; Sousa, 2024). The SNS activation leads to an increased heart rate, elevated blood pressure, and vasoconstriction (Pouchelon et al., 2015; Guyton & Hall, 2021). A reduction in blood flow subsequently lowers blood pressure, triggering compensatory tachycardia. Signals sent to the vasomotor center increase sympathetic tone, prompting the release of norepinephrine and its binding to alpha-1 receptors, which induces arteriolar contraction and increases peripheral vascular resistance. This mechanism attempts to maintain heart rate, CO, and blood pressure. The RAS activation can result from the progression of CHF and/or kidney injury or as a consequence of SNS activation (Sousa, 2024).

Renin is released in response to decreased sodium (Na^+) and chloride (Cl^-) levels in the distal convoluted tubules, initiating the conversion of angiotensinogen to angiotensin I. Through the action of angiotensin-converting enzyme (ACE), angiotensin I is then converted into angiotensin II (Sousa, 2024). This process increases afterload, reduces myocardial contractility, and leads to fluid retention. RAS activation induces renal vasoconstriction and systemic vasodilation as a compensatory measure. However, SNS activation alone can achieve similar effects without directly triggering RAS (Pouchelon et al., 2015). Increased afterload, coupled with reduced myocardial contractility, lowers CO by impairing ventricular ejection. The activation of aldosterone leads to sodium and water retention, exacerbating volume overload. When combined with reduced CO, this results in impaired blood circulation, contributing to congestion. A decrease in CO, whether due to reduced cardiac function or congestion, reduces renal blood volume and glomerular filtration rate (Pouchelon et al., 2015). Additionally, myocardial dysfunction induces inflammation through elevated levels of pro-inflammatory cytokines, contributing to cellular damage and anemia caused by blood stagnation and increased consumption (Mitani et al., 2013). Inflammation, combined with congestion, leads to endothelial injury and the production of reactive oxygen species (ROS), ultimately causing cellular apoptosis and myocardial fibrosis due to oxidative stress (Guyton & Hall, 2021; Sousa, 2024).

Due to cellular damage, the kidneys also experience oxidative stress, a significant loss of nephrons, and a decline in glomerular filtration rate (GFR) (Orvalho & Cowgill, 2017). The reduced production of erythropoietin further contributes to anemia by decreasing the number of red blood cell precursors (Oliveira et al., 2019). As the number of functional nephrons declines, the body compensates by activating RAS to retain urine, reduce electrolyte losses, and regulate blood pressure. While short-term RAS activation helps restore hemodynamic and electrolyte balance, prolonged or repeated activation leads to detrimental effects and the progressive worsening of the disease (Sousa, 2024). Another crucial factor in CRS pathophysiology is systemic arterial hypertension (SAH), which can be situational or primary but is frequently associated with secondary cases of CKD (Sousa et al., 2023). SAH promotes left ventricular hypertrophy, leading to tissue damage and myocardial fibrosis, which further exacerbates heart failure. Hypertension also increases afterload, ultimately reducing CO, renal blood flow, and glomerular filtration rate, thereby worsening kidney injury. Furthermore, SAH contributes to glomerular hypertension, further aggravating CKD by increasing functional overload (Pouchelon et al., 2015; Sousa et al., 2023).

4. Classification and etiology of CRS

Veterinary cardiology and nephrology researchers have proposed a consensus on CRS in cats and dogs to define and characterize the condition, aiding in diagnosis and treatment strategies (Pouchelon et al., 2015). According to this consensus, the preferred term for CRS is "cardiovascular-renal disorder" (C_VRD) because it includes vascular abnormalities in addition to cardiac and renal dysfunctions. For veterinary patients, Pouchelon et al. (2015) suggest classifying C_VRD into three groups based on etiology: C_VRD_H (cardiovascular origin), C_VRD_K (renal origin), and C_VRD_O (non-cardiovascular and non-renal causes). Each category can be further classified as stable or unstable, depending on the variability of disease progression. The central challenge of C_VRD, as noted by Pouchelon et al. (2015), is to understand better the depth and mechanisms of interaction between the heart, kidneys, and the rest of the body. This highlights the increasing need for in-depth research on both systems to clarify their interdependence and improve clinical management.

4.1. C_VRD_H – Cardiovascular

CRS is characterized by a primary cardiac event that compromises renal function. In this condition, patients experience renal impairment as a result of a cardiovascular disorder (Figure 1). Although its prevalence is not yet fully clarified, it is known that as animals age, their predisposition to developing both cardiovascular and renal diseases increases (Pouchelon et al., 2015). Pouchelon et al. (2015) suggest that hypertension, which leads to increased glomerular pressure, is one possible cause of CRS, influencing filtration rates and organ function. Additionally, conditions where renal blood flow is abruptly affected, such as decreased cardiac

output (CO), cardiogenic shock, and hypotensive states, are also associated with CRS. Syndromes involving renal infarctions, such as the presence of thrombi obstructing renal circulation or antigen-antibody complexes from heartworm disease, can also lead to acute renal injury or glomerulonephritis (Pouchelon et al., 2015).

Several authors have noted that animals with cardiomyopathies, even those with mild expression, exhibited azotemia in 50% of cases (Liu et al., 2020) and reduced glomerular filtration rates (Pouchelon et al., 2015). Gouni et al. (2008) conducted a study on 102 felines with HCM phenotype and found that 59% of these animals had azotemia. Fox et al. (2019) demonstrated in a study of cats with HCM that the concomitant presence of CKD was associated with a shorter survival time. Cheng et al. (2022) showed that RAS activity can be compromised following valvular correction surgeries. According to Galizzi et al. (2021), the urine urea/creatinine ratio was higher in animals with stage B2 and C mitral valve disease (MMVD), compared to healthy animals. Giorgi et al. (2022) found that, in a study of dogs with CHF treated with furosemide, 48% of the animals treated parenterally exhibited renal injury, with the majority in stage I (non-azotemic renal failure). However, stages II and III were also present. The higher occurrence of renal injury was associated with the hospitalization process, with high diuretic doses being a contributing factor in home settings (Giorgi et al., 2022).

In a study by Brloznik et al. (2023) with dogs with stage C or D MMVD, 63.2% of the dogs had elevated urea concentrations, and 22.8% had elevated creatinine levels. The authors noted that, although without statistical significance, hospitalized dogs had higher urea and creatinine concentrations compared to those not hospitalized, hypothesizing that unstable CHF could be associated with azotemia, which could influence survival time. Szczepankiewicz et al. (2023) evaluated the use of the renal resistive index (RI), which is associated with arterial resistance, as a method for assessing renal injury in patients with underlying heart disease. They observed that in cardiopathic patients, the RRI was elevated. Yun et al. (2023) highlighted that the presence of MMVD worsens CKD. The data above support the theory that kidneys can be affected by an initial cardiac alteration (Figure 1).

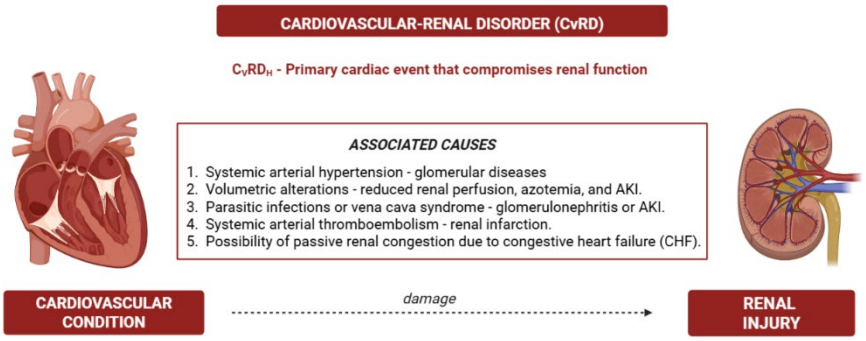

Figure 1 – Factors associated with the occurrence of kidney injury due to primary cardiovascular damage. Consider: C_VRD_H - cardiovascular-renal disorder with cardiovascular origin; AKI – acute kidney injury; CHF – congestive heart failure.

4.2. C_VRD_K – Renal

Patients with C_VRD_K (renal-origin cardiovascular-renal disorder) experience cardiovascular impairment due to renal dysfunction. Unstable C_VRD_K can be observed in cats with urethral obstruction, which can lead to acute cardiac dysfunction, particularly due to hyperkalemia (Pouchelon et al., 2015). Urinary tract obstruction often results in electrolyte imbalances, which can trigger arrhythmias (Ostroski et al., 2017). Stable C_VRD_K is seen in feline patients with chronic glomerulopathy that develop SAH (Morita et al., 2024), which in turn can cause left ventricular hypertrophy and potentially lead to progressive heart failure. According to Pouchelon et al. (2015), several cardiac medications, such as benazepril and enalapril, can affect renal elimination processes, leading to reduced clearance and excessive circulating drug levels. This, in turn, may contribute to arrhythmogenesis, hypotensive episodes, and worsening myocardial function. Additionally, uremic patients may experience a reduction in circulating blood volume due to fluid losses, which can impact CO and further impair proper cardiac function (Pouchelon et al., 2015) (Figure 2).

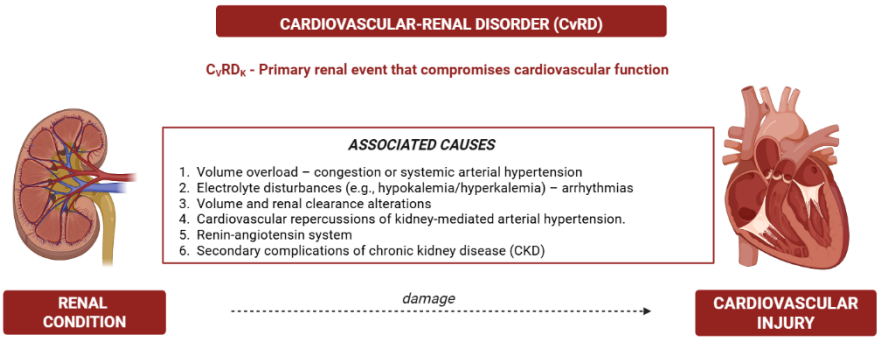

Figure 2 – Factors associated with the occurrence of cardiovascular injury due to primary kidney damage. Consider: CvRDK - cardiovascular-renal disorder with renal origin; CKD – chronic kidney disease.

4.3. CvRDO – Other causes

Patients with CvRDO (other-origin cardiovascular-renal disorder) have an acute or chronic comorbidity that triggers dysfunctions in the cardiovascular and/or renal systems, either acutely or chronically (Pouchelon et al., 2015) (Figure 3). A typical clinical example is cats with hyperthyroidism, which can develop SAH, cardiomyopathy, and impaired glomerular filtration. A study by Kim et al. (2017) demonstrated that myocardial function in diabetic patients may show alterations even before clinical symptoms appear. These early changes can be detected using diagnostic tools like tissue Doppler imaging and strain analysis. Additionally, chronic hyperglycemia can negatively impact myocardial function, even in the absence of underlying cardiovascular disease (Kim et al., 2017). From a renal perspective, diabetes mellitus is associated with renal alterations that require further investigation. However, it is known that hyperglycemia triggers intrarenal adaptive mechanisms that influence glomerular hemodynamics and renal blood flow (Gal & Burchell, 2023).

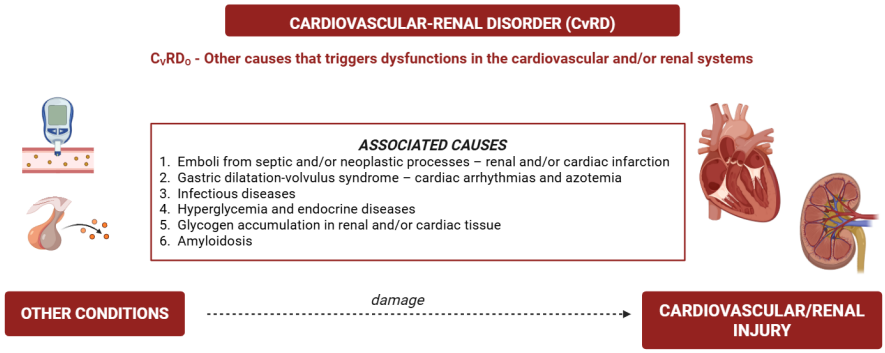

Figure 3 – Factors associated with the occurrence of cardiovascular and/or renal injury due to other damage. Consider: CvRDO - cardiovascular-renal disorder with other origin; CKD – chronic kidney disease.

5. Clinical staging and diagnostic tools

To determine the presence of cardiovascular and/or renal alterations, a comprehensive evaluation of all available information is essential. The medical history, presenting complaints from the pet owner, and findings from the physical examination are valuable in raising clinical suspicion of cardiac or renal involvement. Based on these suspicions, diagnostic tests can be conducted to assess the animal's overall condition. These include complete blood count (CBC), serum biochemistry (such as urea, creatinine, and symmetric dimethylarginine [SDMA]), and urinalysis, among others. Additionally, imaging tests like echocardiography and ultrasonography, as well as electrocardiography (ECG), can provide further clinical insights (Pouchelon et al., 2015; Orvalho & Cowgill, 2017; Luis Fuentes et al., 2020; Wess, 2022). Furthermore, it is crucial to consider each patient's individuality, particularly in felines, and determine the stage of the disease, as it can be classified as either acute or chronic (Pouchelon et al., 2015).

5.1. Staging of cardiovascular disease

Currently, classification systems for staging underlying cardiac diseases have been established to assist in clinical practice, aiding in the diagnosis and therapeutic decision-making process. For dogs, staging has been proposed for the two most common cardiac diseases: MMVD and dilated cardiomyopathy (DCM). The staging system for each condition, as outlined by the American College of Veterinary Internal Medicine (ACVIM), is presented in Tables 1 and 2 (Keene et al., 2019; Wess, 2022). For cats, a classification

system has also been proposed by ACVIM to stage patients with cardiomyopathies, regardless of the specific type of cardiomyopathy. This classification, intended for clinical use, is presented in Table 3 (Luis Fuentes et al., 2020).

Stage		Description
A		- Dogs with a high risk of developing heart failure, **BUT who do not exhibit** any structural abnormalities at the time of evaluation. *Predisposed breeds – small breeds such as Poodle, Dachshund, and Cavalier King Charles.*
B		Dogs that exhibit structural abnormalities (e.g., the presence of mitral valve disease), but have **NEVER HAD CLINICAL SIGNS** of heart failure associated with the condition.
	B1	Asymptomatic animals that exhibit **MILD regurgitation** caused by mitral valve disease. Radiographic and echocardiographic exams show values within normal limits.
	B2	Asymptomatic animals that exhibit **SEVERE regurgitation** with **CARDIAC REMODELING** (left atrial and ventricular enlargement).
C		**- SYMPTOMATIC** animals with severe mitral valve disease sufficient to cause clinical signs of heart failure. *Dogs that respond to the prescribed treatment.*
D		- **SYMPTOMATIC** animals with signs of heart failure but considered to be **REFRACTORY** to the prescribed treatments.

Table 1 – Classification proposed by ACVIM (2019) for categorizing dogs with myxomatous degeneration to facilitate diagnosis and therapeutic strategies. Adapted from Keene et al. (2019).

Stage		Description
A		- Dogs with a morphologically and electrically normal heart. **THERE IS NO** evidence of heart disease. Dogs with a **PREDISPOSITION** to develop dilated cardiomyopathy (DCM). This includes dogs with a positive genetic predisposition for DCM but without detectable evidence of disease. - *Predisposed breeds – Doberman, Irish Wolfhound, Great Dane, Boxer, ...*
B		**- ASYMPTOMATIC DOGS** for congestive heart failure (CHF) with evidence of morphological/electrical abnormalities. Animals may experience syncope. Previously referred to as the hidden stage or silent stage of the disease.
	B1	- **ASYMPTOMATIC DOGS** for CHF. Includes electrical changes **THAT MAY BE** caused by DCM. This arrhythmic stage without signs of cardiac enlargement includes ventricular premature complexes (VPCs) (Dobermans/Boxers) or atrial fibrillation (AF) (Irish Wolfhounds and other giant breeds). Echocardiographic values **NORMAL** or **INCONCLUSIVE**.
	B2	- **ASYMPTOMATIC DOGS** for CHF. They show left ventricular systolic dysfunction (increased left ventricular systole) with or without simultaneous enlargement of the left ventricle in diastole. Electrical abnormalities may be present.
C		**- SYMPTOMATIC DOGS** with current or previous signs of CHF. - Known as the overt stage of DCM. - Dogs that respond to the prescribed treatment.
D		- **SYMPTOMATIC ANIMALS** with signs of heart failure but considered to be **REFRACTORY** to the prescribed treatments. - End-stage of DCM.

Table 2 – Classification proposed by Wess (2022) for categorizing dogs with dilated cardiomyopathy. Adapted from Wess et al. (2022).

Stage		Description
A		**Felines predisposed** to the development of hypertrophic cardiomyopathy phenotype (HCM) (e.g., Maine Coon, Ragdoll, Persian, among others) and other cats. - *Cats that show no signs of cardiomyopathy.*
B		**Asymptomatic felines - cardiomyopathy (subclinical).** This stage is divided into two groups: B1 and B2. **Consider information obtained through clinical examination and tests before staging to facilitate segregation into B1 and B2:** - *Atrial dimension and size (the larger the atrial increase, the worse the consequences).* - *Systolic function of the left atrium (LA) and left ventricle (LV).* - *Degree of LV hypertrophy.*
	B1	Asymptomatic felines with a low risk of developing congestive heart failure (CHF) and thromboembolic events (ATE).
	B2	Asymptomatic felines with a high risk of developing CHF and ATE.
C		- Symptomatic felines with signs of CHF and/or ATE. - *cats that typically respond to the prescribed treatment.*
D		Felines refractory to the prescribed treatment.

Table 3 – Classification proposed by the American College of Veterinary Internal Medicine for categorizing cats with cardiomyopathies. Adapted from Luis Fuentes et al. (2020).

Regardless of the underlying cardiomyopathy, animals are generally staged into five categories. Stage A includes animals that are predisposed to the disease. Stage B (1 or 2) involves animals with structural, functional, and/or electrical damage, but without associated symptoms. Stage C represents animals that are sick and exhibit symptoms of CHF and its consequences, though they respond to therapy. Stage D includes animals that are symptomatic and refractory to conventional medical treatment. These stages enable the clinician to assess the disease's progression and determine if adjustments or modifications are needed in the therapeutic management.

5.2. Staging of kidney disease

To classify and stage animals based on the severity of CKD, the most commonly used system in veterinary medicine is that proposed by the International Renal Interest Society (IRIS) (Tables 4 and 5). The classification of chronic renal disorders is based on the recent IRIS (2023) classification, which categorizes animals according to serum creatinine and SDMA levels into four stages. Additionally, each category outlines the most expected ultrasonographic findings in patients with CKD. These changes are progressive and irreversible, affecting both the medullary and cortical layers, as well as their relationship and definition. Furthermore, in the presence of proteinuria alongside renal changes due to altered glomerular permeability, patients are sub-staged based on the urea/creatinine urinary ratio into three stages: non-proteinuric, borderline proteinuric, and proteinuric. It is also known that renal patients may experience secondary blood pressure changes due to dysregulation of pressure regulation. Therefore, they are further sub-staged based on systolic blood pressure and the risk of organ-target injuries associated with hypertensive damage to organs such as the eyes, nervous system, heart, and kidneys (Morita et al., 2024). Thus, the IRIS 2023 classification enables staging animals based on their underlying kidney disease and its associated consequences, such as proteinuria and hypertension.

Stage		Concentration**		Description
		Serum creatinine *µmol/l* *mg/dl*	**SDMA** *µg/dl*	
1	D	<125 <1.4	< 18	**NON-AZOTEMIC** - Normal blood creatinine or a normal or mild increase in SDMA levels in the blood. - Presence of some other renal abnormality (such as inadequate urinary concentration without an identifiable non-renal cause (in cats), abnormal renal palpation or renal imaging findings, renal-origin proteinuria, abnormal renal biopsy results, or increased blood creatinine or SDMA concentrations in serially collected samples). - Persistent elevation of SDMA levels in the blood (>14 µg/dl) may be used to diagnose early chronic kidney disease (CKD).
	C	<140 <1.6	< 18	
2	D	125 –250 1.4 – 2.8	18 - 35	**MILD AZOTEMIA** - Normal or mildly increased creatinine, mild renal azotemia (the lower end of the range is within reference intervals for creatinine in many laboratories, but the insensitivity of creatinine concentration as a screening test means that patients with creatinine values near the upper reference limit often have impaired excretory function). - Mildly increased SDMA levels. Clinical signs are typically mild or absent.
	C	140 – 250 1.6 – 2.8	18 - 25	
3	D	251 – 440 2.9 – 5.0	36 - 54	**MODERATE AZOTEMIA**. - Many extrarenal signs may be present, but their extent and severity can vary. - If the signs are absent, the case may be considered as early Stage 3, while the presence of many or marked systemic signs may justify classification as late Stage 3.
	C	251 – 440 2.9 – 5.0	26 - 38	
4	D	>440 >5.0	>54	**SEVERE AZOTEMIA**. - Increased risk of systemic clinical signs and uremic crises.
	C	>440 >5.0	>38	

Table 4 – Classification proposed by IRIS (2023) of CKD according to creatinine and symmetrical dimethylarginine (SDMA) concentrations. ** In the case of animals that present serum creatinine values for one stage and SDMA for another, the animal should be classified according to the SDMA value as it is a more sensitive indicator. Example: feline with creatinine concentration of 180 µmol/l (stage 2) and SDMA of 32 µg/dl (stage 3), should be classified as stage 3. *Consider: C – dogs; G – cats; SDMA - symmetrical dimethylarginine; µmol/l – micromole per liter; mg/dl – milligrams per deciliter; µg/dl – micrograms per deciliter;

Understaging due to PROTEINURIA**	
UPCR value	**Stage**
< 0.2	Non-proteinuric
0.2 – 0.5 (dogs) | 0.2 – 0.4 (cats)	Borderline proteinuric
> 0.5 (dogs) | > 0.4 (cats)	Proteinuric
UPCR (urine protein-to-creatinine ratio) should be measured in cats without complicating factors (e.g., inflammation, bleeding, cystitis, among others).	
- Dogs and cats classified as borderline proteinuric should be re-evaluated (e.g., at a 2-month interval).	

Understaging due to BLOOD PRESSURE ***		
Systolic pressure (mmHg)	**Stage**	**Risk of target organ damage.**
< 140	Normotensive	Minimal
140 – 159	Pre-hypertensive	Mild
160 – 179	Hypertensive	Moderate
≥ 180	Severely hypertensive	Severe
*** Systolic blood pressure values should be obtained after multiple measurements.		
- Discrepancies in values should be considered depending on the breed being evaluated (e.g., hunting breeds).		
- Classification should be made after persistent increases during the evaluated weeks (e.g., 2 weeks); thus, a single blood pressure measurement should not be used as a classificatory criterion.		

Table 5 – IRIS (2023) proposed substaging of CKD for protein and systolic blood pressure. *Consider: UPCR – urinary protein creatinine ratio; mmHg – millimeters in the mercury column.

5.3. Complementary exams

5.3.1. Biomarkers

According to Pouchelon et al. (2015), there are no exclusive biomarkers that can definitively prove damage caused by cardiovascular-renal disease in heart disease (C_VRD_H). To measure cardiac damage, biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) can be used (Pouchelon et al., 2015; Langhorn et al., 2018). The most commonly used biomarkers for measuring the severity of cardiovascular injuries (Oyama, 2015) include NT-proBNP, B-type natriuretic peptide (BNP), N-terminal pro-atrial natriuretic peptide (NT-proANP), and cTnI. However, the clarity of their results is less well-defined when compared to markers of renal function (Pouchelon et al., 2015). A significant challenge with these biomarkers is their low utilization in Brazil, making them difficult to access and expensive. These biomarkers are associated with the analysis of organ function or damage. They can be measured to assess the general degree of injury suffered and estimate the progression of the condition (Oyama, 2015). For NT-proANP and NT-proNP (function measurement), their release into circulation occurs after overload conditions (Oyama, 2015; Gavazza et al., 2021). In the case of cTnI, which is linked to cardiac injury, its increase predicts damage specifically in the cardiomyocyte (Gavazza et al., 2021); however, it is not a prognostic indicator of death in critically ill cats (Pelander et al., 2023). cTnI concentrations should be interpreted with caution, whether using commercial assays or i-STAT®, particularly when considering cutoff values for cardiac dysfunctions (Ferasin et al., 2024).

The NT-proBNP, BNP, and NT-proANP are derived from the heart, and among their functions, they regulate plasma volume, sodium excretion, and vascular contractions (Kanno et al., 2016). Liu et al. (2020) conducted a study with biomarkers and found that concentrations of SDMA, NT-proBNP, and creatinine were increased in cats with hypertrophic cardiomyopathy. Lalor et al. (2009) performed a study to assess the concentrations of natriuretic peptides (NT-proBNP and NT-proANP) in cats with hypertension and CKD compared to healthy patients. According to the authors, NT-proBNP measurements can be essential for diagnosing systemic hypertension, with a sensitivity of 80% and a specificity of 93%. However, NT-proANP measurements could not be used for diagnosing pressure elevation due to the small sample size. Still, the authors indicate that further studies are needed to determine its diagnostic value (Lalor et al., 2009). Pelander et al. (2017) conducted a study to analyze associations between concentrations of cTnI and NT-proBNP, as well as other variables related to cardiac and renal function in patients with stabilized CKD. They found that patients with stage III CKD had elevated plasma NT-proBNP values compared to healthy animals. NT-proBNP values increased with elevated creatinine levels, urine protein-to-creatinine ratio (UPCR), and plasma volume factor, while decreasing as the glomerular filtration rate, albumin levels, and erythrocyte volume fraction improved. Regarding cTnI, concentrations increased with age, blood pressure, weight, creatinine, and plasma volume factor. The authors concluded that the increase in these biomarkers does not interfere with the interpretation between dogs with stable CKD and healthy animals.

Renal biomarkers are more commonly used to assess renal injuries, with greater acceptance and understanding, including serum glucose, urinary electrolytes, and others. Depending on the renal region affected, specific regional biomarkers enable a more accurate assessment of the damage (Table 6). Among the various biomarkers, creatinine measurements allow the assessment of GFR and urine production (Wrzesniewska et al., 2024). Protein evaluation helps determine how permeable the glomerulus may be, among other factors that reflect the kidneys' ability to concentrate urine (Pouchelon et al., 2015; Hanås et al., 2020). Despite the difficulties associated with using biomarkers for specific cardiovascular and renal alterations, it is essential to consider the individuality of each patient, as considerable variation can occur depending on racial patterns (Sjostrand et al., 2014). cTnI belongs to the actin/myosin complex (Langhorn et al., 2018) and has typically low concentrations in healthy patients (Pouchelon et al., 2015). Increases in cTnI can occur in cases of primary and secondary cardiac disease (Langhorn et al., 2013). However, more details are needed, as troponin

may also be elevated in other diseases (Pouchelon et al., 2015). Langhorn et al. (2018) conducted a study to investigate whether cTnI concentrations increase in patients with impaired renal function, even in the absence of apparent structural cardiac damage. The study involved 52 cats, divided into three groups (renal dysfunction, primary heart disease, and control), excluding those with comorbidities. The serum cTnI concentrations were 0.052, 0.083, and 0.012 ng/ml, respectively, showing an increase in the groups with renal and cardiac alterations. The authors observed that cTnI concentrations increased in cats with impaired renal function but without notable cardiac disease. They hypothesized that circulatory alterations, along with the presence of toxins, could cause myocardial damage and worsening renal function. Additionally, they suggested that the increase in cTnI could partly reflect cardiac injury. On the other hand, Valente et al. (2020) assessed whether SDMA levels influenced dogs with MMVD, hypertension, and heart failure, but the study could not confirm renal involvement in these patients.

Renal parameters		Test
Glomerular Filtration Rate	Traditional blood and urine tests	Serum Creatinine Plasma clearance techniques
	New potential markers	Symmetric Dimethylarginine (SDMA)
Permeability Selectivity	Traditional blood and urine tests	Serum Albumin Urinary protein-to-creatinine ratio Microalbuminuria
	New potential markers	Urinary Immunoglobulin G
Tubular Damage or Dysfunction	Traditional blood and urine tests	Serum Creatinine Serum Electrolytes Serum Bicarbonate Urinary Glucose Urinary Amino Acids Urinary protein-to-creatinine ratio Urinary Density
	New potential markers	Urinary Gamma-Glutamyl Transferase (GGT) Urinary N-acetyl B-D-glucosaminidase (NAG) Urinary Retinol Binding Protein (RBP) Urinary Cystatin-C Urinary Kidney Injury Molecule-1 (KIM-1) Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) Urinary Clusterin

Table 6 – Biomarkers for assessing kidney function and injury. Adapted from Pouchelon et al. (2015).

Biomarkers such as clusterin and neutrophil gelatinase-associated lipocalin (NGAL) may increase after prolonged periods of pre-renal azotemia in dogs with histopathological injury (Gu et al., 2020). For Jung et al. (2018), concentrations of NGAL ≥ 16.0 ng/mL exhibited sensitivity and specificity above 90% for CRS in dogs with CHF. In dogs with asymptomatic DCM, NGAL concentrations and the NGAL/creatinine ratio serve as indicators of the early stage of renal damage (Wrzesniewska et al., 2024). Cystatin C is a biomarker used to assess tubular damage, associated with urinary excretion (Wrzesniewska et al., 2024). Iwasa et al. (2023) evaluated the potential use of cystatin C in dogs with MMVD and observed that serum concentrations were related to mortality due to the cardiopathy. Dogs with higher cystatin C levels had a shorter survival time, suggesting that elevated protein concentrations are indicative of a poorer prognosis, even when creatinine levels are within the reference range (Iwasa et al., 2023). Troia et al. (2022) and Crosara et al. (2024) assessed the influence of NGAL, a marker of tubular injury, in dogs with MMVD. The authors found a correlation between urinary NGAL concentration and the uNGAL/urinary creatinine ratio with left atrial systolic volume and tricuspid regurgitation, suggesting that tetracamera volumetric overload indices can predict the occurrence of renal congestion in dogs with MMVD (Troia et al., 2022; Crosara et al., 2024). In summary, measuring cTnI, NT-proBNP, SDMA, and urinary gamma-glutamyl transferase (GGT) is easier to perform compared to other biomarkers. cTnI assesses the degree of cardiac injury (prognostic marker), and NT-proBNP measures the level of cardiac dysfunction. SDMA is considered an early marker of renal damage, increasing as the condition worsens, while urinary GGT (Freitas et al., 2014) is associated with tubular injury or damage. Other markers, such as the podocin/creatinine ratio in urine, are being evaluated by Szczepankiewicz et al. (2019) as early biomarkers of glomerular damage in dogs with MMVD, as podocin is a protein located in the glomerular region.

5.3.2. Imaging exams

Among the available diagnostic tests for cardiovascular changes, thoracic radiography stands out as a crucial tool for detecting the presence of cardiac injuries. Additionally, in the case of cardiovascular alterations, echocardiography can evaluate morphology and detect lesions (Chetboul et al., 2015; Pouchelon et al., 2015; Lopes, 2016; Bussadori, 2024). Using M-mode, two-dimensional mode, and Doppler in their various modalities, echocardiography enables the evaluation of the internal heart and associated structures, along with the estimation of the animal's hemodynamics. Moreover, it serves as a gold standard in certain diseases for decision-making because it enables the analysis of blood flow and direction (systolic and diastolic function), as well as cardiac motion (Pouchelon et al., 2015; Lopes, 2016; Bussadori, 2024). Imaging exams have become a viable and necessary option, enabling both morphological and functional evaluation of organs, especially the heart and kidneys. These exams complement therapeutic and surgical decisions, emphasizing the importance of integrating them with the patient's clinical condition (Pouchelon et al., 2015).

Cardiothoracic radiography primarily aims to observe and diagnose cardiac and pulmonary changes, such as alterations in organ size and shape. Additionally, it allows the detection of heart disease with pulmonary reflexes, such as in cases of left-sided CHF

(Mikawa et al., 2020). As another diagnostic screening tool, electrocardiography enables the veterinary clinician to evaluate the heart's electrical activity. It is helpful for rhythm evaluation, arrhythmia detection, and the origin of syncopes (Santilli et al., 2021). Furthermore, by analyzing the impulse, changes in the dimensions of cardiac chambers, certain diseases, and modifications in electrolyte concentrations can also be suggested (Santilli et al., 2021). Abdominal radiographs and ultrasonography are important for diagnosing renal changes (Pouchelon et al., 2015; Sohn et al., 2016; Segev et al., 2024). Radiographs, taken in either ventrodorsal or laterolateral positions, enable the assessment of both kidneys and other organs of the urinary system. In patients with CKD, it is possible to evaluate irregularities of the organ, size, layer definition, and cortical layer changes, among other findings (Perondi et al., 2020; Segev et al., 2024). They can help determine organ size and position, as well as detect the presence of cysts, renal infarcts, effusions, pelvic dilations, and urinary stones (Perondi et al., 2020). To assess organ density, thickness, as well as abnormalities in flow and function, ultrasonography proves helpful (Pouchelon et al., 2015; Segev et al., 2024).

5.3.3. Systemic pressure measurements

Both the cardiovascular system and the kidneys can suffer injuries as a result of hypertensive conditions (Sousa et al., 2023; Morita et al., 2024), and such occurrences are often valuable for clinical monitoring (Pouchelon et al., 2015). Therefore, constant monitoring is recommended (Acierno et al., 2018; Sousa et al., 2023; Sousa et al., 2025). Systolic blood pressure (SBP) values between 160 – 179 mmHg, measured over one to two weeks, indicate patients with moderate hypertension and a moderate risk for organ damage. Values equal to or greater than 180 mmHg indicate cases of severe hypertension, which carries a high risk of organ injury (Acierno et al., 2018; IRIS, 2023). In cats, the association between CKD and SBP remains less clearly defined, warranting further studies. However, it is believed that an increase in SBP is a predispositional factor for CKD (Acierno et al., 2018), as it can cause proteinuria, which in turn may exacerbate kidney disease (Morita et al., 2024). According to Morita et al. (2024), about 89% of hypertensive cats had associated CKD. Hypotension (SBP < 90 mmHg) can also lead to various alterations due to the reduction in circulating blood volume, such as decreased tissue perfusion, reduced GFR, and hypovolemic shock, among others (Morales et al., 2002). Davis et al. (2022) highlight that hypotensive episodes following anesthesia lasting one hour can cause proximal tubular damage and acute kidney injury (AKI) due to ischemia-reperfusion injury.

6. Therapeutic management

Establishing therapeutic management for patients with cardiovascular and renal diseases (CVRD) is a complex task that requires careful consideration from both cardiologists and nephrologists (Orvalho & Cowgill, 2017). For Wrzesniewska et al. (2024), “the co-occurrence of conditions like CHF and AKI/CKD significantly compounds the clinical challenges”. In some cases, attempting to optimize the management of one organ may inadvertently exacerbate the condition of the other system (Pouchelon et al., 2015). For patients with cardiac disorders, the primary goal is to promote aggressive diuresis to relieve congestive signs, promote blood flow, control blood pressure, reduce renal impacts, and prevent the progression of AKI (Borgarelli & Häggström, 2010; Pouchelon et al., 2015). Conversely, for patients with renal disorders, the aim is to implement fluid therapy cautiously. This helps control the risk of electrolyte imbalances (Martins & Shih, 2015) due to excessive minerals and/or nitrogenous compounds, such as urea. However, if fluid therapy is administered too rapidly, it may cause abrupt changes in electrolytes if not carefully monitored. In cases where animals have CKD and CHF concurrently, the aggressive administration of fluids can lead to congestive episodes (Pouchelon et al., 2015). This congestion arises partly because CKD patients often experience significant nephrotic loss with impaired glomerular filtration and excretion. The combination of cardiac and renal diseases is responsible for reducing the survival rate (Martinelli et al., 2016). The accumulation of minerals, such as sodium, in these patients worsens the situation. Administering excessive fluids without sufficient renal excretion capabilities leads to blood volume buildup. Since the heart is already insufficient, it cannot pump properly, resulting in vascular congestion (Martins & Shih, 2015; Oliveira et al., 2019).

6.1. C_VRD_H Management

According to Pouchelon et al. (2015), the management of cardiovascular-renal hybrid diseases (C_VRD_H) must be careful and precise to avoid major renal complications and adverse effects on other organs, while simultaneously reducing signs of hypoperfusion and cardiovascular congestion. Patients should be closely monitored with ongoing evaluation of both cardiac and renal functions. Treating CHF can induce renal disease (Martinelli et al., 2016; Orvalho & Cowgill, 2017). Therefore, a variety of pharmacological treatments may be used to address the failures present and improve the animal's quality of life. For acute and CHF cases, depending on the stage of the disease, diuretics such as furosemide are commonly used (Pouchelon et al., 2015; Acierno et al., 2018). However, it is important to note that, according to the latest consensus, diuretics are not routinely used in cats (Acierno et al., 2018).

Additionally, vasodilators, such as angiotensin-converting enzyme inhibitors (ACE inhibitors) like enalapril, may be utilized (Acierno et al., 2018). In 2025, Lombardo et al. (2025) subcutaneous furosemide may be effective in controlling congestion in cats with an unfavorable response to oral diuresis. Some professionals use these drugs cautiously due to the risk of drug-induced renal injury, but they should be preferred after volume stabilization or in cases of recurrent congestion. They are not recommended as first-line treatment in dehydrated patients (Acierno et al., 2018). Additionally, electrolyte levels, such as potassium and sodium, should be monitored and corrected if needed. Other medications that can be used include amlodipine (Acierno et al., 2018; Morita et al., 2024), diltiazem (Whitehouse et al., 2023), nitroglycerin, hydralazine, and sodium nitroprusside (Ghio et al., 2024). The study by Sabbah et al. (2024) demonstrated that the combination of sacubitril/valsartan improves left ventricular systolic function in dogs

with CRS. These drugs may assist in controlling hypertension, improving myocardial function, and alleviating symptoms of both renal and cardiovascular distress.

6.2. CvRDK Management

Both AKI and CKD occur when the kidneys fail to produce urine, maintain volume, and excrete waste, among other functions (Segev et al., 2024). Due to the reduction of erythropoietin precursors, it is essential to administer medications that stimulate its production, in addition to alkalinizing agents, gastric protectants, phosphate binders, and dietary control (Segev et al., 2024). Adequate volume and pressure are crucial for ensuring tissue perfusion, thereby reducing the risk of renal hypoxemia (Pouchelon et al., 2015; Segev et al., 2024). According to Pouchelon et al. (2015), depending on the presentation of the injury and the stage of disease the animal is experiencing, such as during decompensations, constant monitoring is essential to improve renal and volume function effectively and correctly. Thus, fluid replacement and electrolyte dosages are important to prevent disturbances in other organs, in addition to the kidneys. The use of fluids, diuretics to restore renal flow, and anti-hypertensives to control blood pressure fluctuations are critical components of therapy (Segev et al., 2024).

Additionally, ongoing systemic evaluation is necessary to assess the need for medication substitutions or adjustments in dosage. In the case of diuretics, while their use is beneficial for reducing congestive symptoms, high doses and prolonged use can predispose animals to azotemia (Orvalho & Cowgill, 2017) and pulmonary secretion dryness. The study by Ishizaka et al. (2024) demonstrated that the combination of sacubitril/valsartan improves renal hemodynamics. Volume replacement should be done with fluids that are low in sodium and carefully monitored to prevent excessive fluid administration, which could lead to edema and congestion (Pouchelon et al., 2015; Segev et al., 2024). Moreover, Luis Fuentes et al. (2020) indicate that a respiratory rate above 30 breaths per minute at rest may signal the risk of edema development, emphasizing the need for close monitoring of such vital signs in managing the condition.

6.3. CvRDO Management

In the case of other forms of cardiovascular and renal disease (C_VRD_O), it is essential to detect the presence of the condition and tailor therapeutic management according to the degree of hypertension (IRIS, 2023). Regular monitoring of patients, typically weekly, along with routine laboratory tests, allows for adjustments to treatment based on the individual's responses. Additionally, providing an appropriate diet—low in sodium and phosphate—is a valuable approach for promoting both renal and cardiac well-being (Pouchelon et al., 2015). A recent study by Reynolds et al. (2023) aimed to evaluate the cardiac and renal safety of chronic high-sodium diets in cats. The authors found that the diet did not significantly impact variables such as GFR, blood pressure, creatinine levels, or cardiovascular structure and function. The study concluded that diets containing 3.26 ± 0.30 g/Mcal of sodium in metabolizable energy were safe for healthy elderly cats over 5 years (Reynolds et al., 2023).

7. Conclusions

CRS represents a significant and serious condition that threatens the balance between health and disease. It is important to note that the cardiovascular and renal systems share a common axis. One of the primary goals is to achieve balance by minimizing and delaying existing alterations, thereby preventing further complications. Classifying and staging patients based on the severity of the condition is crucial to ensure success in the established therapeutic protocol. The therapy is essential and focuses on providing life expectancy, but cautiously and effectively. Furthermore, the progression of the disease can be closely monitored, ensuring the patient's well-being and potentially increasing life expectancy. Given that this syndrome is still not fully understood, further studies should be conducted to understand better the factors that contribute to its occurrence.

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