Idiopathic dilated cardiomyopathy in the dog: treatment modalities

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CPD

DEFINITION

Idiopathic dilated cardiomyopathy (IDCM) is a heart muscle disease of unknown aetiology characterised by progressive systolic dysfunction (loss of contractility) of the ventricular myocardium leading to progressive dilation of first the ventricle(s) and later the atria. Some degree of diastolic dysfunction will also be present. In some breeds (see Table 3 previous article: UKVet Vol 8 No 7) ventricular arrhythmias rather than systolic dysfunction indicate the presence of IDCM.

TREATMENT

A good understanding of the underlying pathophysiology enables a sensible approach to the treatment and management of heart failure. Activation of the detrimental neuro-endocrine cascade (first sympathetic stimulation followed by the renin–angiotensin–aldosterone system) and systolic dysfunction predominate in congestive heart failure due to IDCM.

DOGS WITHOUT CLINICAL SIGNS

Treatment of asymptomatic dogs with IDCM remains controversial. There is only one veterinary study (O'Grady, Dobermann population, unpublished 1997) that has shown, as in human medicine, that early use of ACE inhibitors (ACEI) might positively influence the time of development of clinical signs and survival times in DCM.

The use of beta-blockers (see later) in this group of patients is currently under investigation.

DOGS WITH CLINICAL SIGNS

The aims for treatment of dogs with DCM are multiple and therefore polypharmacotherapy is the way forward. No single drug achieves all the required objectives:

1. **Treat the underlying disease.**
2. **Control life-threatening oedema and effusions**: diuretics and thoracocentesis.
3. **Stop the detrimental neuro-endocrine cascade**: ACEI and beta-blockers.
4. **Improve cardiac output**: positive inotropes (dobutamine, digoxin, pimobendan), pre- and afterload reduction (ACEI, nitroglycerine, pimobendan).
5. **Control arrhythmias**

It should be emphasised that the efficacies of drugs used to treat heart failure depend on drug type, underlying disease and individual patient response. There are no set rules and it is important to monitor a patient with heart failure closely. **Adapt the treatment subsequent to repetitive clinical evaluation of the patient**.

From a practical and therapeutic point of view subdivide congestive heart failure into acute, life-threatening failure and more chronic, congestive heart failure.

ACUTE HEART FAILURE THERAPY IN DCM

Strict **cage rest** is essential and stress must be avoided. Ancillary investigations to confirm the cause of acute congestive heart failure may need to be postponed until the patient is stable.

Oxygen supplementation should be established (preferably humidified as an intranasal catheter) (Fig. 1).

Fig. 1: *Humidified intranasal oxygen administration and cage rest are an essential part of the treatment of a dog in acute congestive heart failure.*

In the presence of life-threatening pulmonary oedema **frusemide** administered intravenously (initially 2-4 mg/kg IV q 1-4 h) has an additional and beneficial venodilatory effect. Monitor renal function including serum electrolytes and urine production.

Thoracocentesis alleviates respiratory distress due to severe pleural effusion. It is not advisable to drain ascites unless the effusion is compromising respiration.

Acute reduction of pulmonary venous pressure is achieved by the use of a potent vasodilator to redistribute intravascular fluid volume. Because of the general lack of haemodynamic monitoring in veterinary medicine, topical administration of **nitroglycerine** (2.5 cm/20 kg BW q 8 h) is the most practical and safe vasodilator. It is a venodilator applied to a hairless, well perfused area of skin (medial pinna or groin) (Fig. 2). Wear gloves to apply ointment and provide a warning sign with information about the site of the nitroglycerine administration. Avoid its use in patients with cardiogenic shock. Patients become refractory to nitrates with long-term administration, therefore only use it for three to five days until initial control of pulmonary oedema.

Fig. 2: *Care should be taken (WEAR GLOVES AND USE WARNING SIGN) when nitroglycerine is applied topically. The inner ear pin is a commonly used site.*

Inotropic support is very important with acute heart failure due to IDCM. **Dobutamine** is a synthetic catecholamine (β_1-sympathicomimetic drug) that is more efficacious than digoxin for acute management of profound myocardial failure. It can only be used in an intensive care setting. Dobutamine increases contractility with little change in heart rate or afterload. It is very short lived and therefore best suited as a continuous rate infusion (2.5-15 µg/kg/min dobutamine hydrochloride, titrate up to effect). Efficacy is limited following chronic administration because of down-regulation of β-adrenergic receptors, but administration over three days has a more prolonged effect of up to two to three weeks duration. Serious adverse effects include ventricular arrhythmias and therefore constant ECG monitoring during dobutamine administration is strongly recommended.

Pimobendan can be started immediately (0.1-0.3 mg/kg q 12 h) but when ventricular arrhythmias are present careful titration and ECG monitoring is recommended.

Digoxin is a comparatively weak positive inotrope with a narrow margin of safety. In most cases digitalis glycosides can be administered orally, starting at maintenance dosage (dogs 0.11 mg/m^2 q 12 h). Rapid intravenous digitalisation is rarely necessary in dogs with acute heart failure except to control certain supraventricular arrhythmias.

The **control of haemodynamically unfavourable arrhythmias and life threatening arrhythmias** (Fig. 3) is important but one has to be aware that many arrhythmias will be controlled by controlling the heart failure. Sinus tachycardia does not warrant specific anti-arrhythmic treatment. With atrial fibrillation the aim is to control the ventricular response rate by controlling the congestive heart failure and by oral digitalisation (see above and later). If controlling the heart failure does not abolish supraventricular arrhythmias calcium channel blockers (verapamil 0.05 mg/kg slowly IV) can be used. Ventricular arrhythmias, when they occur as a consequence of DCM, should be treated if they compromise the animal haemodynamically or if they have a malignant aspect (couplets, triplets, R on T, polymorphic). Use lidocaine (intravenous bolus of 2 mg/kg can be repeated four times followed by a continuous rate infusion of 0.025-0.1 mg/kg/min) for rapid control. Beta-blockers (e.g. esmolol, 0.05-0.1 mg/kg slow; propanolol, 0.02-0.08 mg/kg IV slowly) can be tried in case of non-response but their negative inotrope effect should be considered in dogs with DCM.
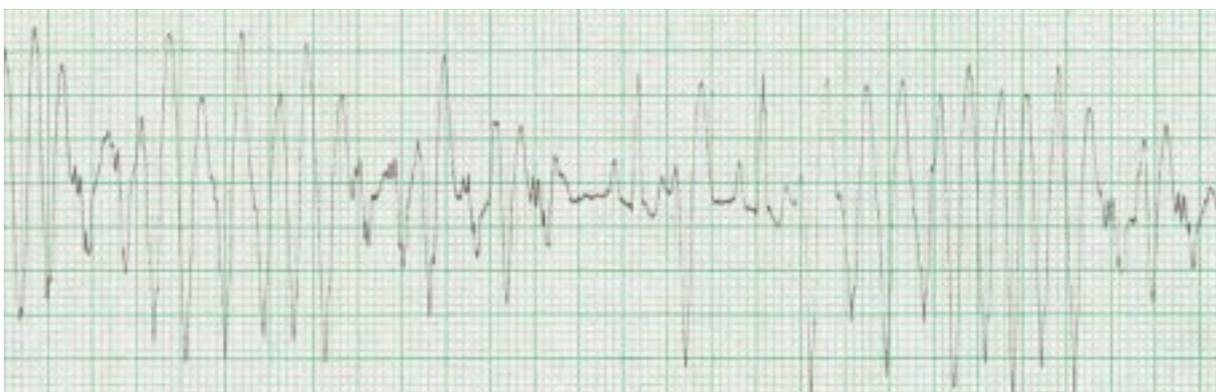

Fig. 3: *An ECG (lead II rhythm strip) of a malignant ventricular arrhythmia that warranted immediate treatment.*

CHRONIC HEART FAILURE THERAPY IN DCM

The heart is more than a pump; it is also a neuro-endocrine organ. Considering the proven efficacy and safety of ACEI in several controlled canine DCM heart failure studies, ACEI are and remain the mainstay treatment of every dog in congestive heart failure secondary to DCM. **Therefore ACE-inhibitors should be given to all patients in heart failure** unless specific contra-indications exist. They have a number of beneficial effects:

- *Vasodilator*: arteriolar and venous dilation occurs as a direct result of the decreased concentration of angiotensin II and as an indirect result of the accumulation of bradykinins. ACEI decrease systemic vascular resistance by approximately 25-30%.

- *Anti-aldosterone effect*: sodium and water excretion is enhanced. The ability of ACE-inhibitors to decrease plasma aldosterone secretion may become attenuated or lost with time ('aldosterone escape').

- *Attenuation of sympathetic drive*: ACEI prevent via angiotensin II inhibition of the central and peripheral effects of the sympathetic nervous system.

- *Renoprotection*: levels of bradykinin and renoprotective prostaglandins are allowed to accumulate.

- *Prevention of remodelling and fibrosis* of the myocardium and vascular smooth muscle by acting on the tissue renin angiotensin system (partially ACE mediated and partially serine protease chymase mediated).

Currently available ACEI in veterinary medicine are **enalapril, benazepril, ramipril and imidopril** (Table 1). It is difficult to determine the optimal dose for any ACEI or to compare relative efficacy of the drugs available. Once daily dosing may be sufficient, although giving an ACEI every 12 hours may be beneficial and preferable to increasing the diuretic dose. In humans higher dosages are used to overcome the 'aldosterone escape' phenomenon that occurs after chronic ACEI therapy and higher dosages and/or more frequent dosing are also advocated when the objective is tissue ACE inhibition. The clinical relevance of ACEI at tissue level in dogs is unknown as are the properties of the available ACEIs to achieve this.

Diuretics are essential in the control of congestive heart failure. Single-agent diuretic therapy is usually not advocated since these drugs activate neuro-endocrine responses that might hasten the progression of heart failure. **Frusemide** (1-3 mg/kg q 8-12 h PO) is the most commonly used diuretic in small animal medicine; it is potent and has few side effects. Once the clinical signs of congestive heart failure are controlled, attempts should be made to reduce the diuretic dose. If very high dosages of frusemide (more than 6-8 mg/kg/day) are required to control the heart failure, another diuretic should be added to the existing treatment (sequential nephron blockade in view of preserving renal function). The author prefers to use the potassium sparing diuretic **spironolactone** (2-4 mg/kg PO q 24 h) as it has been suggested that spironolactone may reduce myocardial fibrosis (reduce anrrhythmias) and may help restore normal baroreceptor function in heart failure. It also competes with aldosterone, an important mediator of the detrimental neuro-endocrine cascade. Its usefulness in veterinary medicine is under investigation.

Pimobendan (0.2–0.6 mg/kg/day in dogs divided over 2 doses) is an inodilator. It acts on cardiac myocytes as a calcium sensitiser, thereby increasing myocardial contractility, and on peripheral vasculature through selective phosphodiesterase III and V inhibition producing peripheral and coronary vasodilation. It promotes general well being by reducing the amount of tumour necrosing factor and cytokines liberated. In the treatment of DCM, pimobendan **in association with** other drugs including frusemide, ACEI and digoxin increases survival times when used in Dobermanns and other large breed dogs but not in English Cocker Spaniels. At lower dosages it is a venodilator with its arteriodilatory and calcium sensitising properties mainly appearing at higher dosages. Its positive chronotropic action (a consequence of increased conduction through the AV-node) is probably dose-dependant.

TABLE 1.

Drug	Preparation	Dose
Benazepril	2.5, 5, 20 mg Fortekor® (Novartis)	0.25-0.5 mg/kg PO q 24 hrs
Enalapril	1, 2.5, 5, 10, 20 mg Enacard® (Merial)	0.5 mg/kg PO q 12-24 hrs
Imidopril	150, 300 mg Prilium® (Vetoquinol)	0.25 mg/kg PO q 24 hrs
Ramipril	1.25, 2.5, 5 mg Vasotop® (Intervet)	0.125 mg/ kg PO q 24 hrs

Digoxin is a comparatively weak positive inotrope with a narrow margin of safety. In most cases digitalis glycosides can be administered orally, starting at maintenance dosage (Digoxin dogs 0.11 mg/m² q 12 h). Digoxin bioavailability varies between different dosage forms (tablets = 60% and elixir =75 %) and brands (Lanoxin, recommended by the author). Because of its narrow therapeutic safety margin, and the individual variation in absorption, metabolism and response, the patient should be observed closely. The most common adverse reactions are gastrointestinal or cardiac in nature. The gastrointestinal signs (anorexia, vomiting, diarrhoea) precede cardiac adverse effects (rhythm disturbances). If these effects occur, withdraw digoxin and reintroduce it at half the initial dosage once signs of toxicity have resolved (48 hours). Monitoring therapeutic levels can be helpful in deciding whether the non-specific gastrointestinal signs are secondary to digoxin toxicity or not (range 0.8-2.0 ng/ml). A patient on long-term therapy should be monitored intermittently for changes that may predispose the development of toxicosis (renal failure, hypokalaemia, reduction in muscle mass). Since there is no predictable relationship between serum level and effect, levels should be measured in patients where the effect appears inadequate or excessive. Serum should be collected 8 hours post tablet once a steady-state has been achieved (after 7-10 days therapy). As well as being a positive inotrope, digoxin has modulatory effects on the sympathetic nervous system which may underlie many of its favourable effects in heart failure. Digoxin restores baroreceptor sensitivity therefore decreasing sympathetic tone. These favourable vagomimetic effects of digoxin are seen even at low doses and so levels at the lower end of the therapeutic range are usually sufficient and should be aimed for (< 1.5 ng/ml).

Betablockers: One of the most profound changes in attitude towards β-blockade has been in the field of DCM. **β- blockers** have traditionally been considered to be contra-indicated in myocardial failure, because of their adverse acute haemodynamic effects (negative inotropy). It now appears that long-term use of β-adrenergic antagonists (> 3 months) is associated with improvement in systolic function in human patients with IDCM and ischaemic heart disease. Veterinary trials are underway but one has to be aware that dogs are often presented in a more advanced stage of the disease and that many breeds of dogs diagnosed with DCM have an average survival of only three months. The mechanism of action of beta-blockers relates to:

- Reversal of the down regulation of β-receptors that occurs with chronically elevated catecholamine levels
- Reversal of the beta-adrenergic signal transduction abnormalities
- An anti-apoptotic and anti-remodeling action

- An improvement in calcium homeostasis of the excitation-contraction coupling
- An increased coronary blood flow and decreased oxygen demand
- Protection against catecholamine induced myocyte toxicity

Certain strict guidelines are recommended for commencing therapy with β-adrenergic antagonists in animals with myocardial failure. **Patients must be stable and compensated** (i.e. no congestive signs) and the doses must be extremely low initially and titrated upwards very slowly at 1-2 week intervals. **The author recommends their use in experienced hands only**. Currently used β-blockers are **propanolol, atenolol, metoprolol and carvedilol**. Propanolol (0.2-1 mg/kg q 8 hrs) is a non-selective β-blocker, where atenolol (0.5-2 mg/kg q 12 hrs) and metoprolol (0.2-0.8 mg/kg BID) are selective β₁-blockers. **Carvedilol** (0.1-0.4 mg/kg q 24 hrs), a non-selective β-blocker with additional vasodilatory effects via α₁ blockade, is still under investigation in veterinary medicine, but has shown to be promising in human patients with DCM.

CHRONIC ANTI-ARRHYTHMIA TREATMENT IN DCM

The most commonly encountered arrhythmias in DCM are atrial fibrillation, supraventricular tachycardia and ventricular tachycardia. Substantial haemodynamic and clinical improvement can often be realised by successful treatment.

In the case of atrial fibrillation due to atrial dilation the aim of treatment is not to convert to sinus rhythm but to reduce the ventricular response rate under 140 BPM. **Digoxin** remains the treatment of choice for controlling the ventricular response rate (max 0.11 mg/m² q 12 h). If digoxin is not sufficient to control the ventricular response rate diltiazem, a calcium channel antagonist (0.5-1 mg/kg q 8 h slow titration because negative inotrope and competition with digoxine), or a low-dose beta-blocker can be added to the digoxin. Calcium channel blockers are less negative inotrope than beta-blockers (which should be avoided in acute heart failure). Diltiazem is more effective than beta-blockers in reducing the ventricular response rate, however it reduces intracellular calcium concentration. Pimobendan's (see above) maximal inotropic effect is mainly seen at higher intracellular calcium concentrations thus one has to be aware that their combination might theoretically be antagonistic.

Beta-blockers (**atenolol** 0.5-2 mg/kg PO q 12 h) and Class I anti-arrhythmics (**mexilitine** 4-8 mg/kg PO q 8-12 h) used to be used to treat ventricular arrhythmias. Recently **sotalol** (0.5-2 mg/kg PO q 12 h), a Class III anti-

arrhythmic with beta-blocking properties, has become very popular for treating ventricular arrhythmias in Boxer cardiomyopathy. Its efficacy in reducing ventricular arrhythmias is equivalent to the combination of atenolol and mexilitine and better than the latter drugs on their own. **Procainamide** is no longer available. Recently **amiodarone** has been introduced for the treatment of refractory ventricular arrhythmias (mainly in Dobermanns) but because of their potential fatal side effects (hepatopathy, immune-mediated anaemia and thrombocytopenia, keratopathy) the author recommends their use under strict monitoring and by more experienced individuals only.

NUTRITION AND OTHER MEASURES
Weight reduction is strongly recommended in obese animals.

Marked restriction of **sodium** is no longer advocated for dogs with congestive heart failure. Such diets are usual unpalatable and it is important that an animal in congestive heart failure has a proper calorie and protein intake. Additionally, reduction in sodium intake will activitate the RAAS system. It is important that sodium intake is kept constant. **Water** should never be restricted in dogs on diuretics.

L-carnitine is expensive and should only be supplemented (50-100 mg/kg q 8 hrs) in animals with L-carnitine deficiency-induced cardiomyopathy. Significant improvement in echocardiographic parameters should be recognised within three months of treatment to confirm a response. Animals with proven taurine deficiency-induced myocardial failure (plasma level < 50 ng/ml) should be supplemented with **taurine** (dogs 500 mg/20 kg q 12hrs; cat 250 mg q 12 hrs).

Fish oil administration decreases cardiac cachexia in dogs with heart failure. It contains **omega-3 fatty acids, eicosapentaenoic acid** (40 mg/kg) and **doxosahexanaenoic acid** (25 mg/kg) that decrease production of cytokines and inflammatory mediators and therefore improves appetite. The author commonly prescribes **cod liver oil** in animals with advanced dilated cardiomyopathy and signs of cardiac cachexia.

An animal in **chronic** congestive heart failure should be encouraged to **exercise** to within its capabilities (a golden cage is not a life style). Fit muscles are better able to withstand the reduced delivery of nutrients than unfit muscles. However, sudden increases in exercise should be avoided.

NEW DRUGS
A whole range of new drugs (e.g. endothelin antagonists, renin inhibitors, angiotensin receptor inhibitors, vasopressin receptor antagonists, neutral endopeptidase inhibitors, exogenous human brain natriuretic peptide, kaliuretic peptide and recombinant anti tumour necrosing factor) are currently under investigation in human medicine but cannot be advocated in veterinary medicine as yet because the appropriate data are lacking.

CONCLUSION
Treatment of dogs with DCM is palliative and warrants **polypharmacotherapy**. ACE-inhibitors should be given to all patients in heart failure unless specific contra-indications exist. It is important to regularly monitor a patient with DCM receiving multiple drugs. Every patient will react differently to different treatments. Where necessary, the treatment should be adapted appropriately depending on the clinical findings. There is no doubt that repetitive monitoring by experienced individuals improves quality and duration of life.

FURTHER READING AND REFERENCES
KITTLESON and KIENLE (1998) Small Animal Cardiovascular Medicine (Mosby).
FOX, SISSON, MOISE (2000) Textbook of canine and feline cardiomyopathy (WB Saunders).
DUKES-MCEWAN (2000) Canine dilated cardiomyopathy. In practice. p 520-530; 620-626.

These multiple choice questions are based on the above text. Readers are invited to answer the questions as part of the RCVS CPD remote learning program. Answers appear on the inside back cover. In the editorial panel's view, the percentage scored, should reflect the appropriate proportion of the total time spent reading the article, which can then be recorded on the RCVS CPD recording form.

1. **Which of the following is not a part of the traditional treatment of acute congestive heart failure in a dog with Idiopathic DCM:**
   a. Strict cage rest
   b. Oxygen supplementation
   c. Frusemide intravenously
   d. Percutaneous nitroglycerine
   e. Intravenous digoxine

2. **Which statement is false regarding the acute treatment of arrhythmias in a dog with DCM:**
   a. Sinus tachycardia does not warrant specific anti-arrhythmic treatment but stabilisation of the underlying congestive heart failure.
   b. With atrial fibrillation controlling the congestive heart failure and oral digitalisation remains the treatment of choice.
   c. Ventricular arrhythmias should be treated by controlling the congestive heart failure whatever aspect they have.
   d. Lidocaine remains the treatment of choice for the treatment of ventricular arrhythmias.
   e. Supraventricular arrhythmias might warrant anti-arrhythmic treatment if controlling the underlying heart failure does not control the tachycardia.

3. **Which statement is false regarding pimobendan in idiopathic DCM:**
   a. It is a calcium sensitiser and thus increases myocardial contractility.
   b. It is a selective phosphodiesterase III and V inhibitor; at lower dosages it is a venodilator and at higher dosages it is an arteriodilator.
   c. It has also a positive influence on general well being by reducing the amount of tumour necrosing factor and cytokines liberated.
   d. It replaces an ACE-inhibitor in the treatment of DCM.
   e. Its positive chronotropic action is probably dose-dependant.

4. **Which statement is false regarding ACE inhibitors:**
   a. They are vasodilators
   b. They have an anti-aldosterone effect
   c. They are positive inotropes
   d. They have renoprotective properties
   e. The tissue renin angiotensin system is only partially blocked by ACEI

5. **At present, taking the pathophysiology and the results of multiple double blinded controlled trials into consideration which of the following drugs should every animal in heart failure receive:**
   a. Pimobendan
   b. ACE inhibitor
   c. Digoxin
   d. Beta-blocker
   e. Frusemide

MERIAL