The Role of Hypochloremia in Heart Failure Progression

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Electrolyte derangements are common in dogs and cats with congestive heart failure (CHF), both before and after diuretic therapy. The importance of hypochloremia in this clinical setting has only recently been recognized in human and veterinary medicine.

CHLORIDE HOMEOSTASIS

Chloride is the most abundant extra-cellular anion in the body. It is important to acid-base balance because of its reciprocal relationship to bicarbonate: chloride excretion increases in acidosis (to conserve bicarbonate) and decreases in alkalosis (to excrete bicarbonate). Similarly, bicarbonate is retained in clinical situations of chloride loss because less chloride is available for exchange (e.g. diuresis).

Chloride balance is regulated by the gastrointestinal tract and the kidneys. It is freely filtered at the glomerulus and then resorbed at the level of the renal tubules by transcellular and paracellular mechanisms. The greatest amount of resorption occurs in the proximal tubules by paracellular routes with a lesser amount through cotransporters (along with K^+) and counter-transporters (opposite to $HCO3^-$, Na^+, $HCOO^-$, and $SO4^-$) that are present on either the luminal or basolateral sides of the tubular cells. The best-known cotransporter of Cl^- (along with Na^+ and K^+) is the NKCC in the thick ascending Loop of Henle, the channel that is inhibited by loop diuretics. Thiazide diuretics inhibit the NCC cotransporter in the distal tubule, and the counter-transporter of $HCO3^-$ and Cl^- occurs in the collecting duct at the Pendrin channel. After tubular resorption, most of the chloride moves from the tubular cells to the blood through voltage-gated chloride channels.

Single nephron tubuloglomerular feedback is dependent on intracellular chloride sensing which modulates glomerular filtration rate and proximal tubular resorption of sodium in response to volume and salt load. The NKCC channel on macula densa cells in the juxtaglomerular apparatus transports chloride into these cells where it is sensed by the with-no-lysine K (WNK) protein kinase. Chloride molecules bind to WNK kinase, but when chloride molecules are scarce, the binding site can be phosphorylated, leading to release of renin and upregulation of NKCC and NCC channels that will increase sodium and water retention; an appropriate response to a low flow state such as volume depletion. Sensing of adequate intracellular chloride concentration inhibits renin release. This fine, local control facilitates renal autoregulation so that glomerular filtration rate and renal blood flow change minimally within the range of normal blood pressures.

THE CHLORIDE THEORY OF WORSENING HEART FAILURE

The chloride theory of worsening heart failure is a recent concept centered on the pivotal role of chloride in the regulation of renin secretion and volume status. It posits that regardless of the cause of hypochloremia in heart failure, this electrolyte disturbance contributes to disease progression because of the cascades that are initiated when renal intracellular chloride is low. Thus, hypochloremia can be a result of disease or diuresis and can also mediate diuretic resistance and poor diuretic responsiveness. In support of this theory are studies that show that hypochloremia is prognostically more important than hyponatremia in heart failure. This theory serves as a springboard for considering therapies to address hypochloremia in an attempt to break the cycle.

Heart failure-associated hypochloremia can be due to depletion (loss as a result of diuretic therapy) or due to dilution (from free water retention). Hypochloremia that is due to loop-diuretic

associated chloride loss is usually accompanied by a normal serum sodium concentration because of the nature of the NKCC inhibition, resulting in twice as much chloride loss in the urine as sodium loss. Mathematical correction results in little change in the chloride value. Hypochloremia that is due to dilution (presumably a result of excessive anti-diuretic hormone) is usually accompanied by hyponatremia because of the effect of excessive free water retention on both electrolyte concentrations equally. Mathematical correction results in an increase in the chloride value. Many patients with heart failure have mixed depletional and dilutional hypochloremia. No studies have tried to relate hypochloremia etiology to prognosis in heart failure.

Hypochloremia is common in people, dogs, and cats with CHF. Roche-Catholy *et al* found that hypochloremia was the most common electrolyte abnormality in diuretic-naïve dogs and cats that were presented for first-time CHF. This group also found that serum chloride concentration was negatively correlated with furosemide dosage at hospital discharge and at end stage CHF in dogs, suggesting negative prognostic value as has been noted in people. Presumably, hypochloremia in diuretic-naïve dogs is a result of free water retention, possibly because of exuberant RAAS stimulation and non-osmotic antidiuretic hormone (ADH) secretion. Adin *et al* found lower serum chloride concentrations in ACVIM Stage D CHF compared to Stage C CHF dogs, which might also be explained by greater ADH influence in dogs with refractory CHF. These studies support hypochloremia as a marker of advanced heart disease and possibly diuretic resistance.

IMPACT OF LOOP DIURETICS ON CHLORIDE HOMEOSTASIS

Loop diuretics are an indispensable part of CHF treatment because they address life-threatening fluid retention. However, these medications do not increase longevity beyond the initial CHF crisis and in fact may contribute to poor outcomes. Loop diuretics interrupt chloride homeostasis and tubuloglomerular feedback because they bind to and inhibit the NKCC on macula densa cells in the distal tubule (as well as NKCC in the ascending Loop of Henle). Although the tubular fluid is rich in chloride and the urine flow is high in the presence of diuretics, transport of tubular chloride into the macula densa cells is blocked. WNK kinases therefore sense low intracellular chloride which initiates the cascades associated with renin release and distal tubular Na+ channel up-regulation. This is a mechanism by which loop diuretics promote diuretic resistance and contribute to disease progression.

METABOLIC ALKALOSIS

Hypochloremia promotes a net bicarbonate gain because of the reciprocal relationship between these anions, but metabolic alkalosis might have other sources in heart failure. Angiotensin II and hypokalemia (which could be caused by a failing heart or diuretic therapy) both increase HCO3- resorption in the proximal tubule, and aldosterone increases H+ATPase in the collecting duct to cause urine acidification. Thus, metabolic alkalosis is intertwined with the vicious cycle of hypochloremia that is only partly due to diuretics.

Metabolic alkalosis is the most common acid-base abnormality in people with CHF and there is some evidence that alkalosis could contribute to diuretic resistance. Metabolic alkalosis reduces the diuretic efficacy of bumetanide by 40% in people and it has been shown to increase distal tubular NCC receptor density in rats. The ALCALOTIC study (https://clinicaltrials.gov/ct2/show/NCT01499485) is underway to determine the prevalence and prognostic importance of metabolic alkalosis in people. Unpublished data from our group (Giorgi, Ward, Mochel, Adin) found that 26% of all dogs and 11% of diuretic-naïve dogs with acute CHF had an elevated serum $HCO3^-$. Serum chloride concentrations were inversely related to serum $HCO3^-$ concentration, both at admission and at an outpatient CHF recheck.

STRATEGIES TO ADDRESS HEART FAILURE RELATED HYPOCHLOREMIA

The cycle of hypochloremic metabolic alkalosis in heart failure is challenging to break because of the underlying etiologies and necessary treatments. Acknowledging the role of hypochloremia in promoting neurohormonal activation and diuretic resistance begs the question of whether raising serum chloride concentrations can positively impact patient outcomes. Because loop diuretic-induced loss is a significant factor in hypochloremia, strategies to avoid overdiuresis or reduce diuretic dosage with adjunctive therapies seem reasonable. Because non-osmotic ADH release likely contributes to free water retention, appropriate RAAS-inhibition and attempts to improve cardiac output (positive inotropes, afterload reduction) could be helpful. Specific ADH antagonists (e.g. tolvaptan) are not financially feasible for most pet owners and have not been shown to unequivocally improve outcomes in people. Because of the effects of hypokalemia on acid-base status and renal ammonia genesis, potassium supplementation can help to address hypochloremia. Lysine monohydrochloride has been evaluated in people with CHF and hypochloremia with mixed results. Potassium chloride supplementation may be a way to enhance serum chloride and potassium concentrations but this has not been evaluated. Acetazolamide is a chloride-retaining diuretic that has been shown to improve serum chloride concentrations in people, and the clinical trial ADVOR (https://clinicaltrials.gov/ct2/show/NCT03505788) is underway to assess for effect on outcomes. We have limited experience using acetazolamide in dogs with CHF and are currently enrolling dogs in an AKC-CHF funded clinical study at the University of Florida to determine the short- and medium-term effect of acetazolamide in hypochloremic dogs with CHF. This study will determine if acetazolamide can raise serum chloride concentrations in dogs with hypochloremia but future studies will be necessary to determine if such interventions will positively affect outcomes.

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Managing Feline Arterial Thromboembolism

Feline arterial thromboembolism (FATE) is a devasting complication of heart disease in cats with median survival after an event of around 6 months. Although hypertrophic cardiomyopathy is the most common heart disease of cats (prevalence around 15%), any cardiac disease that leads to atrial enlargement can predispose to thrombus formation. Virchow's triangle posits that endothelial injury, hypercoagulability, vascular stasis, or a combination of these factors helps to explain the propensity to thrombus formation. Cats with cardiomyopathy have blood stasis in their enlarged left atrium and may be hypercoagulable, both of which predispose them to thromboembolic complications. The risk of FATE in cats with preclinical HCM is about 10% at 5 years post-heart disease diagnosis.

Thromboembolism prevention can be initiated in cats with preclinical heart disease if risk factors are identified. Risk is higher for cats with enlarged left atrial size, low left auricular blood flow velocity (indicating stasis), and echocardiographic "smoke" (swirling of blood flow which is assumed to be a pre-clot phenomenon. Extrapolation of the results of the FATCAT study (which showed a 8.4 month prolongation of time to 2nd thromboembolic event in cats surviving a 1st event treated with clopidogrel compared to low-dose aspirin) to cats with these risk factors is reasonable.

Clinical recognition of FATE is usually not difficult. The most common anatomic site for an embolus to lodege is the distal aorta, causing posterior paralysis. Hallmark physical examination findings are pain, paralysis, pallor and loss of femoral pulses. Any systemic site can be embolized. Congestive heart failure (CHF) is a common occurrence in cats with FATE, with 70% of cats experiencing CHF at the time of the thromboembolic event.

Treatment of FATE is challenging, not only from the standpoint of navigating the crisis but also because the majority of underlying diseases predisposing to FATE, are irreversible. Therefore, even if the cat recovers from the FATE episode and starts thrombus prophylaxis, it remains at risk for future thromboembolic events. Euthanasia is therefore a reasonable option to address FATE. Treatment options include definitive (e.g. thrombolytics) and palliative (supportive treatment), and outcomes are similar with either approach (50% success). A palliative treatment plan should include treatment of concurrent CHF if present, pain control, unfractionated heparin in the hospital, initiation of clopidogrel in the hospital, monitoring of vitals, monitoring of renal function, monitoring of cardiac rhythm, and physical therapy. It can take up to 6 weeks for return of limb function but some cats may require amputation before this time.

Antithrombotic medications for thrombus prevention include clopidogrel (an irreversible platelet ADP receptor inhibitor), rivoroxaban (a factor Xa inhibitor), and low molecular weight heparins (such as dalteparin or enoxaparin). Low dose aspirin (5-20 mg/cat every 3 days) can be added to clopidogrel but is not recommended as sole therapy based on the FATCAT study which showed clopidogrel was superior

to low dose aspirin for prevention of thromboembolic recurrence. Clopidogrel has a bitter taste which can be disguised by placement in a #4 gel capsule (it is not disguised by compounding). It is advisable to limit venipuncture to a peripheral site that can be bandaged for 10-15 minutes after blood draw for patients taking clopidogrel. A 5-7 day withdrawal prior to elective procedures is recommended to lower the risk of clinically important bleeding during surgeries or dentals. Low molecular weight heparins require 1-3 times daily subcutaneous injections by the owners and these drugs are expensive. The clinical efficacy in cardiac disease is untested. The pharmacokinetics of rivaroxaban have been reported and a major benefit of this drug is its ability to ben given once daily by mouth. Clinical trials are underway to assess efficacy in at-risk cats.

Cats with FATE usually have advanced heart disease and clinical problems related to that. It is important to address concurrent complications including CHF, arrhythmias, azotemia, weight loss, and pain.

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Pulmonary Hypertension: Approach to a Difficult Disease

Pulmonary hypertension can be challenging to recognize in the emergency situation and equally challenging to treat. The objectives of this presentation are to understand the various classifications of pulmonary hypertension, review the diagnostic approach to pulmonary hypertension, and understand how treatment might different depending on the etiology. Emphasis on common presentations of this disease and differentiation from cardiac disease will be made with case examples.

The pulmonary vascular system is a low pressure, low resistance, high capacitance system and an increase in the pressure is termed pulmonary hypertension (PHT). Remembering that pressure is influenced by both resistance and flow, PHT may or may not be associated with increased pulmonary vascular resistance. Pulmonary hypertension is an abnormal hemodynamic state that can be caused by different clinical conditions. Pulmonary hypertension can be clinically classified into 6 groups based on general etiologies which can help to inform treatment approaches. Group 1 is pre-capillary pulmonary hypertension and includes familial, toxin-induced, congenital cardiac shunts and idiopathic causes. The recently described rare condition of pulmonary veno-occlusive disease is also considered in Group 1. Group 2 is post-capillary pulmonary hypertension due to primary left-sided heart disease, including mitral regurgitation and dilated cardiomyopathy. Group 3 is pulmonary hypertension resulting from any pulmonary/respiratory disease. Group 4 is due to any cause of pulmonary thromboembolism. Group 5 is due to parasitic disease, such as heartworm disease. Group 6 is pulmonary hypertension from multiple etiologies or unclear etiologies. Groups 2 and 3 are the most common types of PHT in dogs. The pathologic changes that the pulmonary vasculature undergoes in PHT include reversible changes such as medial hypertrophy and intimal proliferation, up to irreversible changes such as plexiform lesions and necrosis. Directed treatment of the underlying cause during earlier stages is more likely to have a beneficial outcome.

The signalment, history and physical examination findings of pulmonary hypertension might differ depending on the underlying cause, but in many cases, the clinical findings are very similar to primary heart disease causing congestive heart failure. The most common presenting complaints are syncope and dyspnea. The treatment of pulmonary hypertension and congestive heart failure are very different, so early diagnosis and rapid institution of the appropriate treatment is critical. Point of care ultrasound is very helpful for the rapid identification of an enlarged right heart and normal left atrial size, both of which are consistent with PHT and not consistent with left-sided congestive heart failure. Thoracic radiographs that are supportive of PHT include main and branch pulmonary artery enlargement, lack of left atrial enlargement, possibly right ventricular enlargement, and in some dogs, a patchy interstitial pattern that is due to uneven pulmonary vascular constriction. Emergency treatment with sildenafil in addition to oxygen for those dogs that are dyspneic, can be life-saving. A full echocardiogram can be done after the patient is stable to confirm suspected pulmonary hypertension and assess severity. Other diagnostics might also be indicated to investigate a potential underlying cause (e.g. routine bloodwork, coagulability testing, CT etc).

Sildenafil is the drug of choice for PHT except for Group 2 (post-capillary PHT/left-sided heart disease). Sildenafil is a PDE-5 inhibitor that causes selective pulmonary arteriolar dilation to reduce pressure in the lung vasculature. A clinical response can be seen in many dogs within a few dosages. Sildenafil is used with caution if at all in dogs with post-capillary PHT because an increase in flow from the right heart to the left heart associated with pulmonary vasodilation has the potential to worsen left sided congestive heart failure. Pimobendan is useful for dogs with Group 2 PHT (post-capillary) because it lowers left atrial pressure and in dogs with congestive heart failure but is not clearly indicated in dogs with Group 1 (idiopathic) and Group 3 (pulmonary disease) PHT. Anti-thrombotics are clearly indicated when hypercoagulability underlies Group 4 PHT (thromboembolic disease), but might also be useful for other causes of PHT based on a study indicating platelet hyper-reactivity in dogs with PHT.

The prognosis for dogs with PHT depends on the underlying cause. Dogs with post-capillary PHT seem to do better than dogs with pre-capillary PHT. Although many dogs will respond clinically to sildenafil with a reduction in syncope and resolution of dyspnea, the underlying disease process is often difficult to primarily treat and so it continues to progress. In conclusion, PHT can be challenging to diagnose and treat and often has a poor long-term prognosis. However, quick recognition and treatment with sildenafil and other, directed therapies can improve the quality of life for many dogs with PHT.

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Using Cardiac Biomarkers in Clinical Practice

Cardiac biomarkers are increasingly being used to screen dogs and cats for heart disease and can add information regarding severity, prognosis and response to treatment. Cardiac biomarkers are substances that can be measured as indicators of normal biologic processes, pathogenic processes or a response to therapeutic intervention. The most commonly studied cardiac biomarkers in veterinary cardiology are cardiac troponin I (cTnI) and NT-proBNP. These biomarkers can supplement current diagnostic testing for cardiac disease or can be useful in some clinical situations as screening tests. It is important to recognize that these are not stand-alone tests and when abnormal, they should prompt further investigation into the possibility of heart disease.

<u>B-type natriuretic peptide (BNP)</u>

B-type natriuretic peptide (BNP) is released from the ventricles in response to stretch or stress. With cardiac disease, the proportion of BNP released from the ventricles increases and the amount released is proportional to disease severity. It is released as a prohormone that is cleaved to an active component C-BNP and an inactive component NT-proBNP. The active C-BNP mediates vasodilation and diuresis but has a very short half -life making it a poor target for assay detection. The inactive portion NT-proBNP has a longer half-life and is the target for current diagnostic testing.

Studies evaluating NT-proBNP have generated values that are useful in specific clinical situations and it is important to interpret any given NT-proBNP concentration in light of the signalment and clinical question to be answered. Based on studies in small breed dogs with heart murmurs, a NT-proBNP concentration of >900 pmol/L (Idexx) is suggestive of heart disease and echocardiography is recommended. In dogs with established mitral valve disease, a value >1500 pmol/L (Idexx) is suggestive of impending congestive heart failure in the next 6-12 months and warrants close monitoring of the patient (Reynolds 2012, Serres 2009, Chetboul 2009). Various studies in Dobermans have suggested a lower cutoff value for the detection and prediction of DCM in Dobermans (Idexx cutoff is >735 pmol/L) (Gordon 2013 ACVIM proceedings, Singletary 2012, Wess 2011). NT-proBNP is most accurate for this purpose when combined with Holter monitoring. NT-proBNP has also been evaluated for its ability to differentiate cardiac from respiratory causes of dyspnea. A value <900 pmol/L in a dyspneic dog suggests CHF is unlikely while a value >1800 pmol/L suggests CHF is likely. A value less than 270 pmol/L in a dypsneic cat suggests CHF is unlikely while a value >270 pmol/L is supportive of CHF as the cause of dyspnea. NT-proBNP has also been evaluated in asymptomatic cats at risk for heart disease (e.g. murmur present) and various studies support a cutoff of 100 pmol/L for detection of heart disease in this population. A snap NT-proBNP test is available from IDEXX . For this test, a snap negative correlates with a value <100pmol/L and snap positive correlates with >270 pmol/L. Because there is a “grey zone” with this test, it can be viewed as useful for ruling out moderate to severe heart disease (if the snap is negative) and for detecting moderate to severe heart disease (if the snap is positive), however, it may miss cats with mild heart disease (false snap negative). It is critical that the clinician interpret the NT-

proBNP results in light of the clinical question to be answered as well as other diagnostic testing. Indiscriminate testing of animals not at risk for heart disease would be expected to result in a higher false positive rate than has been reported in studies that targeted animals at risk for heart disease. In most situations, a positive test result should prompt an echocardiogram and sometimes thoracic radiographs, blood pressure and bloodwork as part of further evaluation. Future studies will likely be aimed at determining how NT-proBNP can help guide therapy initiation and monitor response to therapy.

Cardiac Troponin I (cTnI)

Cardiac troponin I (cTnI) is an intramyocardial protein, that when detectable in the bloodstream, indicates myocardial cell injury or death. As such, it is a nonspecific finding that can be associated with many causes of myocardial cell injury including myocardial infarction, myocarditis, cardiomyopathy, congenital heart disease, chronic valve disease and systemic diseases affecting the heart (e.g. hyperthyroidism, GDV, anemia, toxicities, infections, brachycephalic syndrome, trauma, hypoxia, renal failure). The degree of cTnI elevation parallels the extent of myocardial injury and so it can be useful for prognostication. After a single insult, troponin is released within hours, peaks around 24 hrs and returns to baseline by 2 weeks through renal clearance. Serial evaluation, therefore helps to separate acute from ongoing injury.

A number of studies have evaluated cardiac troponin I in dogs and cats with various heart diseases. Low-level elevations (up to approximately 2 ng/ml) are common with congenital and acquired heart disease while massive elevations seem to be most consistent with myocardial infarction or myocarditis. Troponin analysis may have prognostic benefit in some conditions. Troponin was found to be elevated in the majority of dogs with GDV and the value was related to both severity of ECG changes and survival (Schober 2002). Another study by Schober (1999) found elevated troponin in about ½ of dogs with motor vehicular trauma and ECG abnormalities in about 1/3 of these dogs. Cardiac troponin I has also been found to be elevated in dogs before and after cardiac pacing, with a possible myocarditis association. In critically ill ICU patients with no detectable heart disease, troponin elevations were predictive of short-term death. These studies, among others, highlight that cardiac injury occurs with both cardiac and extracardiac disease and that it can be an important contributor to prognosis. We currently consider cardiac troponin I testing for patients with arrhythmias, especially when the patient is not from a breed known to have a genetically based cardiomyopathy (i.e. a myocarditis screen) and when acute ST segment changes are noted on the ECG. We also use troponin evaluation as part of screening tests for Dilated Cardiomyopathy and Hypertrophic Cardiomyopathy in conjunction with other tests including echocardiography. We encourage other services within our hospital to consider troponin testing in critically ill patients with GDV, motor vehicular trauma or other systemic diseases with potential for cardiac involvement. Analyzers capable of detecting lower troponin values (high sensitivity cTnI analyzers) are also available and results suggest prognostic information can be gained in dogs with degenerative mitral valve disease (Hezzell 2012) and other conditions; this has also been demonstrated in human medicine and will likely be an area of further study. An elevated troponin concentration should prompt the clinician to pursue further diagnostics including echocardiography, ECG or Holter monitoring, blood pressure, bloodwork, thyroid evaluation and sometimes infectious disease testing.

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Advances in the Medical Management of Heart Failure in Dogs

Congestive heart failure is the end result of advanced heart disease and is facilitated by overactive sympathetic and neurohormonal influences that retain sodium and water. Standard medical therapy for CHF in dogs includes furosemide, pimobendan, an ACE-inhibitor, and spironolactone, and in cats includes furosemide, an ACE-inhibitor, clopidogrel (or other antithrombotic) and often pimobendan (off-label). Despite the expectation that underlying cardiac disease will progress, our goals are still to provide a good quality life for as long as possible for our patients living with heart disease. Despite research to find a genetic cause and the few centers that offer a more definitive approach to treatment with cardiac surgery, the vast majority of animals with heart disease are treated medically. The main goals of treatment are to improve cardiac output, relieve and prevent congestion, delay progression and extend lifespan. Multimodal therapy using diuretics, inhibitors of the renin-angiotensin-aldosterone system (RAAS) and pimobendan are used to support the failing heart.

Loop diuretics are the mainstay for relief of congestion. These drugs inhibit the Na/K/2Cl cotransporter in the ascending thick Loop of Henle to cause electrolyte and water loss into the urine, which in turn pulls edema from the lung interstitium according to Starling's forces. Furosemide is the most common loop diuretic used but there are some situations where torsemide might be a better choice due to its pharmacokinetic advantages. Torsemide is 10-20x more potent than furosemide and unlike furosemide, has high and consistent bioavailability and longer duration of action. Both medications can cause adverse effects of dehydration and electrolyte depletion that need to be closely monitored for in addition to monitoring for CHF resolution.

The most common inhibitors of the RAAS that are clinically used include ACE-inhibitors and spironolactone, however, angiotensin receptor blockers are sometimes used in heart disease. ACE inhibitors prevent the formation of Angiotensin II from Angiotensin I and this has beneficial effects of reducing angiotensin II-mediated vasoconstriction, sodium retention and aldosterone secretion (that causes sodium and water retention and myocardial fibrosis). Approximately 30-40% of dogs show aldosterone breakthrough even with appropriate ACE-inhibitor therapy, and therefore comprehensive RAAS suppression with an ACE-inhibitor and spironolactone is recommended for dogs with CHF.

Pimobendan is a cornerstone treatment of CHF in dogs and has dual actions of positive inotropy (increasing contractile force) and vasodilation (making it easier for the left ventricular to pump blood forward). Pimobendan has been shown to improve quality and quantity of life for dogs with DCM and MR.

The treatment of cats with CHF is similar to dogs with a few exceptions. Cats are susceptible to the volume-depleting effects of loop diuretics and therefore lower doses are recommended compared to

dogs. The speaker typically uses ACE-inhibitors once daily instead of twice daily in cats. Although there has historically been concern about side effects of spironolactone in cats, it seems to be well tolerated in the speaker's practice and can be useful for some cats with heart failure. Many cardiologists use pimobendan in cats with CHF (even with HCM) but it is important to recognize (and convey to owners) that this is an off-label use. Although a retrospective study showed longer survival in cats with CHF that received pimobendan, a recent prospective study was not able to show benefit. Cats with LV outflow obstructions may not tolerate pimobendan. Close monitoring after initial pimobendan dosing is recommended, but the speaker has found this to be a helpful treatment for many cats with CHF. Cats with heart disease severe enough to cause CHF almost invariably have severe LA enlargement and therefore have risk for thromboembolic complications. Antithrombotics (typically clopidogrel) are recommended to reduce this risk.

CHF recurrences will inevitably occur and there can be many different ways to handle these situations. Often diuretic dose escalation is the first approach but consideration to using adjunctive treatments is reasonable because of the adverse effects of high dose diuretics. Ancillary approaches could include the addition of a vasodilator to off-load the ventricle, escalation of pimobendan dose, moderate sodium restriction, cavity centesis if effusions are present, avoidance of NSAIDs, and treatment of proteinuria if present. A need for higher and higher furosemide doses should prompt a transition to torsemide, which can rescue some dogs with recurrent CHF.

Because CHF is a progressive disease and we rarely repair the root problem of mitral valve degeneration, recurrences and complications are to be expected. Most dogs with advanced recurrent CHF need more than standard therapy and are often require a polypharmacy approach to control their CHF.

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The Vicious Cycle of Cardio-Renal syndrome

Cardiovascular renal disorders are common in veterinary medicine, and dysfunction of both organ systems is a common cause of demise for dogs and cats with heart disease. This lecture will delineate the major categories of cardio-renal syndrome and focus on treatment and management strategies to address concurrent heart and kidney disease.

Cardiorenal syndrome (also called cardiovascular renal disorders in veterinary medicine) can be defined as acute or chronic dysfunction of one organ that induces acute or chronic dysfunction of the other. It is most often clinically manifested as azotemia and diuretic resistance in patients with congestive heart failure (CHF). Cardiorenal syndrome in dogs has been shown to negatively affect survival and therefore early recognition is important to optimize management of both conditions.

The consensus statement on Cardiovascular-renal axis disorders published in 2015 in the Journal of Small Animal Practice categorizes them into 3 etiologies based on initiating cause: 1) Cardiovascular diseases 2) Renal diseases 3) Systemic diseases. There are a number of common mechanisms for crosstalk between the kidneys and the heart regardless of initiating etiology. These include the renin-angiotensin-aldosterone system, neurohormonal mechanisms, inflammation, oxidative stress, uremic toxins and possibly epigenetic modifications. Even when cardiac disease is the driver of cardiorenal syndrome, reductions in cardiac output are not clearly involved in the pathogenesis of disease progression. Instead, poor arterial vascular filling and venous congestion seem to promote common mechanisms involved in cardiorenal syndrome. Although most CHF patients are total body water and salt expanded, the kidneys do not sense this, partly because intravascular fluid is disproportionately in the venous system and because diuretics interfere with salt sensing at the level of the kidney. Salt avidity is high in heart failure patients, driving neurohormonal activation and more fluid retention. Venous overfilling in CHF adversely affects the kidneys because renal congestion reduces glomerular filtration and therefore renal function.

Accurate diagnosis of cardiac, renal, and systemic disease is important to the management of cardiovascular renal disorders, and a variety of imaging and laboratory diagnostics can be used to assess cardiac and renal function. Management of patients with cardiorenal syndrome is challenging and often focuses on symptom management. Euvolemia is difficult to achieve because of the opposing treatment approaches for clinical signs related to heart disease (e.g. diuretics needed to treat congestive heart failure) and renal disease (e.g. fluid therapy for azotemia). A balanced approach focusing on patient clinical signs is needed to avoid see-sawing between symptomatic heart failure and renal failure. Renin-angiotensin-aldosterone system (RAAS) inhibitors are protective in both cardiac and renal disease, however, this benefit is balanced against the lower glomerular filtration rate that is a result of less angiotensin II influence on the efferent arteriole. The level of azotemia or glomerular filtration rate at which RAAS inhibitors should be continued or should be lowered / withdrawn is an area of uncertainty in human and veterinary medicine but several trials are underway in people to address this question. Pimobendan is beneficial in congestive heart failure and does not adversely affect renal function. It

would seem beneficial for renal disease because of its positive inotropic effect, however, this has not been proven. Other management strategies must be tailored to the individual patient, but consideration of some specific issues is useful: blood pressure control, complicating urinary tract infections, complicating anemia, the use of cavity centesis rather than diuretic dosage escalation to address fluid retention, critical assessment of diuretic dose (enough or not enough), assessing diuretic response by measuring urine sodium concentrations, electrolyte supplementation, appetite stimulation, anti-nausea medications, moderate salt restriction, and optimization of nutrition.

Case examples will be used to discuss some common clinical scenarios encountered when managing heart failure patients with cardiorenal syndrome, with an emphasis on addressing worsening renal function in the setting of advanced heart disease and heart failure.

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Getting the most out of bloodwork in the heart failure patient

We are all very used to looking at renal panels on our heart disease patients, but could we be getting more information out of this commonly run lab panel? There are subtleties present in the assessment of BUN, creatinine, sodium, potassium, chloride, and bicarbonate that can help us better understand the underlying cardiac and renal diseases, the effects of medications, and insights into prognosis.

Renal function is commonly assessed by BUN and creatinine, however, it is well accepted that these are not sensitive indicators of renal disease and can be impacted by other factors such as hydration (especially for BUN), and muscle mass (for creatinine). Ideally these tests would be interpreted in conjunction with a urinalysis, but this is not always feasible in the heart failure patient, and loop diuretics interfere with urine concentrating ability. Azotemia is not uncommon in patients with congestive heart failure (CHF) and can be due to medications, renal disease, poor cardiac output, or a combination of these factors under the umbrella of cardiovascular renal disorders. A rise in creatinine is more concerning for renal injury than a rise in BUN which can occur due to poor renal perfusion / low GFR. An increase in BUN without an increase in creatinine often signals dehydration (if gastrointestinal bleeding has been ruled out) which might be supported by other findings such as hyperphosphatemia, high proteins, loss of body weight and physical exam findings of volume depletion, which should prompt a decrease in diuretic dosage as long as the patient does not have active signs of CHF. Other considerations in addition to careful diuretic dosage reduction (while monitoring RR closely) for patients that develop azotemia include temporarily stopping or lowering the ACE-I dose to improve GFR, considering the use of benazepril or halving the dose of enalapril, and optimization of CHF therapies that will allow for the lowest possible diuretic dose (e.g. increase pimobendan, amlodipine for afterload reduction in dogs with mitral valve disease). Urinary tract infection should be ruled out. Sometimes fluid therapy is needed if azotemia is severe, but this should be done cautiously and with RR monitoring to avoid re-induction of CHF. Appetite stimulants and ant-nausea medications can be prescribed to support the patient during this time.

Low serum sodium concentrations have negative prognostic value in dogs with CHF. Dogs with CHF almost always have increased total body sodium from CHF-associated sodium avidity even if their serum sodium concentrations are normal or decreased. The latter indicates free water retention from antidiuretic hormone (ADH) causing dilution of the sodium concentration. Hyponatremia in a CHF patient is very difficult to address. Improving forward flow with higher doses of pimobendan or amlodipine (for mitral valve disease) can help to reduce the stimulus for renin-angiotensin-aldosterone system (RAAS) activation and ADH release. RAAS inhibitors are important as well. Specific ADH antagonists (e.g. tolvaptan) are financially out of reach for most clients but can be given in select situations.

Potassium is wasted from the body as a direct effect of loop diuretics and can be compounded by inappetence and RAAS activation. Hypokalemia can have negative effects including arrhythmia formation, muscle weakness and enhanced toxicity with digoxin administration. RAAS inhibitors (e.g.

ACE-inhibitors and spironolactone) aid in potassium retention but sometimes oral potassium supplementation is needed to keep the serum potassium concentration in the reference range, especially when high dose diuretics are needed.

Chloride is the most abundant extra-cellular anion in the body and important to both acid-base status and RAAS activation. Chloride is inversely related to bicarbonate, and loop diuretic-induced chloride loss is usually accompanied by bicarbonate retention leading to metabolic alkalosis. Hypochloremia is the most common electrolyte abnormality in CHF in both people and dogs and carries more negative prognostic value than sodium. Hypochloremia in CHF can be due to loss (from a loop diuretic) or dilution (like sodium, from free water retention) and mathematical correction of chloride for a "normal" sodium, can help determine if free water retention is causing dilution. An increase in the chloride concentration after mathematical correction indicates a diluting effect of excessive ADH on chloride concentrations and is usually accompanied by hyponatremia as well. Hypochloremia can contribute to the progression of heart disease because it stimulates RAAS activation so that low serum chloride is both a marker and a mediator of advanced heart disease and diuretic resistance. Hypochloremia is difficult to address but improving forward flow (pimobendan, amlodipine) as well as avoiding over-diuresis with loop diuretics can be helpful. Sodium-free chloride supplementation and specific chloride-retaining diuretics (e.g. acetazolamide) are under study in human and veterinary medicine.

Metabolic alkalosis usually accompanies the hypochloremia of CHF especially when it is driven by loop diuretics. There is some evidence that metabolic alkalosis can contribute to diuretic resistance, and so action to lower serum bicarbonate is advisable (by using the lowest effective diuretic dose and employing adjunctive therapies such as increased pimobendan dose, amlodipine, and RAAS inhibitors). Acetazolamide is under study because of its potential to address hypochloremic metabolic alkalosis.

Clinical cases will be used to further discussion about biochemical abnormalities and how to address them in CHF patients.

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Darcy Adin

Proceedings

How to Give What Medications and When

A good understanding of the natural history of degenerative mitral valve disease and the ACVIM staging system is the basis for understanding when to start medications. Mitral valve disease is the most common heart disease in dogs and generally has a long preclinical phase even though a small percentage of dogs will progress rapidly. Only about 25% of affected dogs will experience congestive heart failure (CHF), however, so it is important to educate clients on the importance of monitoring and to use an evidence based approach to instituting medications.

No treatment is recommended for dogs without cardiomegaly (stage B1) but owners should be counseled about the disease progression what to monitor for. Pimobendan is recommended for dogs with either radiographic or echocardiographic cardiomegaly (stage B2) but without clinical signs as this has been shown to delay the onset of congestive heart failure by 15 months when started at the B2 stage. Once cardiomegaly is present, home resting respiratory rate monitoring also becomes important to facilitate early detection of congestive heart failure. Inhibitors of the renin-angiotensin aldosterone system (RAAS) such as ACE inhibitors and spironolactone are not uniformly indicated in Stage B2 disease, however, dogs that have severe cardiomegaly might benefit from RAAS inhibition moreso than dogs with minimal cardiomegaly and so medications such as enalapril (or benazepril) and spironolactone can be used in the later stages of B2 as there becomes concern for impending CHF.

The onset of CHF (stage C) might be mild, allowing for outpatient treatment, or it might be severe, requiring hospitalization. Dogs that are hospitalized are treated with oxygen, parenteral furosemide, and pimobendan and after discharge, ACE inhibitor and spironolactone are added. The concurrent use of a loop diuretic (such as furosemide), pimobendan, an ACE inhibitor and spironolactone is called quad therapy. Medical management of CHF in dogs ideally includes all four of these medications which are complementary and serve address the multifaceted clinical issue of CHF. Diuretics are essential for fluid removal from the lungs or body cavities but after CHF is controlled, the lowest effective dose should be used to keep CHF from recurring. Pimobendan is an inodilator that improves contractile function of the heart and lowers vascular resistance, thereby improving forward flow. ACE inhibitors reduce the formation of angiotensin II which can have multiple maladaptive effects including sodium and water retention and aldosterone formation. Because some dogs can still produce aldosterone despite having an ACE inhibitor on board, spironolactone is recommended to protect against tissue binding of aldosterone as well.

Despite optimal medical management of CHF, the average survival time is approximately one year and dogs will eventually succumb to their disease or complications / side effects of medications. Newer treatment approaches are increasingly available and include mitral valve repair surgery under cardiopulmonary bypass, and transapical edge-edge repair using a clamp placed across the mitral valve during a beating heart procedure. Although these are exciting options that can significantly improve or resolve heart disease, the vast majority of dogs will still be treated medically. Standard treatment with

quad therapy is successful for many dogs but there are other options available for dogs that become refractory to these (Stage D). These medical approaches include additional diuretics, vasodilator therapy, and salt restriction while providing nutritional support and manual fluid removal for ascites or pleural effusion. Additional therapies and close monitoring can help to extend good quality of life for some patients.

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Proceedings

Spectrum of Cardiology Care: When Referral is not an Option

There are many indications for referral of patients with heart disease to a veterinary cardiologist, but there are also numerous scenarios that veterinarians encounter where referral is not a feasible option for pet owners. It is important to remember the goal when deciding how to approach a clinical situation where finances or other factors dictate minimal diagnostics and referral isn't possible. Usually this goal is to identify patients who are at risk for adverse outcomes and to intervene if possible.

Detecting those patients with heart disease is the first step and patient profiling, good history taking and physical examination can go a long way towards determining which tests will provide the best value. It is helpful to formulate several plans that can be used depending on the resources available. Radiographs are accessible in most situations and so it is helpful to understand what radiographs can and can't determine when it comes to diagnosing heart disease. Radiographs are useful for distinguishing ACVIM Stage B1 from B2 disease in dogs with preclinical mitral valve disease and are the test of choice for diagnosis of congestive heart failure. Therefore, radiographs are a very good choice for staging of dogs with mitral valve disease. Although they are not useful for evaluating cardiac function or internal size, in most instances, thoracic radiographs can provide sufficient information to formulate a treatment plan for dogs and cats, even if a definitive cardiac diagnosis is not known. Several studies have shown that thoracic radiographs can detect Stage B2 in dogs if conservative cutoffs are used (VHS >11.9, VLAS >2.3), therefore allowing the clinician to practice evidence based medicine to start pimobendan in Stage B2 dogs with mitral valve disease. Thoracic radiographs are also very useful for understanding the cause of cough in dogs with heart disease, which in many cases is due to concomitant airway disease or mainstem bronchus compression.

Home resting respiratory rate monitoring allows for early detection of congestive heart failure by the owner in the home environment. If the veterinarian and owner have good communication, mild increases in resting respiratory can trigger an early discussion about medication adjustments which might prevent the need for hospitalization and associated expenses. Most healthy dogs and dogs with controlled congestive heart failure have resting or sleeping respiratory rates below 30/minute, so increases above that or significant changes from the dog's baseline might indicate the development of congestive heart failure. This is a simple and powerful monitoring tool in the home environment.

Thoracic radiographs can also be useful for detection of cardiomegaly and congestive heart failure in cats, although diagnosis of the specific underlying cardiomyopathy requires echocardiography. However, since no medications have been shown to delay progression in preclinical disease, this information is not essential to initiate close monitoring of the cat and clopidogrel. If radiographic cardiomegaly is present, then the left atrium is likely enlarged which carries a risk of thromboembolic disease; therefore, even without knowledge of the cardiomyopathy type, anti-thrombotic therapy is likely indicated. For dyspneic or tachypneic cats, thoracic radiographs provide confirmation of

congestive heart failure. The SNAP NT-proBNP test can be helpful in the emergency situation when it is unclear if the cat is dyspneic from respiratory disease or congestive heart failure.

Cage-side ultrasound (POCUS, TFAST) can be viewed as an extension of the physical examination and has a role in rapid diagnosis and treatment of dogs and cats presented for acute signs of heart disease, usually in the emergency setting. Body cavity effusions might indicate congestive heart failure if other findings corroborate severe heart disease. Left atrial size, left and right ventricular size, and subjective assessment of function utilize basic views to help the clinician rapidly determine if heart disease is severe enough to cause the clinical signs. With basic training, clinicians can become comfortable utilizing cage-side ultrasound in the emergency setting to rapidly direct treatment. This should be viewed as complementary to the exam and thoracic radiographs with the understanding that a full echocardiogram is needed to evaluate all aspects of cardiac size and function and come to a definitive diagnosis.

Despite best efforts there are some instances where referral to a cardiologist is needed to adequately diagnose or treat patients. These situations include a loud or persistent murmur in a young animal suggestive of congenital heart disease, when the cause of clinical signs remains unclear despite basic testing, and when there is a poor response to treatment suggesting there might be an alternative diagnosis to the one being treated for. However, these are rare situations, and mitral valve disease, the most common heart disease seen in practice, can often be treated appropriately based on examination and thoracic radiographs.