DILATED CARDIOMYOPATHY THERAPY

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Hannah Stephenson discusses approaches to treating this condition, which is common in large-breed animals such as Dobermanns, and different drug methodologies

Summary

Dilated cardiomyopathy (DCM) is a disease of the heart muscle characterised by dilation and impaired contractility of the left or both ventricles. It is a diagnosis of exclusion, which can only definitively be determined by echocardiography. Dogs with DCM eventually develop congestive heart failure, at which point treatment with “quadruple therapy”, consisting of furosemide, an ACE-inhibitor, pimobendan and spironolactone is indicated. Many dogs with DCM also present with arrhythmias, which frequently also require treatment. Anti-arrhythmic therapies can have unwanted side effects, and therefore definitive diagnosis of the arrhythmia by ECG is imperative, and frequent monitoring of the patient on anti-arrhythmic therapy is advisable. Unfortunately, little is known about treating the preclinical stages of DCM in dogs, but ACE-inhibitors have recently proven to slow progression of the disease in Dobermanns. Hopefully, the results of the PROTECT trial will provide information on the use of pimobendan in preclinical disease. Use of drugs in the preclinical stages might improve survival in a disease that currently carries a guarded prognosis.

Key words

large breeds, dogs, cardiomyopathy, echocardiography, dilation, therapy

DILATED cardiomyopathy (DCM) is a disease of the heart muscle characterised by dilation and impaired contractility of the left or both ventricles¹.
In humans, DCM can occur secondary to viral, autoimmune, alcoholic or toxic injury, but 30 to 50 per cent of cases are now thought to be inherited. In dogs, no definitive underlying causes have been identified, although hypothyroidism and taurine deficiency have been suggested to play a role. This, and the much smaller genetic “pool” of the canine population, means that the prevalence of inherited DCM in dogs is likely to be much higher.

Familial DCM has been shown to occur in a number of predisposed dog breeds, and research is ongoing to identify the underlying genetic mutations. Dilated cardiomyopathy is usually a disease of large and giant breed dogs, most notably the Dobermann, the Irish wolfhound, the Newfoundland and the great Dane.

Exceptions include the English cocker spaniel and a family of Portuguese water dogs in the US. DCM is also seen with increased frequency in the St Bernard, the Labrador retriever and the dogue de Bordeaux, among others. Boxers are also affected by a specific cardiomyopathy – arrhythmogenic right ventricular cardiomyopathy (or boxer cardiomyopathy), which usually presents with severe ventricular arrhythmias, causing syncope or sudden death. Occasionally, dogs present with left ventricular dilation and congestive heart failure.

Idiopathic DCM is a diagnosis of exclusion. Dilation and impaired systolic function of the left ventricle can occur secondary to a number of congenital and acquired heart diseases, such as patent ductus arteriosus or end-stage myxomatous degenerative valvular disease (MDVD). Additionally, similar echocardiographic findings can be seen secondary to prolonged tachyarrhythmias (tachycardiomyopathy). Therefore, it is important to ensure all other underlying causes have been excluded before a definitive diagnosis of idiopathic DCM is made. Confusingly, multiple conditions can occur in the same dog (such as DCM plus MDVD) and, therefore, the clinician must sometimes make a judgement as to whether the dilated cardiomyopathy is primary or secondary. For further details on diagnosing dilated cardiomyopathy, see the article Small Animal Dilated Cardiography in VT 41.26.

**Treatment**

- **Congestive heart failure**

Dilated cardiomyopathy results in reduced cardiac output. This stimulates activation of compensatory mechanisms, such as the renin-angiotensin aldosterone system (RAAS) and the sympathetic nervous system, which initially serve to improve cardiac output and maintain blood pressure.

However, ultimately, they have negative side effects, resulting in congestive or forward heart failure. In animals with congestive heart failure as a result of DCM, treatment is aimed at alleviating clinical signs, and attempting to improve the systolic function of the failing heart. The drugs and dosages commonly used in dogs are summarised in Table 1.
The treatment mainstay for congestive heart failure is diuresis, and the most commonly used drug is the loop diuretic furosemide. When used intravenously, furosemide is also a venodilator. Therefore, this route of administration can be useful in very dyspnoeic animals. Low doses (1mg/kg to 2mg/kg) of furosemide used more often (every one to two hours) can be very effective, without the excessive reduction in preload that occurs after high-dose boluses.

Renal function and electrolyte concentrations should be monitored regularly, particularly when high doses of furosemide are used, and following any change in dose.

Dogs prescribed diuretics should always be administered an angiotensin-converting enzyme (ACE) inhibitor, as the volumedepleting effects of the diuretic will further stimulate the RAAS. The RAAS acts to cause vasoconstriction, and sodium and water retention, in an attempt to maintain blood pressure. This is eventually detrimental, as excessive sodium and water retention promote the development of effusions, and vasoconstriction increases the afterload on the failing heart. ACE-inhibitor drugs should, therefore, always be prescribed to dogs with congestive heart failure. Benazepril, enalapril, imidapril and ramipril are all licensed in the UK. As ACE inhibitors are vasodilators, blood pressure should be normal and not low before these drugs are introduced.

Aldosterone and angiotensin-II also promote myocardial remodelling and myocardial fibrosis. ACE-inhibitors can reduce these adverse effects, but aldosterone-antagonist drugs have been used for the same effect. Spironolactone has been shown to reduce mortality in humans and to reduce the risk of cardiac-related death or euthanasia in dogs with congestive heart failure due to MDVD. It is suggested that this beneficial effect is not just due to its potassium-sparing diuretic effects, but also to its beneficial effects on cardiac remodelling. Presumably, these effects also apply to DCM. Therefore, spironolactone is used in the majority of patients with congestive heart failure in our clinic.

Pimobendan is a phosphodiesterase III inhibitor with calcium-sensitising properties, which is both a positive inotrope and a balanced vasodilator. The improved systolic function of the heart, in addition to the reduction in afterload, improves cardiac output. Unlike other positive inotropes, pimobendan does not increase myocardial oxygen demand and, therefore, is “safe” to use in congestive heart failure. Logic dictates that a positive inotrope should be beneficial in dogs with DCM, and this drug has been shown to prolong time to development of refractory pulmonary oedema or death in Dobermanns with DCM. The positive inotropic effects are superior to those of digoxin and, therefore, the latter drug should be reserved for antiarrhythmic therapy.

• Anti-arrhythmic therapy

None of the drugs used to control arrhythmias in dogs are licensed in this species. All anti-arrhythmic drugs have the potential to be pro-arrhythmic, and, therefore, the electrocardiograph (ECG) must be interpreted correctly prior to therapy being started. To avoid pro-arrhythmic side effects, anti-arrhythmic drugs (with the exception of beta blockers) should be stopped abruptly if
necessary, rather than tapering the dose.

• **Atrial fibrillation**

Atrial fibrillation in DCM occurs secondary to atrial stretch and, therefore, electrical conversion back to sinus rhythm is usually not attempted or possible. In humans, studies have shown no difference in survival between those treated with rate or rhythm control\(^\text{14, 15}\).

Two main drugs are used for rate control in dogs – diltiazem and digoxin. Diltiazem is a calcium channel blocker that slows conduction through the atioventricular node and is particularly useful in controlling supraventricular arrhythmias. Its mechanism of action, however, also makes it a negative inotrope. Although this would seem contraindicated in dogs with impaired systolic function, the control of heart rate in dogs with atrial fibrillation can significantly improve cardiac output; by increasing diastolic filling time and thereby contractility (Frank-Starling mechanism). In addition, rapid heart rates can themselves result in impaired contractility and tachycardiomyopathy\(^\text{15}\).

Digoxin is a vagomimetic agent that slows conduction through the atrioventricular (AV) node. It is also a weak positive inotrope and has, therefore, been used historically for this purpose in dogs with DCM. Digoxin has a narrow therapeutic index and toxicity is frequently seen, particularly in giant breeds, which seem to be more sensitive to its effects. This drug should be used cautiously and loading doses should not be used.

Serum levels should be measured five to seven days after starting treatment and doses up-titrated only if necessary. There is evidence from human medicine that digoxin’s beneficial vagomimetic effects can be achieved at serum levels lower than reference intervals currently published by laboratories. Therefore, I aim for a trough serum level of 0.5ng/ml to 0.9ng/ml. Dogs that have good rate control but have serum levels below laboratory reference intervals should not have their doses increased. Conversely, dogs with trough serum levels at the high end of reference intervals should, if possible, have their dose reduced. Signs of digitoxicity, such as inappetence, vomiting or diarrhoea, should prompt immediate withdrawal of the drug, possibly with the reintroduction of a lower dose. The dose should also be reduced in dogs with renal disease, hypokalaemia or cachexia.

Diltiazem has a very rapid onset of action (a number of hours after oral administration of the modified release preparation), while digoxin can take a number of days to be effective and reach a steady state. Diltiazem is, therefore, often more useful in very rapid heart rates where rapid control is beneficial. However, research suggests that both drugs in combination are more effective than either drug alone for reducing heart rate\(^\text{16}\).

• **Ventricular arrhythmias**
Unless ventricular tachycardia is documented on an ECG, it can be very difficult to assess the severity of ventricular arrhythmias on a short rhythm strip. Arrhythmias can be precipitated and/or worsened by circulating catecholamines. Therefore, an ECG in veterinary surgery may tell an inaccurate story.

Conversely, the most severe and complex arrhythmias may not occur while the ECG is being taken, and thus the need for medication might be underestimated. Fast ventricular tachycardia can progress to ventricular fibrillation and sudden death, so it is important to recognise these arrhythmias when they occur.

The best way to assess the severity of arrhythmias is to use a 24-hour ECG (Holter) monitor, and this is an important part of the work-up of predisposed breeds, such as Dobermanns. Guidelines exist for the normal numbers of VPCs expected in 24 hours in normal dogs (usually less than 20/24 hours) and when treatment should be initiated. As a rule of thumb, more than 1,000VPC/24 hours with complex arrhythmias (high numbers of couplets, triplets and runs), the presence of ventricular tachycardia or complex arrhythmias in a symptomatic patient, are indications that treatment should be initiated. However, little published evidence suggests that antiarrhythmic treatment reduces the likelihood of sudden death from ventricular arrhythmias.

In an emergency situation (persistent ventricular tachycardia), the class 1b drug, lidocaine, should be administered intravenously. Safe, oral, class 1b drugs, such as mexiletine, are now very difficult to obtain and other drugs are usually considered for long-term management. The most frequently used antiarrhythmic since the withdrawal of mexiletine from the human market, is sotalol, which has both class-III and class-II activity. It is less negatively inotropic than other beta-blocking drugs and is usually safe to administer to dogs with impaired systolic function. While beta-blocking drugs are considered a standard of care for humans with DCM, they seem to be poorly tolerated by dogs with congestive heart failure. These drugs are generally not used as antiarrhythmic, or otherwise, in dogs with DCM and congestive heart failure.

• Preclinical disease

It has been known for some time that administrating ACE-inhibitors to humans with impaired systolic function significantly reduces the incidence of heart failure and the rate of related hospitalisations, as compared with placebo (SOLVD\textsuperscript{17}).

While this has also been suggested to be the case in dogs, this was only recently published in a retrospective study in Dobermanns\textsuperscript{18}. In this study, administering benazepril to Dobermanns with occult DCM increased the median time to onset of clinical signs. The evidence from human and veterinary literature would suggest that administrating an ACE-inhibitor to dogs with occult DCM could be beneficial and prolong time to onset of congestive heart failure.

There is no evidence to suggest that other drugs are beneficial in treating occult stages of DCM. To
the author’s knowledge, beta blockers are rarely used and the benefit or otherwise of these drugs in occult DCM in dogs is unknown. The PROTECT study ([www.nedc.me.uk/mainsite/health/dcm_protect_project.html](http://www.nedc.me.uk/mainsite/health/dcm_protect_project.html)) has been investigating the benefit of using pimobendan in Dobermanns with preclinical DCM. The investigative phase of this placebo-controlled clinical trial is now finished.

**Prognosis**

Even with medical treatment, the prognosis for dogs with DCM and heart failure must be guarded. Generally, fewer than 40 per cent of dogs survive to one year following diagnosis[^19] ,[^20].

The presence of pulmonary oedema has been identified as a negative prognostic indicator[^21], and a higher stage of heart failure (usually determined using the International Small Animal Cardiac Health Council classification) has been suggested to correlate with reduced survival times[^22].

Other echocardiographic variables have also been associated with shorter survival times in dogs with and without congestive heart failure, as has the presence of VPCs on ECG[^19],[^21],[^22]. In the UK, the great Dane has a poorer prognosis[^21].

Early identification of occult DCM might allow initiation of ACE-inhibitor treatment early in the course of disease, which may delay progression to congestive heart failure or cardiac-related death. It remains to be seen if the same is true of pimobendan. Ultimately, identification of the genetic mutation(s) responsible for DCM in dogs will assist selective breeding programmes and, hopefully, reduce the incidence of this disease in the dog population.

**References**