New Perspectives on Diagnosis and Treatment of Canine Congestive Heart Failure
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Congestive heart failure (CHF) is a common sequela to severe cardiac disease. Myxomatous mitral valve disease and dilated cardiomyopathy (DCM) are the most common heart diseases in dogs to result in CHF. CHF develops when the left ventricular diastolic filling pressures are substantially increased, leading to elevated left atrial and pulmonary capillary wedge pressure. Pulmonary venous distension may be seen on thoracic radiographs prior to overt pulmonary edema. When the left atrial pressure increases above 20 mm Hg, pulmonary edema forms. Initially, there is interstitial pulmonary edema, and alveolar edema occurs with progressive increase in pulmonary capillary wedge pressure.

Right-sided CHF occurs when right ventricular diastolic pressure, right atrial pressure, and central venous pressures increase over 15 mm Hg. Right-sided CHF is evidenced by jugular venous distension, hepatomegaly and ascites, and possibly pleural effusion and peripheral edema.

When stroke volume is decreased, there is decreased renal blood flow and decreased sodium delivery to the macula densa of the kidney, which activates the renin-angiotensin-aldosterone system (RAAS) to increase intravascular volume by increasing sodium and water retention. The net effect of RAAS activation is maintenance of systemic organ perfusion by increased systemic vascular resistance, increased blood volume through sodium and water retention, increased sympathetic tone by increasing norepinephrine, vasopressin and endothelin-I, and counter-regulate nitric oxide, natriuretic peptides, and prostaglandins to further increase systemic vascular resistance. Except for the generation of renin by the kidney, all components of RAAS are present at the myocardial level (as well as in many other organs), and are capable of generating high levels of angiotensin II (ATII) and aldosterone locally, which induce myocardial hypertrophy and fibrosis. Aside from cardiac ACE, other pathways including chymase, ACE-2, cathepsins, and tonin convert ATI to ATII. In fact, in dogs, cats, and humans, chymase is responsible for 90% of myocardial ATII formation.

**Diagnosis of CHF**

Clinical signs of coughing, tachypnea, dyspnea, orthopnea may be seen in animals with heart failure. Other nonspecific history may include exercise intolerance, lethargy, anorexia, or weight loss. Syncope may be seen in dogs with heart failure. The main diagnostic tool for diagnosis of CHF is thoracic radiographs. Vertebral heart score may be useful to quantify heart size. The length of the long axis of the heart is measured from the level of the carina to the left ventricular apex. A perpendicular line is drawn at the widest part of the short axis of the heart. The long axis and short axis lengths are then converted to the length of vertebrae, starting at the cranial aspect of T4, and then added together for total vertebral heart scale. Normal VHS in cats is 6.9–8.1, and normal VHS in dogs is 9.7 ± 0.5. VHS of 10.7 vertebrae or larger accurately (78% accuracy) discriminates dogs with cardiomegaly and heart disease from normal dogs. In dogs, identification of perihilar
to caudodorsal interstitial to alveolar pulmonary infiltrates, along with cardiomegaly and in particular left atrial dilation are the main criteria for diagnosis of CHF, and pulmonary venous distension is also often seen. An echocardiogram is necessary to identify the etiology of the heart disease and is also helpful to confirm whether there is significant enough heart disease present to cause dyspnea in patients with pulmonary infiltrates.

The ACVIM consensus statement of diagnosis and treatment of mitral valve disease utilized an ABCD staging system to help define appropriate workup and treatment depending on the severity of the disease, which can be helpful to adopt into general clinical practice. Dogs with no cardiovascular abnormalities that are genetically predisposed to develop cardiac disease may be considered Stage A (i.e., Cavalier King Charles Spaniels). Asymptomatic dogs with a cardiovascular abnormality (i.e., murmur) are a Stage B, which is subdivided into B - no cardiac enlargement, and B2 - cardiac enlargement but no congestive heart failure. A Stage C dog has either current congestive heart failure or history of heart failure, and receives heart failure medications. Dogs with refractory heart failure that have symptoms despite maximal furosemide dose of 4 mg/kg PO TID, an ACE inhibitor, and pimobendan are Stage D.

Measurement of circulating biomarkers such as brain natriuretic peptide (BNP) is useful to help distinguish whether dyspnea is due to CHF or primary respiratory disease in dogs and cats. NT-proBNP, the precursor of the biologically active BNP, has a longer circulating half-life and data suggests that it is a promising cardiac biomarker of disease and failure. A commercially available test (Cardiocare®, IDEXX Laboratories) has been evaluated for differentiation of CHF from primary respiratory disease in dyspneic dogs, and a cutoff of > 1725 pmol/L is highly sensitive (88%) and specific (77%) for diagnosis of CHF. Likewise, a cutoff of > 445 pmol/L is moderate to highly sensitive (83%) and specific (90%) for distinguishing dogs with asymptomatic heart disease from normal control dogs. A strict protocol exists for collection and processing of NT-proBNP samples.

**TREATMENT OF CONGESTIVE HEART FAILURE**

Recently, the ACVIM Cardiology Consensus Committee on treatment of myxomatous mitral valve degeneration outlined the standard of care for treatment of heart failure to include triple therapy of furosemide, an ACE inhibitor, and pimobendan. The author has summarized the most pertinent findings from clinical trials in dogs with heart disease below, to justify why the consensus statement has been made.

ACE inhibitors have been the standard choice for RAAS antagonism and are indicated for treatment of CHF in people, dogs, and cats. Dogs and people benefit from improved quality of life as well as survival. The IMPROVE trial showed that enalapril resulted in very modest acute reductions of pulmonary capillary wedge pressure and arterial blood pressure in dogs, but greater long term clinical improvement was seen only in the DCM group and not the mitral regurgitation group. Other clinical trials found improved symptoms and survival in both DCM and mitral regurgitation groups. There is a lack of evidence showing beneficial effects of early ACE inhibitor treatment in asymptomatic dogs with mitral regurgitation in the absence of CHF. Two large-scale, blinded, randomized, placebo-controlled clinical studies (SVEP and VETPROOF) of dogs with mitral regurgitation without CHF failed to show an improvement in survival or increased time until development of CHF when treated early with enalapril. ACE and aldosterone escape is a problem in some
people and animals (dogs and cats) treated with ACE inhibitors, and is characterized by progressive increases in ATII and aldosterone over time despite low ACE activity. Aldosterone antagonists or angiotensin receptor blockers may be added in conjunction with ACE inhibition for more complete RAAS inhibition.

The standard therapy for CHF of all causes includes furosemide (1–4 mg/kg PO BID–TID for stable patients), an angiotensin converting enzyme (ACE) inhibitor, and pimobendan. The dose and route of administration of furosemide varies depending on the severity of the CHF and the stability of the patient. Dogs with mild heart failure may be managed with lower furosemide doses (1–2 mg/kg PO q24h BID), while dogs with severe or refractory heart failure require the highest oral dose of 4 mg/kg PO TID. Furosemide is within the most powerful class of diuretics, the loop diuretics, which inhibit the Na⁺/K⁺/2Cl⁻ cotransporter in the thick ascending loop of Henle, leading to urinary loss of water, sodium, chloride, potassium, calcium, and magnesium. It is highly protein bound (86–91%), which traps the diuretic in the vascular space to deliver it to the proximal renal tubule, where 55% is excreted in the urine, and 45% is eliminated by the liver. Therefore, there must be adequate blood flow to deliver the furosemide to the kidney (a problem with low output heart failure), and adequate renal function to excrete the drug. Renal insufficiency prolongs the plasma half-life of furosemide since the excretion is slower. Nonsteroidal antiinflammatory drugs also reduce the diuretic response to furosemide by increasing the solute reabsorption at the thick ascending LOH. Oral bioavailability is only ~ 50% with marked individual variability. When administered intravenously, the diuretic effect is seen 5 minutes post-IV injection, with a peak diuretic effect 30 minutes post IV injection, and duration of diuresis 2–3 h. Venodilation is seen 5–15 minutes after IV injection. When given orally, the diuretic effect is seen by 1 h, with a peak effect at 1–2 h and duration of diuresis 6 h.

Pimobendan (0.25 mg/kg PO BID) is an exciting drug used for treatment of dogs with CHF secondary to DCM or mitral regurgitation. Pimobendan is a phosphodiesterase III (PDE III) inhibitor and a calcium sensitizer, which exerts powerful positive inotropic and vasodilatory effects. Inhibition of PDE III results in decreased degradation of cAMP, resulting in increased phosphorylation of protein kinases, and positive inotropic and lusitropic (relaxation) effects. Pimobendan also sensitzes the myofilaments (troponin C) to calcium to enable increased contraction. PDE III inhibition in the vasculature leads to vasodilation of the systemic arterioles and pulmonary vasculature. The combination of a positive inotrope and vasodilation leads to increased cardiac efficiency without increasing the myocardial oxygen consumption. In normal dogs, pimobendan produces moderate reductions in systemic and pulmonary vascular resistance, a decrease in left ventricular filling pressure, a moderate increase in heart rate, and a moderate increase in cardiac output. It also increases myocardial blood flow and improves diastolic function. Pimobendan reduced the mitral regurgitant fraction in dogs with experimentally created mitral regurgitation.

In an open-label study, pimobendan reduced heart failure score in dogs with CHF compared to digoxin. Pimobendan improved survival in 15 Dobermans with DCM (mean survival 128 days vs. 63 days for placebo group) and had greater time before treatment failure. Similarly, another small-scale blinded, placebo-controlled study in 16 Dobermans with CHF showed a marked improvement in survival in dogs treated with pimobendan as well as background therapy of benazepril, spironolactone, and furosemide.
compared to placebo and background therapy (median survival time 130 days vs. 14 days, respectively).\textsuperscript{10} Pimobendan has also been studied in dogs with heart failure due to myxomatous valve degeneration. VETSCOPE was a placebo-controlled, blinded, prospective, randomized trial that compared the effects of pimobendan vs. benazepril in 76 dogs with mitral regurgitation and moderate CHF. Dogs treated with pimobendan had greater improvement in heart failure score, vertebral heart score, and increased overall efficacy compared to the benazepril group. There was a dramatic improvement in survival in the pimobendan group (430 days vs. 228 days in the benazepril group). Similarly, the Quality of Life and Extension of Survival Study (QUEST) was a multicenter, blinded, positive controlled study that evaluated the effect of pimobendan \textit{(n = 124 dogs)} compared to benazepril \textit{(n = 128 dogs)} in dogs with mild to moderate congestive heart failure secondary to myxomatous mitral valve degeneration. Like the VETSCOPE study, the QUEST study found a significant improvement in survival time (91% extension of survival) in dogs given pimobendan (MST 267 days) compared to dogs given benazepril (MST 140 days), and there was a 25% reduction in risk of dying or being removed from the study due to treatment failure, and greater than 20% reduction in risk over a prolonged period of time (120–329 days). There was no difference in number of dogs reaching the end-point, but they lived longer and reached the clinical end-points later than dogs treated with benazepril.

In patients with myocardial failure (i.e., DCM), positive inotropic therapy with digoxin is indicated. Large dogs with severe mitral regurgitation also often develop myocardial failure, although not to the degree of dogs with DCM, and they may benefit from digoxin. Small dogs with chronic refractory severe mitral regurgitation may possibly have symptomatic improvements when given digoxin. Digoxin increased vagal tone, improves baroreceptor function, and increased diaphragm muscle tone, which may help patients with progressive heart failure. An important use of digoxin is to help slow the ventricular response rate of atrial fibrillation by increasing vagal tone and prolonging atrioventricular nodal conduction.

In refractory cases of severe CHF that have maximized the oral Lasix dose, addition of a second diuretic such as a thiazide may be necessary to control fluid accumulation. Spironolactone is a much weaker diuretic than both thiazides and loop diuretics, and may not add enough additional diuresis for adequate fluid control, but may have attractive ancillary properties as a neurohormonal antagonist. Since up to 40–50% of dogs and cats have elevated aldosterone concentrations despite receiving ACE inhibitors (i.e., ACE escape), there is rationale to add an aldosterone receptor blocker to the medical regimen in animals with progressive heart failure. In dogs with refractory CHF due to mitral regurgitation, another option is afterload reduction with an arteriolar vasodilator. Amlodipine and hydralazine are effective in reducing systemic arterial pressure (10–40 mm Hg) and reducing the mitral regurgitant fraction by approximately 15%. Low-salt diets are indicated in refractory CHF patients receiving the previously mentioned pharmacologic treatments. Low-salt diets (0.15–0.2 g sodium/1000 kcal) will help limit sodium and water retention. Dogs with mitral regurgitation and CHF fed low-salt diets along with standard background therapy had smaller left atrial and left ventricular diastolic and systolic dimensions than when they were fed a moderate sodium diet.

Aldosterone receptor antagonists (i.e., spironolactone and eplerenone) have gained great attention in the veterinary community following the announcement of improved survival in people treated with
spironolactone in the RALES clinical trial. Caution should be exerted before extrapolating positive effects seen in people who mostly had ischemic heart disease to dogs with other cardiac diseases. The mortality benefit was due to a decrease in sudden death, and was mostly seen in people with higher baseline circulating collagen markers of myocardial fibrosis. Recently, the only large-scale, blinded, placebo-controlled, multicenter clinical trial has been completed evaluating the effect of spironolactone in dogs with moderate or severe mitral regurgitation. Although the dogs (n = 212) were classified as having mild (Class II) or moderate (Class III) heart failure, the inclusion criteria were not specific for heart failure, and only 40% of dogs required furosemide at baseline. Although the study demonstrated that dogs treated with spironolactone (+ ACE inhibitor, +/- furosemide, +/- digoxin) had a 55% reduction in risk of cardiac-related death, euthanasia due to worsening mitral regurgitation, or severe worsening in mitral regurgitation, there was a very low event rate (with many dogs having less severe mitral regurgitation), making it questionable whether many of the dogs actually had congestive heart failure at entry. It is difficult to assess when in the clinical course of mitral regurgitation that a possible beneficial effect of spironolactone could be seen based on this study. There are no other clinical trials in dogs with spontaneously developing CHF, and more studies are needed to evaluate whether these seemingly strong benefits are reproducible, and at what stage of disease the benefit may occur.

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