CLASSIFICATION AND ADVANCES IN THE MANAGEMENT OF CANINE HEART FAILURE
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The approach to the management of heart failure depends on the underlying disease, its severity, and the type of signs present. Figure 1 (below) outlines the authors’ use of drug classes for heart failure according to severity using the ACVIM classification and is accompanied by a table with drug indications and dosages, based on the clinicians’ therapeutic goals. Note that the ACVIM, ISACHC and NYHA classification schemes (Figure 2) are neither identical nor easily interchangeable, but they have been presented to show their approximate relationship.

Although controlled exercise has proven to be beneficial in people with stable heart failure, some exercise restriction is logical in all forms of heart failure and can be progressively increased as the disease progresses. Since sodium retention is a major contributor to congestion, dietary sodium moderation/restriction has long been used in the management of heart failure. Recently, it has become clear that extreme sodium restriction actually activates the renin-angiotensin aldosterone system (RAAS) and may contribute to renal dysfunction. Also, it tends to make diets unpalatable. For these reasons, we now recommend only moderate salt restriction (e.g. senior or “early cardiac” diets containing approximately 0.22% sodium by dry weight) although, terminally, more extreme sodium restriction (e.g. a cardiac diet containing approximately 0.10% sodium by dry weight) may be necessary. Moderate sodium restriction is generally instituted in NYHA phase II (ACVIM stage B2).

Diuretic therapy has long been the cornerstone in the management of congestive signs and is employed in late phase II or III (ACVIM stage B2 and C). We now know that extensive diuresis activates the RAAS system. For this reason, diuresis should not be used as monotherapy and the lowest dosage required to control congestion should be found in order to avoid RAAS activation, dehydration, azotemia, and hypokalemia. With angiotensin converting-enzyme inhibitors (ACE-I), the diuretic dosage can typically be reduced. Terminally, increasing levels of diuresis may be necessary. Furosemide (Lasix) is by far the most commonly used diuretic and is the drug of choice for emergency management of pulmonary edema. In the event of refractory heart failure, continuous rate IV infusion (CRI) of furosemide has shown to provide a greater diuresis when compared to IV bolus. In refractory cases and in cases complicated by hypokalemia, the potassium-sparing diuretic spironolactone may provide an additive effect. There is also promise that a more potent loop-diuretic, torsemide, may be of use in refractory cases and this drug will be discussed during this presentation.

Aldosterone (and its major secretagogue, angiotensin II) have been implicated in the pathologic remodeling—inflammation, hypertrophy, fibrosis—of cardiovascular and renal tissues. Therefore, the primary rationale for adding spironolactone as adjunctive therapy for heart failure is now MR (specifically, aldosterone) blockade. As such, spironolactone, has received renewed interest with a report that life expectancy was prolonged in humans with heart failure when spironolactone was administered concurrently with conventional therapy in NYHA phase II, III, and IV patients with reduced ejection fraction. Because spironolactone is a weak diuretic, particularly at the modest dosage used in these studies, the investigators concluded that benefits were due to blunting the adverse effects of aldosterone (aldosterone breakthrough). Spironolactone has now been shown to give similar results in
canine heart failure and spironolactone (or related drugs such as eplerenone) are now commonly used in heart failure in both man and dog. In our laboratory, an experimental model of RAAS activation, has shown us that aldosterone levels may be elevated despite therapy with ACE-I (aldosterone breakthrough). In a clinical study, aldosterone breakthrough was documented in nearly 40% of patients with heart disease (both symptomatic and asymptomatic). The authors feel that these data support the use of spironolactone with the ACE-I, regardless of the stage of heart disease. Alternatively, the patient’s RAAS activation can be monitored (i.e. by the urine aldosterone to creatinine ratio; UAldo:C) and spironolactone could be added if aldosterone levels are rising from baseline despite ACE-I therapy. A combination product (benazepril and spironolactone) has been recently approved for use in dogs in the EU. Lastly, the use of an ACE-I and spironolactone has been shown to be safe and with clinically important increases in serum potassium concentrations being rare.

Direct acting vasodilators have largely been replaced with the advent of ACE-I. Nevertheless, nitroglycerin remains useful in emergency situations to reduce preload and pulmonary edema. Nitroprusside (as a CRI) can be used in the hospital to rescue dogs failing, despite polypharmacy. Vasodilators, such as the calcium channel blocker, amlodipine, can be added to ‘at home’ therapy to reduce cough due to severe myxomatous mitral valve disease (MMVD).

ACE-I have become a cornerstone in the chronic management of heart failure and may be employed early (NYHA phase II; ACVIM stage B2) for reasons outlined above. There is evidence that they slow progression of heart failure in people and animals and that they prolong life, improve quality of life and exercise capacity, reduce electrolyte abnormalities, and blunt pathological remodeling. As suggested above, diuretic dosages can often be reduced in the presence of concomitant ACE-inhibition. Although controversial, there are now data to indicate that ACE-I initiated prior to the onset of heart failure can modestly delay the onset of heart failure (approximately 4 months). More interestingly, when followed to death, dogs having received enalapril prior to the onset of heart failure enjoyed a 9-month survival benefit (all causes of mortality), as compared to those treated with a placebo.

New agents (or new uses for older agents) have targeted the neurohormonal abnormalities attendant to heart failure. These include neutral endopeptidase inhibitors (e.g. nepriysin), which interfere with the breakdown of ANP, a hormone, which has many effects opposite that of the RAAS, and angiotensin II receptor blockers (e.g. losartan), which have similar effects as ACE-I, but by blocking receptors rather than formation of angiotensin II. Antioxidants and anti-cytokine therapies may see greater use in the future as well.

Beta-Blockers, such as metoprolol, carvedilol, and bisoprolol have earned a place in the management of stable heart failure with reduced ejection fraction in humans. Their rationale is derived from the large body of evidence as to the harmful nature of the sympathetic nervous system in the syndrome of CHF. Their use has been slowly accepted because of the negative inotropic effect and difficulties in titrating to an effective dose. Nevertheless, improved quality of life, exercise tolerance, and survival have all been experienced in multiple human clinical trials involving carvedilol, metoprolol, and bisoprolol. There is evidence that sympathetic tone is increased in dogs with occult dilated cardiomyopathy (DCM) and this provides rationale for the use of beta-blockers in this group of dogs. There are data on beta-blockers in experimental MR, indicating hemodynamic and remodeling benefit with high dosages of atenolol. A recent trial evaluating bisoprolol in asymptomatic but moderate to severe MMVD was stopped early, as no overall benefit was found in an interim analysis. Dosing these agents is somewhat difficult in small dogs, requiring slow up-titration of the dosage, and often requires special formulation.

Inotropic therapy, other than digoxin, has fallen largely into disfavor amongst human cardiologists because they do not prolong life, may worsen arrhythmias, increase heart rate, and/or increase risk of sudden death, can be given only intravenously, and newer therapies have replaced them.
Dobutamine, dopamine, and milrinone can be used intravenously in cases of myocardial failure to rescue phase IV dogs. Digoxin, on the other hand, continues to be used because it is the only positive (although only weakly so) inotrope that is orally available, slows heart rate, and normalizes baroreceptor function. In addition, the RADIANCE and DIG trials in humans showed patients in heart failure denied digoxin had worsening of signs, quality of life, exercise tolerance and hemodynamic status. Digoxin is also indicated in heart failure, accompanied by supraventricular tachycardia. A theoretical argument for digoxin can be made in dogs with heart failure, normal sinus rhythm and maintained myocardial function, only if the owners cannot afford pimobendan. However, discretion must be used in these dogs as other drugs will control signs with less danger of toxicity. Therefore, in some dogs (e.g. 4 pound Pomeranian with MMVD), the owner, inherent appetite, renal function, and severity of signs must be considered. In general, digoxin could be instituted in 1) late phase II NYHA heart disease (ACVIM stage B2), with myocardial failure; 2) phase III (at same time as diuretic) in dogs without myocardial failure (MMVD); 3) or in any dog with atrial fibrillation and a rapid ventricular response or other supraventricular tachycardia.

**Pimobendan**, a newer calcium sensitizing/phosphodiesterase 3 inhibiting inotrope, better termed an inodilator (inotrope and mixed vasodilator), has dramatically altered the way we manage heart failure. This drug, currently being used widely at 0.25 to 0.3 mg/kg q 12h works, in part, by sensitizing the troponin C complex to calcium. The aforementioned association between positive inotropes and sudden death has not been recognized with pimobendan, probably because there is less or no increase in intracellular calcium and because of its arteriolar dilating capacity, which unloads the ventricles. Prospective studies by Fuentes, et al. and O’Grady et al. demonstrated improved survival in Doberman pinschers with CHF due to DCM. A retrospective study, comparing dogs treated with pimobendan to historical controls treated without pimobendan, by Gordon et al. in dogs with MMVD showed improved survival, vertebral heart score, heart and respiratory rate, and left atrial size, without evidence of arrhythmogenesis. The more recent QUEST Trial prospectively showed improved clinical outcomes (survival benefit = 4 months) in dogs with heart failure due to MMVD, as compared with ACE-I (benazepril). In our practice, this drug is often increased to three-times daily dosing in dogs with refractory heart failure and may be used as an emergency treatment for heart failure, as well. If uremia develops in a patient receiving polypharmacy, the first change in the authors’ clinics is often a careful decrease in the furosemide dosage with a concurrent increase in pimobendan dosage. The PROTECT study in Doberman Pinschers with pre-clinical DCM (no symptoms, but echocardiographic evidence of DCM present) showed that pimobendan prolonged the time to clinical disease and prolonged survival when compared to placebo. The EPIC Trial, published in 2016, demonstrated a benefit (delay in onset CHF/cardiovascular death/treatment failure as combined endpoint) in Stage B2 MMVD. Importantly, to be included, dogs had to satisfy three cardiomegaly entry criteria (LA:Ao > 1.6, vertebral heart score > 10.5, and normalized left ventricular end diastolic dimension > 1.7) and could not have previously been in congestive heart failure. Dogs with severe pulmonary hypertension were also excluded. These results suggest that the administration of pimobendan dogs with preclinical MMVD (stage B2) is safe, significantly prolongs the time to the onset of clinical signs, and extends survival.

**Sympathomimetic drugs**, such as dobutamine and dopamine, can be used to support cardiac function and blood pressure acutely. Veterinary cardiologists have most often employed dobutamine for the emergency management of heart failure in dogs. This agent, a synthetic sympathomimetic, produces improvement in cardiac performance via stimulation of Beta-1 receptors – leading to increased intracellular calcium and therefore, myocardial contractility. Dobutamine has relatively little effect on heart rate, is minimally proarrhythmic, and has a very short half-life (1-2 minutes). The short half-life is advantageous in that if adversity results, it can be quickly discontinued. A major disadvantage to this drug, ironically, is its short half-life, which requires that it be administered as a CRI. Additionally, it
results in down-regulation of Beta-1 receptors 48-72 hours after its institution, rendering the drug ineffective after this time. In addition, there is concern that the positive dromotropic effect of dobutamine in dogs with atrial fibrillation not receiving medical therapy for rate control (digoxin, diltiazem) may increase AV nodal conduction to a degree that a life-threatening ventricular response rate results, potentially leading to ventricular fibrillation. There are no clinical trials involving dobutamine in natural canine heart disease. Although myocardial dysfunction does develop in long-standing MMVD, it is not easily documented. Inotropic agents may, therefore, seem less logical in this setting. Their supposed efficacy is likely due to several factors. First, there is evidence for systolic dysfunction in moderate to severe MMVD. Second, inotropic agents are not limited to improving contractility, as they provide beneficial effects on diastolic function, afterload reduction, and reduce mitral valve annulus size, thereby reducing MMVD.

**Miscellaneous agents** such as taurine and L-carnitine are nutritional additives that respectively have been advocated for heart failure in cats and dogs. Taurine supplementation in standard diets has all but eliminated feline dilated cardiomyopathy. The jury is still out regarding the overall utility and specific indications for L-carnitine in dogs. Cocker spaniels with dilated cardiomyopathy have responded to taurine plus L-carnitine supplementation. Similarly, L-carnitine deficiency has been documented in a family of Boxers with left ventricular systolic dysfunction and supplementation may be beneficial in this presentation. Fish oils may improve appetite and blunt cardiac cachexia, and coenzyme Q10 has its advocates in the management of heart failure due to DCM. Bronchodilators are generally reserved for dogs with known (or suspected) lower airway disease or other respiratory disease, and these agents do not represent part of the routine protocol for the management of heart failure.

Lastly, some centers now employ **surgical procedures or interventions**, such as trans-apical mitral valve implantation (TAMVI), in MMVD, mitral valve reconstruction under cardiopulmonary bypass in dogs with advanced MMVD, and stem-cell therapy in dogs with DCM.

**Classification of Heart Disease**

*Figures 1 & 2* An overview of the ACVIM classification system for MMVD. The older NYHA and ISACHC systems are shown in Figure 2, for comparison.
ACVIM CONSENSUS: Rx MR CLASSIFICATION

Asymptomatic

A B1B2 CaCc DaDc ACVIM

At Risk
Murmur & Enlargement
Murmur & No Enlargement
Failure or History: At Home
Failure or History: Hospitalized
Refractory: At Home
Refractory: Hospitalized

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ISACHC (International Small Animal Cardiac Health Council) Classification System
Class Ia: Disease present but dog is asymptomatic and has no cardiomegaly. Class Ib: The dog is asymptomatic but cardiac enlargement (remodeling) is noted. Class II: The dog is comfortable at rest, but exercise may produce fatigue, dyspnea, or coughing. Class IIIb: Congestive heart failure (dyspnea, coughing, collapse, anorexia, anxiousness) is present and hospitalization is necessary. Class IIIa: Congestive heart failure is present but therapy can be carried out at home.

Modified NYHA System (Ettinger and Suter, 1970): Class I: Normal activity does not produce undue fatigue, dyspnea, or coughing; Class II: The dog is comfortable at rest, but ordinary physical activity causes fatigue, dyspnea, or coughing; Class III: The dog is comfortable at rest, but minimal exercise may produce fatigue, dyspnea, or coughing, Signs may also develop while the patient is in a recumbent position (orthopnea); Class IV: Congestive heart failure, dyspnea, and coughing are present even when the dog is at rest. Signs are evident at rest.
**Figure 3.** ACVIM CONSENSUS COMMITTEE ON MMVD – 2009.
Black lettering below ACVIM Classification Scheme indicates recommendations of all 10 of panelists (defined as “Consensus”. Grey lettering below indicates that the majority, but not all 10 panelists, supports the recommendation. The bracketed recommendations are the additional recommendations of the authors, but not the Consensus Panel.
Pimo* indicates that the likelihood that the level of evidence of the EPIC trial will allow the 2017 Consensus Panel to recommend pimobendan for ACVIM Stage B2 MMVD.

*Predicted for 2017 consensus, based on newly published data. Bracketed [Spirono] represent the authors’ recommendations.
Figure 4. The authors’ recommendations for the treatment of canine dilated cardiomyopathy are shown using the ACVIM Heart Disease Scheme.
Figure 5. An overview of the authors’ approach to handling congestion and (below) other aspects of heart disease using the ACVIM Classification Scheme. Note the Tuft’s University url for sodium-appropriate diets. No salt restriction is necessary prior to the onset of CHF, although “retraining” the palate of the asymptomatic dog to desire less salt may be useful. However, as cardiac disease progresses, moderate salt restriction (eg, an appropriate moderately salt-restricted Senior Diet is employed, with severe salt restriction (Cardiac Diet) withheld until absolutely necessary in dogs in which congestion cannot be adequately controlled pharmacologically. The need for this is uncommon.
Medical Management of Factors Contributing to Signs of Systolic Heart Failure in Dogs

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<th>FACTOR</th>
<th>STRATEGY</th>
<th>AGENT AND DOSAGE</th>
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<tr>
<td>Fluid retention/Excessive Preload</td>
<td>Salt restriction &amp; Diuresis</td>
<td>Senior diet, renal diet or, late in course, heart (heavily salt-restricted) diet</td>
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<td>Furosemide 1 - 4 mg/kg s.i.d.-t.i.d. IV,IM,SC or PO or CRI at 0.66 mg/kg/hr&lt;br&gt;Torsemide 0.2 mg/kg PO s.i.d.-t.i.d.&lt;br&gt;Hydrochlorothiazide or Aldactazide 2 - 4 mg/kg q.o.d.- b.i.d. PO&lt;br&gt;Spironolactone 2.0 mg/kg s.i.d. PO&lt;br&gt;Triamterene 2 - 4 mg/kg/day PO</td>
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<td></td>
<td>Venodilation</td>
<td>Nitroglycerin 2% ointment 1/4 inch/5kg t.i.d. topically for 1st 24 hours&lt;br&gt;Enalapril 0.5-1 mg/kg s.i.d.-b.i.d. PO&lt;br&gt;Benazepril 0.25-0.5 mg/kg s.i.d. PO&lt;br&gt;Prazosin 1 mg t.i.d. if &lt;15 kg; 2 mg t.i.d. if &gt;15 kg&lt;br&gt;Sodium nitroprusside 1 - 5 μg/kg/min IV</td>
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<td>Neurohormonal Aberration</td>
<td>Blunt RAAS</td>
<td>Enalapril and benazepril (as above)&lt;br&gt;Spironolactone 2.0 mg/kg s.i.d. PO</td>
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<td>Blunt SNS</td>
<td>Angiotensin II receptor blocker (e.g. Losartan) dosage TBD</td>
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<td>Increased afterload</td>
<td>Arterial vasodilation</td>
<td>Digoxin 0.003 - 0.01 mg/kg or 0.22 mg/m² body surface b.i.d. PO for maintenance.&lt;br&gt;Propranolol 5 - 40 mg t.i.d. PO&lt;br&gt;Atenolol 0.25 -1 mg/kg PO s.i.d.-b.i.d.¹&lt;br&gt;Carvedilol 0.1-0.2 mg/kg s.i.d PO, increasing to 0.5-1mg/kg b.i.d. over 6 wks</td>
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<td>Diminished contractility</td>
<td>Positive inotropic support</td>
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<td>Digoxin 0.003 - 0.01 mg/kg or 0.22 mg/m² body surface b.i.d. PO for maintenance. Rapid oral: 0.01 mg/kg b.i.d. - 0.02 mg/kg t.i.d. for 1 day, then to maintenance. Rapid IV: 0.01 - 0.02 mg/kg given one half IV immediately and one fourth IV at 30- to 60-minute intervals p.r.n. Dobutamine 1.5 - 20 μg/kg/min IV for &lt;72 hours Dopamine 2 -10 μg/kg/min IV for &lt;72 hours Amrinone/Inamrinone 1 to 3 mg/kg IV followed by 10 to 100 μg/kg/min Milrinone 30 - 50 μg/kg/min IV over 10 minutes followed by 1 to 8 μg/kg/min Pimobendan 0.25 mg/kg b.i.d. PO</td>
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<tr>
<th>Abnormal HR: Bradyarrhythmia</th>
<th>Normalize HR, rhythm</th>
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<td>Atropine sulfate 0.01 - 0.04 mg/kg SC or IM Glycopyrrolate 0.005 - 0.01 mg/kg SC or IM Terbutaline 1.25 - 2.5 mg b.i.d.-t.i.d. PO Pacemaker implantation</td>
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<td>Digoxin: Same as above Esmolol 100-500 μg/kg IV rapidly; Atenolol 0.25 to 1 mg/kg PO s.i.d.-b.i.d.¹ Propranolol 5 - 40 mg t.i.d. PO; 0.1 to 0.3 mg/kg IV slowly Verapamil¹ 1 - 5 mg/kg t.i.d. PO; 0.05 to 0.25 mg/kg IV slowly Diltiazem¹ 0.5-1.5 mg/kg t.i.d. PO; 0.1-.25 mg/kg over 2 min IV</td>
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<td>Lidocaine 2 - 4 mg/kg IV; repeat up to 8 mg/kg over 20 minutes Procainamide 5 - 15 mg/kg t.i.d.-q.i.d. PO; 5 to 10 mg/kg IV Esmolol, Propranolol, Atenolol: Same as above Sotalol 1-2 mg/kg b.i.d. PO Mexiletine 4 – 8 mg/kg t.i.d. PO Amiodarone 10-20 mg/kg s.i.d. x 7-10 days, then maintain at 5 mg/kg q24h s.i.d PO Amiodarone (Nexterone) 2mg/kg IV over 10 minutes, then 0.8 mg/kg/hr for up to 6 hrs Tocainide 5 - 10 mg/kg t.i.d. PO</td>
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¹Calcium channel (verapamil and diltiazem) and Beta blockers (propranolol, esmolol, atenolol) should be used with caution in patients in heart failure. q o d = every other day; s.i.d. = once daily; b.i.d. = twice daily; t.i.d. = three times daily; q.i.d. = four times daily; IM = intramuscularly; IV = intravenously; SC=subcutaneously; PO = per os; prn = as needed.