Management of congestive heart failure on a budget

Congestive heart failure can account for up to 38% of all cases of dyspnoea. While CHF can be managed well, with strong evidence for multi-drug therapy, treatment can be a costly exercise and successful management is ultimately often limited by financial considerations. Treatment of CHF is similar irrespective of underlying cause, but a diagnosis can aid prognosis and alter recommended follow-up. Reported median survival times in dogs with CHF are reported to be between 6-12 months, writes Chris Linney BVSc GPCertSAP CertAVP(VC) MRCVS RCVS, advanced practitioner in veterinary cardiology, Cardiology Department, Willows Referral Service, UK

Congestive heart failure (CHF) is a common cause of dyspnoea in dogs and cats, accounting for 12%[1] and 38%[2], respectively, of cases presenting with respiratory signs to a referral centre. Prompt assessment and recognition of CHF is essential for a positive outcome.

With a variety of treatments available for CHF management, decision-making regarding the most essential medications can be complex for the practitioner. The American College of Veterinary Internal Medicine (ACVIM) Consensus Statement[3] applied an evidence-based medicine approach to the diagnosis and management of canine chronic valvular heart disease, providing an overview of what is considered the current acceptable approach to management of these cases. Based on the ACVIM staging, this article concentrates on the management of stage C – patients with past or current signs of heart failure – and stage D patients, those with end-stage heart failure.

While a gold standard of care may include regular reassessment, blood sampling, repeat imaging and other ancillary tests, financial limitations may prevent the clinician performing regular, full reassessment. This article aims to highlight the justifications for assessment and also, where financial considerations exist, how best to manage a patient with CHF on a budget.

WHAT IS HEART FAILURE?

Heart failure is a syndrome where the heart cannot pump blood at the rate required to supply the metabolic demands of tissues and maintain normal pressures. CHF is whereby abnormal cardiac function results in the accumulation and retention of water and sodium, most frequently resulting in pulmonary or systemic volume overload leading to congestion (Figure 1).

With the development of CHF there are two main compensatory mechanisms; these are the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). These mechanisms result in vasoconstriction, water retention, increased heart rate and increased contractility, which support cardiac output initially; however, with progression of heart disease, these become maladaptive and actually worsen the clinical picture (Table 1) .

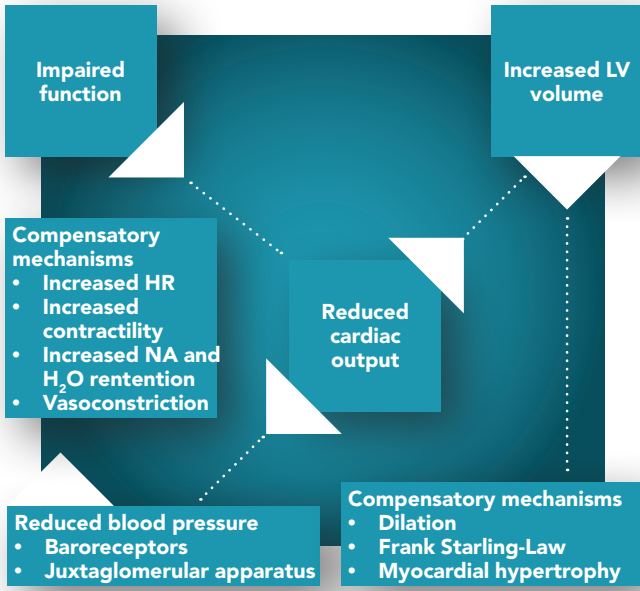

Figure 1: Compensatory mechanisms of heart failure.

Compensatory mechanism	Effects
Sympathetic nervous system	Myocardial cell death Myocardial hypertrophy Increased afterload Arrhythmias
Renin-angiotensin-aldosterone system	Cardiac remodelling Cell death Fibrosis Increased preload Increased afterload

Table 1: Maladaptive effects of the sympathetic nervous system and renin-angiotensin-aldosterone system in CHF.

WHEN TO INTERVENE?

The vast majority of the current evidence base supports the use of cardiac medications at the onset of symptoms of CHF; the gold standard approach to confirm a CHF includes a combination of thoracic radiography (Figure 2) and

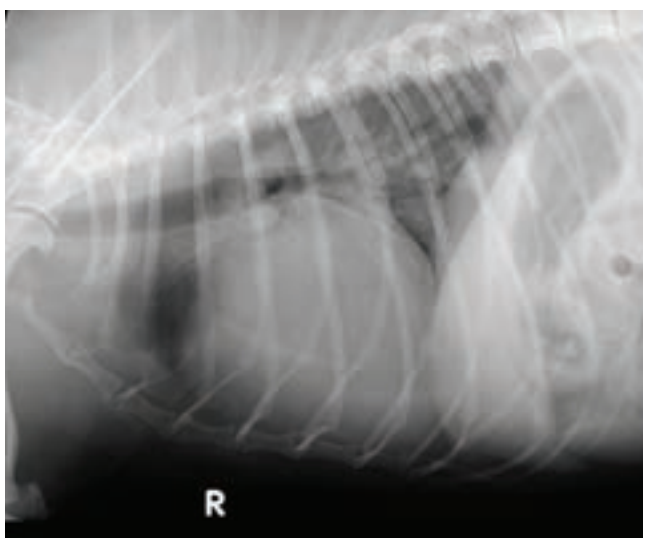

Figure 2: Conscious right lateral thoracic radiograph of a Cavalier King Charles Spaniel demonstrating an interstitial-to-alveolar pattern, predominantly in the perihilar region with moderate-marked cardiomegaly. The dog was diagnosed with CHF secondary to myxomatous degenerative valvular disease (MDVD).

echocardiography to both classify and determine severity of cardiac disease.

While these tests are considered 'gold standard', with thoracic radiographs considered a 'minimum' standard by most cardiologists, there may be cost considerations and therefore other diagnostics may be preferred before opting for these tests. At times, the clinical picture may warrant a trial of medications based on clinical signs alone (Table 2) although care must be taken not to be mislead by partial responses which may signify incorrect initial diagnosis. In human medicine, initial decision-making is often based on a combination of clinical signs and the measurement of N-terminal brain natriuretic peptide (NT-proBNP).

Clinical signs associated with CHF	
Dyspnoea	Coughing
Tachypnoea	Inappetence
Orthopnoea	Ascites
Exercise intolerance	Jugular distension
Lethargy	Pulmonary crackles*
Weakness	

Table 2: Clinical signs associated with CHF. *Pulmonary crackles should be interpreted with caution as many lower airway diseases (eg. pulmonary fibrosis) may result in this clinical finding.

Following large-scale clinical trials, NT-proBNP is now considered a standard of care with the UK's NHS NICE guidelines for the screening and diagnosis of CHF. NT-proBNP is released from the ventricle (and atria of diseased hearts) in response to ventricular stress and/or stretch. One of the most established uses of NT-proBNP assay in dogs and cats is to allow distinction between cardiac and non-cardiac causes of dyspnoea.[4] A number of studies have been performed in veterinary medicine with promising results for assessment of the presence of cardiac disease in the dyspnoeic patient (Table 3). A point-of-care NTproBNP SNAP test is available for cats for in-clinic use.

Species	Cut-off values (pmol/L)	Sensitivity (%)	Specificity (%)
Canine	1,158	86	81
Feline	265	90	88

Table 3: NT-proBNP reported cut-off values for differentiating cardiac versus non-cardiac causes of respiratory signs in dogs, with sensitivities and specificities. Values closer to the cut-off have more margin for error.[5,6]

As with any test, non-cardiac disease can contribute to elevations of NT-proBNP (ie. false positive results). These include, but are not limited to, anaemia, renal insufficiency, hyperthyroidism and pulmonary hypertension. It is therefore important to use tests where there is a strong index of suspicion or interpretation of results may prove difficult (Table 4). NT-proBNP assay in combination with thoracic radiographs can significantly improve diagnostic accuracy and confidence in the diagnosis of CHF.[7]

Respiratory rate has also been shown to be a sensitive and specific indicator of CHF in dogs with a history of cardiac

disease and other signs compatible with CHF. A cut-off of 41 and 34 breaths per minute at rest is considered a reliable screening tool in the aid of diagnosing of CHF in the myxomatous degenerative valvular disease (MDVD) and dilated cardiomyopathy (DCM) patient, respectively.[9] Equally, dogs with a respiratory sinus arrhythmia have high vagal tone, a finding that is abolished in CHF as a result of activation of the renin-angiotensin-aldosterone system and high sympathetic drive; therefore, dogs with a heart murmur and a respiratory sinus arrhythmia are less likely to have CHF.

Some dogs with MDVD may have very loud murmurs (grade VI/VI) and yet have a completely normal respiratory rate and pattern and, therefore, no supporting signs of CHF; there is no strong evidence to support starting treatment on murmur grade alone. A louder murmur does suggest more advanced MDVD, but one must have diagnosed MDVD to conclude this. It has also been reported that a proportional number of dogs with MDVD may also have concurrent bronchomalacia;[10] these patients will typically be coughing and radiographs would be necessary to further assess the underlying cause of clinical signs. Frequently, a dog will develop tachypnoea prior to the onset of coughing associated with fulminant pulmonary oedema due to positioning of cough receptors in the airways; coughing can be triggered by fulminant oedema within the airways while tachypnoea may occur with interstitial oedema alone.

The presence of a loud murmur can signify MDVD; however, there are a large number of conditions that may result in a heart murmur and, therefore, investigations to assess the significance of a murmur are recommended. As previously mentioned, biomarkers can be elevated with systemic disease and a number of conditions (eg. anaemia, hyperthyroidism, pregnancy) can result in murmur and/or the development of CHF. It is therefore important to assess for these conditions before diagnosing primary heart disease. The evidence base for early intervention, ie. prior to the onset of CHF, is limited. There is recent evidence from the PROTECT study (a multicentre double-blinded placebo control trial) for the use of pimobendan in pre-clinical or occult DCM with an improvement in survival times.[11] Currently, there is no substantial evidence base for the use of pimobendan in pre-clinical MDVD; however, results of a recent clinical trial (EPIC; Evaluating Pimobendan in Cardiomegaly) should be available in 2016 that may alter treatment recommendations for this indication.

Guidelines for differentiation of cardiac vs non-cardiac causes of respiratory signs in dogs and cats using NT-proBNP assay[8]

- **Low or normal NT-proBNP concentration is most consistent with a non-cardiac cause of current signs, whereas elevated NT-proBNP is more suggestive of a cardiac cause, such as CHF**
- **In animals with asymptomatic heart disease, an increased NT-proBNP concentration can confound the diagnosis of a non-cardiac cause of the respiratory signs**
- **Results should be viewed in context of the medical history, physical examination, and traditional diagnostics, such as thoracic radiography**

Table 4: Guidelines for differentiating cardiac from non-cardiac cause of respiratory signs using the NT-proBNP assay (taken directly from Oyama, 2013).

HOW IMPORTANT IS A SPECIFIC DIAGNOSIS?

MDVD represents the most common acquired cardiac condition in the dog, representing 75% of all cases. Typically, smaller breed dogs are more likely to develop MDVD, although breeds such as border collies, German shepherd dogs and Labradors, along with other large breed dogs, can also develop this condition. DCM is more typically seen in large breed dogs. These are both acquired conditions that become apparent with age; congenital heart disease is seen across the breeds with increased prevalence in some breeds over others. Full cardiac assessment for a patient suspected to have CHF might include full bloods, blood pressure, biomarker tests, echocardiography and thoracic radiographs as well as taking the clinical picture into account (Table 6).

Treatment of CHF is similar for patients with clinical DCM and MDVD, and treatment recommendations can be considered appropriate for both conditions (Table 7). Differentiation of the condition is unlikely to change the immediate management strategy and pharmaceutical datasheets do not distinguish doses of CHF medications based on underlying cause. While CHF is treated similarly, it must be borne in mind that there may be rarer causes of CHF including congenital heart disease (such as patent ductus arteriosus and valvular dysplasia) or acquired heart disease such as nutritional disease (including taurine-responsive DCM as seen in Newfoundlands and American Cocker Spaniels and, less commonly, in cats) or infectious endocarditis that may result in CHF but require alternative, more appropriate treatment strategies.

FUROSEMIDE

The mainstay of treatment for CHF should always include a loop diuretic such as furosemide. Furosemide is a loop diuretic that acts within the ascending limb of the loop of Henle and inhibits an electrolyte channel, preventing reabsorption of water. Furosemide's main indication in CHF is to address pulmonary oedema and reduce fluid retention. Furosemide can be given by a number of routes; given intravenously, there is a venodilatory effect in humans, which helps to reduce preload more rapidly. Given orally, cardiovascular effects begin as soon as 15 minutes post-administration. The typical starting dose is 1-2mg/kg PO BID-TID, this can be uptitrated and downtitrated as necessary to maintain a stable resting respiratory rate.

Another loop diuretic that has recently been licensed is torasemide. This has shown promise in chronic cases that develop furosemide resistance and has recently been licensed for use as a first-line alternative to furosemide. The recommended dosing is 0.1-0.6mg/kg PO SID, starting at lower doses initially with gradual uptitration, with close monitoring of renal function and electrolytes recommended. There is also evidence that there is an additional aldosterone antagonistic effect that is also beneficial for CHF patients.

The use of loop diuretics alone will cause activation of the RAAS system and, therefore, the concurrent use of an ACE-inhibitor is also recommended.

PIMOBENDAN VERSUS BENAZEPRIL

Evidence-based medicine cites pimobendan as the next most important in the treatment of CHF for survival benefit.[12] Based on results from the QUEST study, dogs with CHF, secondary to DCM or MDVD, given pimobendan, in conjunction with furosemide, had a longer median survival time than those receiving benazepril (267 days versus 140 days). Pimobendan is given at 0.1-0.3mg/kg PO BID with a high bioavailability when given on an empty stomach. There is an intravenous preparation of pimobendan available; however, oral treatment has a rapid onset. Pimobendan can be used in cats although its use is off-label, however a number of clinical studies have shown its use can increase survival times for cats with CHF. The use of loop diuretics will cause activation of the RAAS system, and pimobendan does not reduce RAAS activation,[13] so the concurrent use of an ACE-inhibitor is also recommended where possible.

WHICH ACE INHIBITOR?

A number of ACE inhibitors are available, including benazepril, ramipril, imidapril and enalapril, with similar levels of ACE inhibition. Typical starting doses for benazepril are 0.25-0.5mg/kg PO SID, dependent on species. Pharmacokinetic data suggest that doses of up to 0.5mg/kg PO BID can be well tolerated and provide better ACE inhibition; however, this should always be done with close assessment of renal parameters and is also administered off-licence.

SPIRONOLACTONE VERSUS FUROSEMIDE?

The use of spironolactone instead of furosemide is not recommended at this time. Furosemide is a potent loop diuretic with a high ceiling limit (ie. incremental dosing causes increased effect) whereas spironolactone has only mild diuretic effects. There is, however, a good evidence base for the use of spironolactone in both humans and dogs, with CHF showing improved survival times and time to sudden death.[14] Cardalis (CEVA) is a combined spironolactone-benazepril tablet and is marketed as cost-effective and reported to give better compliance.

WHAT LEVEL OF MONITORING IS NECESSARY? TIPS FOR OWNERS MONITORING AND ADJUSTING DOSES

Owners should be trained to monitor respiratory rate and a number of mobile phone applications are available for counting respiratory rate at home. Determining a patient's resting respiratory rate to allow owner-adjustment of diuretics can be very useful and the most cost-effective way of monitoring CHF therapy. Once a resting/sleeping respiratory rate has been measured, the owner can use this as a baseline to increase or decrease furosemide dose under veterinary supervision. As there is a risk of azotaemia with increasing furosemide and ACE inhibitors, ideally urea, creatinine and electrolytes should be assessed one week after a dose increase. Clinical signs of azotaemia could be used where finances are limited and would include anorexia, lethargy, vomiting, polyuria, polydipsia and diarrhoea. These can be difficult for an owner to discern and it is therefore best to perform blood tests to assess azotaemia.

SHOULD WE BE USING DIGOXIN?

Prior to the development of pimobendan, digoxin was a treatment choice for the management of CHF. Digoxin has diuretic properties and is a mild positive inotrope while having negative chronotropic effects. Its use as a mainstay treatment in CHF as an inotrope has been superseded by the superior drug, pimobendan, and the main indication is its use in atrial fibrillation (AF). Studies suggest, however, that heart rate control in AF is superior when it is administered in combination with diltiazem and digoxin's therapeutic, rate-control effects are often seen at lower serum levels.[15] Digoxin has a number of potential side effects (Table 5) and the lowest therapeutic dose for rate control is much lower than doses necessary for inotropic and diuretic effects. Higher doses are more likely to result in digitoxicity and potentially result in an increase in ventricular arrhythmias, both of which may have an impact on quality of life. Dogs receiving digoxin are frequently also in CHF, and a fine line between managing CHF and avoiding significant azotaemia is important; it must be remembered that renal dysfunction can worsen digitoxicity. The use of digoxin should be with therapeutic monitoring of serum levels one week after dose increase; with cost constraints, monitoring heart rate and for signs of digoxin toxicity (Table 5) is recommended.

Potential side effects of digoxin	
Cardiac	**Atrioventricular conduction abnormalities** **Ventricular arrhythmias**
Gastrointestinal	**Anorexia** **Nausea** **Vomiting** **Diarrhoea** **Abdominal discomfort**
Neurological	**Fatigue** **Generalised muscle weakness** **Other human signs: headache, confusion, hallucinations**
Others	**Gynaecomastia** **Cutaneous skin reactions**

Table 5: Possible side effects of digoxin, increasing incidence with increased digoxin serum levels.

	Lowest	Low	Mid	Mid-High	Optimal
Clinical signs	•	•	•	•	•
Thoracic radiographs	•	•	•	•	•
NT-proBNP	•	•	•	•	•
Echocardiography				•	•
Haematology and biochemistry				•	•
Blood pressure					•

Table 6: Author's recommended approach to diagnostic modalities to confirm CHF for general practitioners for a dog or cat with an index of suspicion, based on budget. Multimodal diagnostic work-up is likely to provide the most accurate clinical picture.

	Lowest	Low	Mid	Mid-high
Furosemide	•	•	•	•
Pimobendan	•	•	•	•
ACE inhibitor			•	•
Spironolactone				•

Table 7: Author's recommended approach to treatment choice based on budget. The use of furosemide without an ACE inhibitor is not ideal although, based on the QUEST study, dogs have improved survival times on a combination of furosemide and pimobendan versus ACE inhibitor. Multimodal therapy is likely to provide the best outcomes.

FOLLOW-UP

Follow-up is critical after stabilisation of CHF, and effective assessment of the success and tolerability of cardiovascular drugs is one of the key aims to successful follow-up. Follow-up assessment should be scheduled for stable patients approximately one week after discharge or following a change in therapy. Follow-up should assess:

- Medication review to include assessment of drugs, doses, compliance and any difficulties;
- Quality of life assessment, including appetite, activity, sleeping pattern, exercise tolerance, respiratory signs and urinary habits;
- Assessment for drug toxicities;
- Re-evaluation with physical examination to include body weight and condition score;
- Repeat investigations such as echocardiography and thoracic radiography as indicated;
- Arterial blood pressure measurement as necessary;
- Assessment of renal function and electrolytes as necessary;
- Serum drug levels if indicated (eg. digoxin, amiodarone, if used).

CONCLUSION

CHF can be managed well on a budget. The evidence base for a multi-therapy approach is ever increasing and, as such, financial considerations are important. Ideally, renal function and electrolytes should be assessed one week after changing furosemide dosing and every three to four months thereafter. In conjunction with this, body weight, systolic blood pressure monitoring where appropriate and follow-up radiography and Doppler echocardiography should also be monitored periodically.

While a gold standard approach is considered optimal, the evidence base to support regular blood testing is limited and a simple respiratory rate measurement at home is considered one of the gold standard tools for monitoring response to CHF therapy in a home setting.

REFERENCES AVAILABLE ON REQUEST

READER QUESTIONS AND ANSWERS

1. WHICH DRUG WILL CAUSE THE GREATEST EXACERBATION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM?

A: Pimobendan
B: Furosemide
C: Benazepril
D: Spironolactone
E: Digoxin

2. WHICH DRUG, USED ALONGSIDE FUROSEMIDE, HAS THE BEST EVIDENCE FOR INCREASING SURVIVAL TIMES THE DEVELOPMENT OF CHF?

A: Pimobendan
B: Spironolactone
C: Benazepril
D: Digoxin
E: Torasemide

3. THE MAJORITY OF RELEASED NT-PROBNP IS IN RESPONSE TO:

A: Renin-angiotensin-aldosterone activation
B: Ventricular and atrial stretch
C: Reduced cardiac output
D: Pulmonary oedema
E: Vasodilation

4. ACCORDING TO THE ACVIM CONSENSUS STATEMENT FOR THE DIAGNOSIS AND TREATMENT OF CANINE CHRONIC VALVULAR HEART DISEASE, WHICH STAGE DENOTES PATIENTS WITH PAST OR CURRENT CLINICAL SIGNS OF HEART FAILURE ASSOCIATED WITH STRUCTURAL HEART DISEASE?

A: Stage A
B: Stage B
C: Stage C
D: Stage D
E: Stage E

5. OF THE FOLLOWING, WHAT IS THE CURRENT GOLD STANDARD TO DIAGNOSE PULMONARY OEDEMA IN VETERINARY MEDICINE?

A: Presence of a loud heart murmur (≥grade 3/6 systolic murmur)
B: NT-proBNP assay
C: Doppler echocardiography
D: Respiratory rate
E: Thoracic radiographs

ANSWERS: 1: B, 2: A, 3: B, 4: C, 5: E