CANINE DILATED CARDIOMYOPATHY:

FROM GENETICS TO CLINICAL DIAGNOSIS

Abstract

Introduction: Dilated cardiomyopathy (DCM) is common in mainly large or giant breeds of dogs, with prevalence of nearly 60% reported in the Dobermann. Given breed prevalence, a genetic basis to the disease has long been suspected, but the genetics is complex in most breeds, not a single gene disorder with Mendelian inheritance. Echocardiography is used to identify the DCM phenotype, although there may be equivocal echo findings especially when screening. It is important to exclude other causes of the DCM phenotype.

Objectives:

1. To discuss how to make the diagnosis of DCM, and to exclude other causes of the DCM phenotype.
2. To review the genetic basis of DCM in breeds where this is known.
3. To review the management of dogs with DCM.

Methods: DCM manifestations may vary according to breed. In the Dobermann, they may present with the classical DCM phenotype on echocardiography, but some may present with arrhythmias (arrhythmogenic cardiomyopathy). There are good guidelines for diagnosis of DCM in Dobermanns, based on echocardiography and Holter monitoring, but such data are sparse for other breeds. Screening can be fraught, since “equivocal” diagnoses are disliked by owners and breeders. Management of DCM mainly addresses the consequences, with congestive heart failure control, support of systolic dysfunction and antiarrhythmic therapy. Dogs with preclinical DCM are usually identified by prospective screening, and the PROTECT study showed that Pimobendan slows progression in Dobermanns (no evidence in other breeds).

Conclusions: DCM is common in certain breeds of dogs but may be clinically silent.

Keywords: DCM, Echocardiography, Holter monitoring, Genetics, Congestive heart failure.

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Introduction

Dilated cardiomyopathy (DCM) is the second most common acquired heart disease in dogs and in certain large or giant breeds, it is the most common. Prevalence may be very high in certain breeds; especially Dobermanns, with an estimated life-time prevalence of nearly 60% (identified by prospective screening) (Wess et al. 2010A).

Identifying clinical DCM is the “tip of the iceberg”. These are dogs presenting with clinical signs such as onset of congestive heart failure or syncopal episodes due to arrhythmias. Preclinical disease is a prolonged phase which may be detected by prospective screening, strongly recommended in certain breeds, especially Dobermanns. If these dogs are not recognised, they may acutely decompensate (e.g. during or following general anaesthesia or surgery).

The diagnosis of DCM is made based on echocardiography and / or 24 hour ambulatory ECG (Holter) monitoring – the latter in specific breeds like the Dobermann where ventricular arrhythmias may be the main manifestation of the disease and occur without or prior to any echocardiographic changes. Note: this is still considered to be “dilated cardiomyopathy” even though the left ventricle is not dilated (yet). A better term is “arrhythmogenic cardiomyopathy”. Note that in Boxer dogs (and some British Bulldogs), although they may present with a dilated cardiomyopathy phenotype (and congestive heart failure), based on the histological appearance of the myocardium, they are better defined as “arrhythmogenic right ventricular cardiomyopathy” or ARVC.

Note that, prior to diagnosis of DCM, active exclusion of other conditions which may result in a similar echocardiographic phenotype or a ventricular arrhythmia need to be actively excluded.

Prevalence of DCM

Where figures are reported, the following prevalences have been documented in certain breeds:

Breed	Estimated prevalence (%)	Reference
Dobermann	58.2	Wess et al. 2010A
Great Dane	35.6	Stephenson et al. 2012
Irish Wolfhound	24.2	Vollmar 2000
Deerhound	21.6	Dutton et al. 2022
Newfoundland	17.6	Dukes-McEwan 1999
Weimaraner	9.8	Filipejová et al. 2024

Genetics implicated in canine DCM

With the high prevalence in certain breeds, and especially certain families, DCM has long been considered to have a genetic basis to the condition.

However, while it was initially suspected to be a monogenic disorder, with Mendelian inheritance is certain breeds (most commonly thought to be an autosomal dominant trait), recent work indicates that even in a specific breed, different genetic causes have been reported. Most is known in Dobermanns, and in Dobermanns, the genetic causes may be different in the USA to UK / Europe. It is interesting to note that the clinical manifestation of DCM in a given breed is similar regardless of genetic aetiology.

The following genes (or loci) have been implicated in canine DCM:

Breed	Gene / Genetics	Published
Dober-manns	PDK4 TITIN Multigenic CFA 5 locus CFA5 – RNF207 +/- PRKAA2 RNF207 CFA 16	Meurs et al. (2012). *Hum Genet.* **131**(8):1319-1325. Meurs et al. (2019). *Hum Genet.* **138**(5):515-524. Simpson et al. (2015). *PeerJ.* 2015 **3**:e842. Mausberg et al (2011). *PLoS One* **6**(5):e20042. Niskanen et al (2023). *Genome Medicine* **15**;73 Dutton et al. 2025. Polenberg et al. 2024
Irish Wolf-hounds	Multiple loci (CFA 37 & 5 other suggestive)	Philipp et al. (2012). *PLoS One* **7**(6):e36691. Simpson et al. (2016). *Biomed Res Int.* 2016:6374082.
Great Danes & Newfound-lands	Suspected multigenic	Björnerfeldt et al. 2011. *Proceedings of the European Society of Human Genetics Meeting.* P.09.083 Amsterdam RAI, Amsterdam. May 28 – 31, 2011. p 286.
Standard Schnauzer (Giant Schnauzer)	RBM20	Dissertation, University of Missouri. Gilliam, D.H. & Johnson, G.S. (2016). https://mospace.umsystem.edu/xmlui/handle/10355/56525 Leach SB et al. (2022) *J Vet Cardiol.* **40**:119-125.
Boxer	Striatin (or not)	Meurs et al. 2010. *Hum Genet.* **128**(3):315-324. Meurs et al. 2013. *J Vet Intern Med.* **27**(6):1437-1440. Cattanach et al. 2015. *Vet Rec.* **176**(19):492.
Welsh Springer spaniel	R9H	Yost et al. 2019

Nova Scotia duck-tolling retriever	LMNA	Bannasch DL et al. 2023. *Sci Rep*. **13**(1):19077.
Portu-guese water dogs (juvenile form)	CFA 8	Werner et al. 2008. Genomics **92**; 517 - 521

It is likely that one or more genes confer susceptibility to DCM, and other factors (epigenetics, environment, nutrition etc.) may make it more likely to be penetrant. DCM likely represents a “final common pathway” of one or more of a variety of mechanistic pathways, including abnormalities in force generation or transmission, problems with energy production or utilisation, deranged metabolism, perturbations in nuclear or cytoskeletal integrity, altered calcium cycling or other ion channel issues.

Certainly, more needs to be discovered.

Manifestations of DCM

Although Boxers (ARVC) and Dobermanns appear to be different because of the predisposition to ventricular arrhythmias, other breeds do have ventricular arrhythmias (e.g. Great Danes). Echocardiographically, DCM appears remarkably similar in the different breeds. Some breeds (especially ARVC breeds) have more right heart involvement – including Irish Wolfhounds. All breeds with advanced disease but predominantly left heart involvement can also develop right sided congestive heart failure (biventricular failure).

Histopathology identifies two major forms of DCM – the attenuated wavy fibre form (more ubiquitous) and the fibrofatty infiltrative form (Tidholm & Jonsson 2005). Even within a breed, both forms are reported or a mixture of forms seen in the same individual (Aupperle et al. 2013). Presumably, the fibrofatty form is more likely to be a substrate for arrhythmias. The histopathology of ARVC shows dramatic fatty replacement of cardiomyocytes.

A list of breeds or breed types and their common manifestation is shown in the table. However, it should be noted that this may vary in different countries or continents.

Breeds presenting with classical DCM (echocardiographic) +/- congestive heart failure	**Breeds which may present with an arrhythmogenic cardiomyopathy / ventricular arrhythmias**
Dobermanns	Dobermanns (arrhythmias can precede the DCM phenotype).
<u>Giant or large breeds</u>: Great Danes St Bernards Newfoundlands Irish Wolfhounds Scottish Deerhounds Dogues de Bordeaux Old English Sheepdogs Golden retrievers Weimaraners	Boxer dogs with arrhythmogenic right ventricular cardiomyopathy (ARVC) - can also have a DCM phenotype.
<u>Spaniel breeds</u> American cocker spaniel English cocker spaniel - In both breeds, exclude taurine deficiency English Springer spaniel - need to exclude athletic heart phenotype	English Bulldogs may also have a form of ARVC (often with right sided congestive heart failure or a DCM phenotype).
Portuguese water dogs – a juvenile DCM	
Standard Schnauzers	

Echocardiographic diagnosis of DCM

Dilated cardiomyopathy (DCM) is readily diagnosed on echocardiography with criteria proposed by the European Society of Veterinary Cardiology DCM taskforce (Dukes-McEwan et al. 2003).

The characteristic features include:

1. Left ventricular dilatation
2. LV is rounded (increased sphericity)
3. LV is hypokinetic (reduced LV systolic function)
4. LV walls are relatively thin.

In dogs with clinical signs of DCM, the diagnosis is usually clear (after active exclusion of other cardiac disease which could also meet the criteria listed above). However, when screening dogs for preclinical, DCM, there is a continuum as the dog progresses from being normal to eventually meeting the criteria for DCM. Therefore, it is not unexpected that some dogs will be defined as being equivocal – serial screening is required (e.g. annually) to document whether they progress to develop DCM in the future.

When screening, echocardiographic reference ranges are required – ideally which are specific for that breed (Wess et al. 2017; Wess 2022). If breed specific reference ranges are not available, then body weight associated reference ranges can be compared with echocardiographic values obtained. Ideally, 2D assessments of left ventricular volumes should be used (Wess et al. 2010B), but M-mode reference values are also available based on body weight (Visser et al. 2019, Esser et al. 2020; Wess et al. 2021).

Arrhythmogenic cardiomyopathies

Atrial fibrillation is common in DCM and when it occurs in clinical disease, it is likely secondary to the atrial stretch, and it is typically a fast, irregular tachyarrhythmia. However, in some giant breeds (especially Irish Wolfhounds, it can occur without evident structural or functional cardiac disease on echocardiography, and then it may be at slow rate, similar to the dog's normal heart rate. However, it is still believed to be an early manifestation of DCM (Vollmar et al. 2019), rather than the atrial fibrillation resulting in a secondary cardiomyopathy (e.g. tachycardia induced cardiomyopathy or ectopy associated cardiomyopathy). Rate control is really important in order to reduce rate of progression of myocardial dysfunction (Pedro et al. 2023).

Ventricular arrhythmias are common in certain breeds of dogs with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy (e.g. Dobermann, Boxers, some great Danes, some Weimaraners etc.). In clinical cases, dogs may present with e.g. ventricular tachycardia, or having suffered a syncopal episode. The diagnosis is therefore made on ECG at presentation. However, prospective screening for arrhythmogenic cardiomyopathies requires ambulatory ECG recording (minimum 24 hours). Note that there may be considerable day to day variability in number of ventricular ectopic complexes / 24 hours (Spier & Meurs 2004), and so longer recordings (e.g. 4 days) may be superior (Gunasekaran et al. 2020).

In most dogs (e.g. Dobermanns), fewer than 50 ventricular premature complexes (VPCs) per 24 hours is considered normal. However, cut-offs for abnormal vary with breed and publication. In Dobermanns, >300 VPCs / 24 hours is considered abnormal (Wess et al. 2017). There is therefore an equivocal range of ventricular ectopy, which should prompt serial screening (repeat Holters).

Secondary cardiomyopathies

It should be noted that idiopathic DCM is a diagnosis of exclusion. Before making this diagnosis, it is important to exclude other congenital or acquired heart disease which may lead to this phenotype. Dogs receiving potentially cardiotoxic chemotherapy such as the anthracyclines, doxorubicin or epirubicin may develop DCM with cumulative doses. Myocarditis may also result in myocardial failure and a DCM phenotype, and aetiologies may be more common in certain countries (e.g. *Trypanosoma cruzi* in Southern USA). A recent concern has been the association of DCM with grain-free diets or other boutique diets with a high percentage of peas, potatoes or lentils or legumes as their carbohydrate course. A thorough diet history is therefore essential in dogs presenting with a DCM phenotype, since correcting the diet may lead to some reverse remodelling of the phenotype. This is more likely to be suspected in atypical breeds diagnosed with DCM, but it is especially important to check “typical” breeds, who may already have a genetic predisposition to developing DCM. Some but not all may be taurine deficient (more likely in Golden retrievers, cocker spaniels (English and American) and taurine supplementation alone may not correct this (or prevent it when on a grain free diet). The phenotype is often very advanced with a very rounded LV with relatively thin walls and very poor systolic function (Adin et al 2019).

In the presence of ventricular arrhythmias, the possibility of systemic disease resulting in the arrhythmias also needs to be considered. As well as blood work to look for systemic conditions, abdominal ultrasound also needs to be considered.

Management of dogs with DCM

Typically, dogs present with classical DCM with onset of congestive heart failure. However, it should be recognised that this is “tip of the iceberg” – and there can be a prolonged preclinical phase, over years.

Prospective screening (e.g. by echocardiography; possibly prompted by abnormal cardiac biomarker results (NT-proBNP and high sensitivity Troponin I; Dukes-McEwan et al. 2022) may identify preclinical DCM. Screening is recommended in breeds at high risk for DCM.

Staging of dogs with DCM has recently been proposed (Wess 2022):

Stage	Description
Stage A	Dogs at risk for developing DCM e.g. all Dobermanns, or those dogs known to have a genetic mutation increasing risk.
Stage B (mainly asymptomatic dogs)	Dogs with echocardiographic or electrical (arrhythmia) signs of DCM identified by screening. No evidence of congestive heart failure but may have syncopal episodes with arrhythmias.
• Stage B1	Electrical abnormalities (e.g. VPCs in Dobermanns or Boxers, AF in giant breeds).
• Stage B2	Left ventricular systolic dysfunction, usually resulting in left ventricular dilatation. The left atrium may or may not be dilated. Arrhythmias as in stage B1 may be present concurrently. Often called preclinical, subclinical or occult DCM.
Stage C	Echocardiographic evidence of DCM with present or previous signs of congestive heart failure (CHF) (overt DCM); may be stable on CHF treatment.
Stage D	End-stage DCM, with signs of CHF refractory to treatment; individualised optimisation of treatment required.

Clinical DCM (congestive heart failure; Stages C or D)

Radiographs are considered the method of choice to confirm the diagnosis of cardiogenic pulmonary oedema (left sided congestive heart failure). However, echocardiography may indicate B-lines ("wet-lung") and sometimes effusions (pleural and / or abdominal; usually with right sided congestive heart failure). In left sided congestive heart failure, there will be a dilated left atrium with increased left sided filling pressures. Management of clinical DCM has recently been reviewed (Crosland et al. 2024)

Treatment must include diuretics (furosemide or torasemide) and Pimobendan, which improves outcome in dogs with DCM (Luis Fuentes et al. 2002). Logically, since congestive heart failure and administration of diuretics activates the renin-angiotensin-aldosterone system (RAAS), ACE-inhibitors and spironolactone can be added to counteract this.

Treatment of significant arrhythmias (any of stages B, C, D).

The diagnosis of arrhythmias require an ECG (if arrhythmia present at time of examination) but better, 24 hour ambulatory ECG (Holter) monitoring.

Atrial fibrillation should be assessed for the ventricular response rate. It is important to apply rate control if this is excessively fast (aiming for <125 bpm/24 hours) on Holter evaluation – this improves prognosis (Pedro et al. 2023). In preclinical dogs with "lone AF", watchful monitoring can be applied, or an attempt at DC cardioversion (especially if known recent onset). When rate control his required, the combination of Diltiazem with Digoxin is usually superior to either drug alone. Although beta blockers can be

used for rate control, they should be avoided in dogs with congestive heart failure, or those with impaired LV systolic function, as they may not be tolerated.

Malignant ventricular arrhythmias
No drug is proven to reduce the risk of sudden death in dogs with ventricular arrhythmias. However, the Holter results can be improved with fewer ventricular premature complexes or less complexity of ventricular arrhythmias.

Sotalol is most commonly used, despite it being negatively inotropic, since it is usually well tolerated, and cheaper and more widely available in most countries than mexiletine.

Treatment of arrhythmias associated with dilated cardiomyopathy (whether or not there are any echo changes) have recently been reviewed (Davis et al. 2024).

Preclinical DCM (Stage B2)

The PROTECT study indicate that Pimobendan will delay progression of Dobermanns with DCM to onset of congestive heart failure or death (Summerfield et al. 2012). There is less robust evidence for ACE inhibitors as well (e.g. Benazepril) (O'Grady et al 2009). These findings are extrapolated to other breeds.

The positive inotropy and arteriodilator effect of pimobendan (improving forward stroke volume) can result in decrease of left ventricular or overall cardiac size.

Nutraceuticals
Taurine or L-carnitine is indicated in patients which are deficient (e.g. some Golden retrievers, American or English Cocker Spaniels, Newfoundlands, Boxers). In absence of proven deficiency, these are unlikely to cause any harm. Dogs with DCM and congestive heart failure can progress to develop cardiac cachexia, and fish-oil supplementation (high omega-3 with EPA and DHA) can be beneficial.

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