Use of cardiac medications in congestive heart failure cases

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ABSTRACT

Congestive heart failure (CHF) is a common consequence of severe heart disease and is frequently encountered in clinical practice. Depending on the severity of clinical signs, treatment may require acute (hospital-based) or chronic (home-based) management.

This article focuses on the various cardiac medications available and commonly used to treat CHF in dogs and cats. Drug dosages are included as a guideline only. The reader is strongly encouraged to consult and follow the manufacturer instructions and the drug formulary indications.

Congestive heart failure (CHF) is a complex clinical syndrome triggered by any structural or functional cardiac disease that impairs the ability of the heart to receive or eject blood (diastolic and systolic dysfunction, respectively).

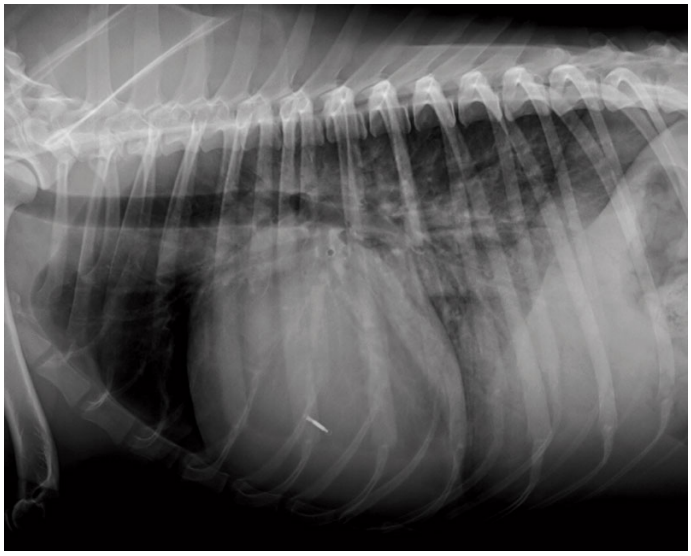

Figure 1a. Lateral radiograph of a dog with generalised cardiomegaly, vessel enlargement and diffuse lung opacity, particularly in the more caudal and ventral lung fields where air bronchograms are visible. These radiographic signs suggest heart disease and cardiogenic pulmonary oedema.

Compensatory mechanisms to help maintain cardiac output, adequate arterial blood pressure and perfusion of critical organs (for example, brain, heart or lungs) are mediated by neural and hormonal messengers, such as catecholamines, renin, angiotensin and aldosterone.

These neurohormonal mechanisms have beneficial short-term effects and result in increased heart rate and cardiac contractility, peripheral vasoconstriction and fluid and sodium retention by the kidneys. However, in the long-term, they result in excessive fluid retention, elevated pressure within the venous circulation and accumulation of fluid in the extracellular space (pulmonary oedema with or without pleural effusion [in cats] in case of left-sided CHF or pleural/peritoneal/pericardial effusion in case of right-sided CHF)[1].

Clinical signs depend on the site of fluid accumulation and may include compromised respiratory function (dyspnoea, tachypnoea or increased respiratory effort), exercise intolerance, lethargy, weakness or collapse, abdominal distension, anorexia and diarrhoea[2,3]. A presumptive diagnosis is usually made on the patient's clinical signs, signalment, history and physical examination findings.

Thoracic radiography is a readily available confirmatory test and usually shows cardiomegaly, venous congestion and pleural effusion or pulmonary oedema[3] (**Figure 1**). In cases where thoracic radiography does not provide a clear answer, a quick echocardiographic examination allowing visualisation of the cardiac chambers and pericardial space, evaluation of the left atrial size and cardiac contractility may help diagnosis[4] (**Figure 2**).

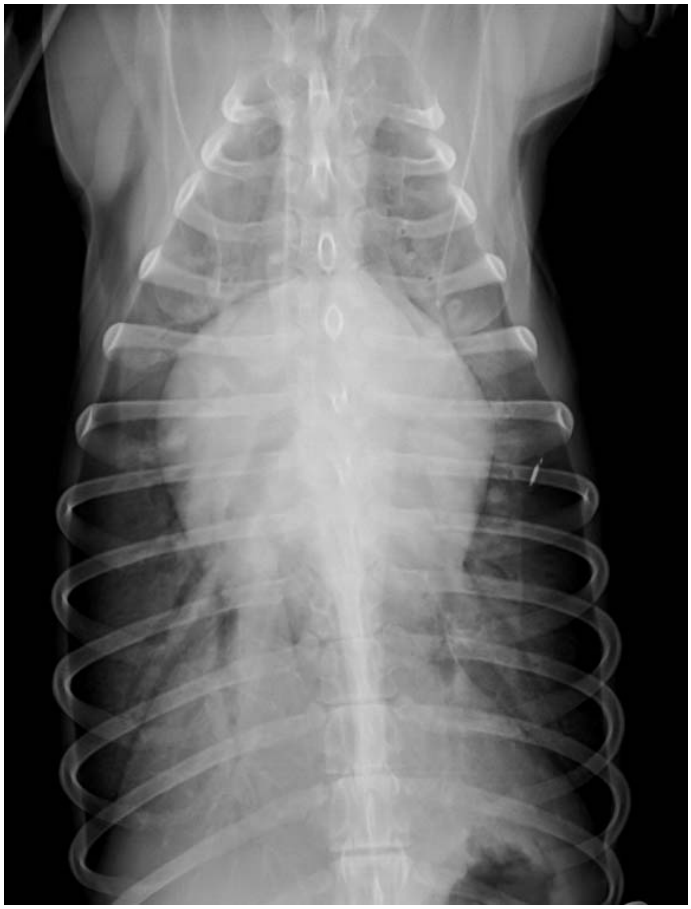

Figure 1b. Dorsoventral radiographs of a dog with generalised cardiomegaly, vessel enlargement and diffuse lung opacity, particularly in the more caudal and ventral lung fields where air bronchograms are visible. These radiographic signs suggest heart disease and cardiogenic pulmonary oedema.

In all cases, it is important to remember patients in CHF are often critical and can rapidly deteriorate with handling, so stress should be minimised. Diagnostic tests – particularly in severe cases – may need to be performed after initial stabilisation of the patient.

Treatment

Treatment recommendations vary depending on the severity of clinical signs. Emergency management of CHF often includes oxygen therapy, thoracocentesis in case of pleural effusion, limitation of stress – which may include the use of sedatives – and adequate pharmacologic treatment[5].

Recommendations by the American College of Veterinary Internal Medicine (Speciality Cardiology; ACVIM Cardiology) consensus statement for the chronic management of CHF include furosemide, angiotensin-converting enzyme (ACE) inhibitors and pimobendan in symptomatic patients (stage

C)[5]. Spironolactone is also routinely used by most cardiologists in stage C5 and is recommended in refractory cases of CHF (stage D; **Table 1**).

Cardiac medications

Loop diuretics

Loop diuretics act on the thick ascending loop of Henle and are the most effective and potent diuretics. By reducing the intravascular hydrostatic pressure, they decrease the formation of oedema and cavitary effusions representing the mainstay of CHF treatment[5,6].

Furosemide has been commonly used in CHF patients in the past and still represents the first line diuretic in veterinary medicine[5]. Torasemide is a newer diuretic similar to furosemide, but is more potent, with a longer diuretic action (12 hours versus 6 hours) and some potassium-sparing activity due to aldosterone antagonism[7-9].

Dosages

The dose of furosemide required by a dog or cat in CHF may be difficult to determine. Guidelines for management of acute pulmonary oedema in dogs recommend the use of 1mg/kg to 4mg/kg as IV boluses every one hour to six hours, or constant rate infusion (1mg/kg/h) for refractory cases, depending on the severity of clinical signs. Once the respiratory rate decreases, the dose is rapidly tapered to a lower dose[5]. Cats are more sensitive than dogs to dehydration and azotaemia[10], and lower doses are usually used (1mg/kg to 2mg/kg every one to eight hours).

Once the acute phase has been managed, oral furosemide is continued commonly at a dose of 2mg/kg every 12 hours. The dose is then titrated to meet the patient's needs5. Owners are often asked to keep a chart of the respiratory rate at rest/sleep and, based on this, the lowest most effective dose is used[11]. In fact, the dosage may vary between 1mg/kg to 2mg/kg PO every 12 hours and 4mg/kg to 6mg/kg PO every 8 hours. Kidney function and electrolytes are monitored to promptly detect abnormalities5.

Torasemide was not licensed for veterinary use until recently and has been typically used as an adjunctive treatment for CHF – especially in cases that develop furosemide resistance – with good results. The licensed formulation has a reported potency of 20 times that of furosemide and the recommended dosage is 0.1mg/kg to 0.6mg/kg once daily. As for other diuretics, monitoring of renal function and electrolytes is recommended during treatment[6,8].

ACE inhibitors

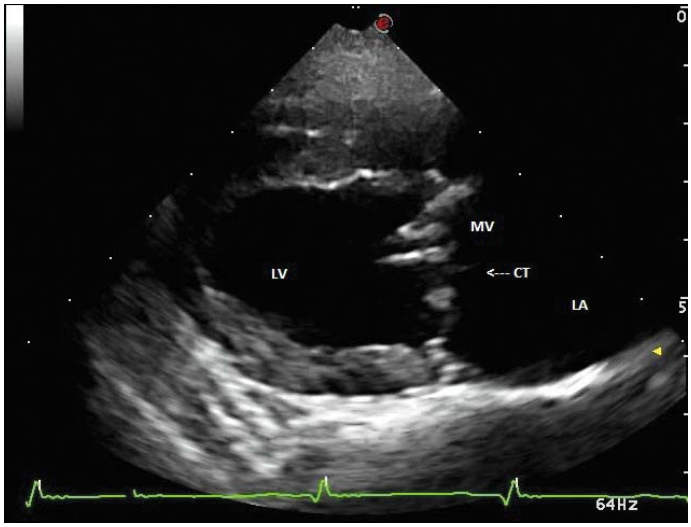

Figure 2. Right parasternal long axis view of a dog with degenerative mitral valve disease. Thickening and prolapse of the mitral valve (bulging of the valve toward the left atrium), marked left atrial enlargement and a small echoic linear structure suggestive of ruptured chordae tendineae are identified.

ACE inhibitors represent a cornerstone in the chronic management of CHF. They are used in veterinary practice to counteract the renin-angiotensin-aldosterone system (RAAS) by blocking the conversion of angiotensin I to angiotensin II, with consequent reduction of its deleterious chronic effects (vasoconstriction, water and sodium retention and myocardial remodelling)[1].

In dogs with CHF, several studies have shown ACE inhibitors improve quality of life and survival[12-16] and, among cardiologists, there is consensus on their use in chronic CHF management, while there is no agreement regarding their use in the acute phase[5]. In fact, they are withheld by some specialists during acute severe CHF because of the possibility of reducing renal perfusion and glomerular filtration rate[17].

In cats, ACE inhibitors are not licensed for treatment of CHF and studies regarding their efficacy are lacking. Despite this lack of data, cardiologists use them in chronic CHF as adjunctive treatment.

Generally, renal parameters and electrolytes are monitored over time for an earlier detection of drug adverse effects.

Dosages

ACE inhibitors used include benazepril, enalapril, ramipril and imidapril, with the following dosages:

- Benazepril: dogs/cats 0.25mg/kg to 0.5mg/kg PO once daily[18,19].
- Enalapril: dogs 0.5mg/kg PO every 12 hours to 24 hours; cats 0.25mg/kg to 0.5mg/kg PO

once daily[18].
- Ramipril: dogs/cats: 0.125mg/kg to 0.25mg/kg PO once daily[18].
- Imidapril: dogs 0.25mg/kg PO once daily[18].

Inodilators

Inodilators are a class of drugs characterised by a combination of positive inotropic (increased contractility) and vasodilatory effects. Various agents with different mechanisms of action belong to this class, but pimobendan is the most commonly used in veterinary medicine[20].

Pimobendan has a dual mechanism of action – it is a phosphodiesterase III inhibitor leading to arterial and venous dilation, and a calcium sensitiser that results in positive inotropy[20].

Several studies have shown the benefit of oral pimobendan treatment in dogs with CHF (PITCH study, VetSCOPE and QUEST)[21-24] both in terms of survival and quality of life, making this inodilator a first-line drug to use in CHF, together with loop diuretics and ACE inhibitors. In fact, the ACVIM (Cardiology) consensus statement recommends the use of pimobendan in both the acute and chronic management of CHF due to mitral valve disease, while off-label high dosage is used by some cardiologists in refractory cases[5]. An IV formulation is available in the UK, allowing an alternative route of administration that may prove useful in acute cases.

Although pimobendan is not licensed for use in cats, retrospective studies have suggested it is well tolerated and shown some benefits in various forms of cardiac disease[25-27]. It is usually added to classic CHF treatment when systolic dysfunction, refractory heart failure or azotaemia are present[3], but studies are required to evaluate its efficacy in these clinical settings.

Dosages

Dosages of pimobendan are:

- Dogs: 0.25mg/kg to 0.30mg/kg PO every 12 hours to administer on an empty stomach[23,28]; 0.15mg/kg IV followed by oral treatment. Off-label high dose in refractory CHF 0.25mg/kg every 8 hours[5].
- Cats: (off-label) 0.25mg/kg PO every 12 hour to administer on an empty stomach[27] (generally 1.25mg tablet per cat every 12 hours).

Mineralocorticoid receptor antagonist

Table 1. Treatment recommendations for congestive heart failure treatment (modified from the American College of Veterinary Internal Medicine [Speciality Cardiology] consensus statement)[5]

Stage B – asymptomatic patients		
No treatment at this stage. Pimobendan in Dobermanns with dilated cardiomyopathy.		
Stage C – symptomatic patients		
	Consensus	**No consensus**
Acute (hospital-based)	• oxygen • sedation (if animal is stressed) • centesis to remove effusions if they impair breathing • furosemide • pimobendan (use in cats in case of systolic dysfunction and azotaemia) • nitroprusside, hydralazine (in severe cases)	• ACE inhibitors • nitroglycerin ointment
Chronic (home-based)	• furosemide • ACE inhibitors • pimobendan (use in cats in case of systolic dysfunction and azotaemia)	• spironolactone • antiarrhythmics (digoxin, diltiazem and beta blockers) • cough suppressants and bronchodilators
Stage D – symptomatic patients refractory to treatment		
	Consensus	**No consensus**
Acute (hospital-based)	• as stage C • nitroprusside and hydralazine (more vigorous vasodilation compared to stage C in cases that tolerate it)	• pimobendan (increased off-label dose) • dobutamine • sildenafil • bronchodilators
Chronic (home-based)	• as stage C • spironolactone	• other diuretics • pimobendan (increased off-label dose) • sildenafil • antiarrhythmics (digoxin, diltiazem and beta blockers) • cough suppressants and bronchodilators

Table 1. Treatment recommendations for congestive heart failure treatment (modified from the American College of Veterinary Internal Medicine [Speciality Cardiology] consensus statement)[5].Spironolactone has received increased interest after it was shown aldosterone receptor blockage in human patients with advanced CHF reduces morbidity and mortality[29]. Aldosterone concentration is known to increase in CHF as a result of the activation of RAAS[1] and chronic treatment with ACE inhibitors appears to be insufficient to completely block the production of angiotensin II and aldosterone – known as aldosterone escape or breakthrough[30].

In veterinary medicine, a study conducted in dogs with CHF due to degenerative mitral valve disease showed spironolactone, when added to conventional treatment, decreased the risk of cardiac death, euthanasia or CHF worsening[31]. However, some cardiologists raised concerns about the study's design and disputed a survival benefit could be proved[32].

Nonetheless, most cardiologists, including the author, use spironolactone routinely in dogs with CHF and the ACVIM (Cardiology) consensus recommends its use in refractory cases[5].

Dosage

Spironolactone has the following dosage:

- Dogs and cats: 2mg/kg PO every 24 hours[32-34].

One potential adverse effect to note is severe ulcerative facial dermatitis reported in a study regarding Maine coon cats that were receiving a higher-than-recommended dose (2mg/kg every 12 hours)[35]. Regular monitoring of renal function and serum potassium levels is recommended in dogs

with renal impairment, as they may have increased risk of hyperkalaemia during treatment.

Vasodilators

Vasodilators act on arteriolar or venous smooth muscle and cause vasodilation. They can be classified as venodilators, arteriolar or balanced (arteriolar and venous) dilators and are generally used for treatment of severe or refractory cases of CHF[5,18]. By reducing the peripheral vascular resistance, they reduce the pressure against which the heart must pump (afterload), allowing an increased cardiac output with the same force of myocardial contraction.

Nitroprusside is a potent balanced vasodilator for IV administration that has to be used with extreme caution and requires continuous monitoring of the systemic arterial blood pressure.

Nitroglycerine is a venodilator generally used as a transdermal formulation (patches or ointment). It is safer to use and does not require constant blood pressure monitoring, but its efficacy is debatable.

Hydralazine is a very potent arteriolar dilator for oral use.

Dosages

Dosages of the aforementioned vasodilators are:

- Nitroprusside: dogs/cats 0.5mcg/kg/min to 10mcg/kg/min (doses towards the lower end are used and titrated upward by 0.5mcg/kg to 1mcg/kg every 10 minutes to 15 minutes until clinical improvement is observed, accompanied by a 5% to 10% decrease in blood pressure – target systolic blood pressure greater than 85mmHg). The maximal dose reported is 10mcg/kg/min, but a much lower dose is recommended (maximal dose usually not above 5mcg/kg/min). Prolonged treatment increases the risk of toxicity and, for this reason, it is rarely used for longer than 24 hours to 48 hours[5,18].
- Nitroglycerin: semi-quantitative dosage based on the size of the patient. Applied on a hairless area (usually inner ear pinnae, axilla or groin). Generally used for 24 hours as tolerance to the effects of the drug develops quickly. Some cardiologists use it intermittently (12 hours on and 12 hours off the drug)[5,18].
- – Small dogs: 6mm to 12mm of transdermal ointment; medium dogs: 12mm to 25mm; and large dogs 25mm to 50mm every 6 hours to 12 hours[18].
- – Cats: 3mm to 6mm of transdermal ointment every 6 hours to 12 hours[18].
- Hydralazine: start with a low dose and titrate upward based on clinical and radiographic improvement of CHF signs. Blood pressure monitoring is recommended[5,18].
- – Dogs: 0.5mg/kg to 3mg/kg PO every 12 hours[18].
- – Cats: 2.5mg/cat to 10mg/cat PO every 12 hours[18].
- **Some drugs in this article are used under the cascade**.

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