ADVANCES IN UNDERSTANDING OF CANINE DILATED CARDIOMYOPATHY

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SIMON SWIFT describes how, in many cases of dilated cardiomyopathy, genetic factors are increasingly thought to be responsible for the condition.

ELEVEN years ago, dilated cardiomyopathy (DCM) was described in veterinary textbooks as representing a “common end stage of myocardial failure, resulting from a wide variety of insults to the myocardium; the offending primary cause is no longer apparent at presentation” (Cobb, 1999).

While this may be true in some cases, there is a realisation that genetic factors are responsible in many cases. DCM is characterised by systolic dysfunction and dilation of either the left ventricle or both ventricles (Figure 1). It is a common cause of heart disease and failure (Figure 2) in large and giant-breed dogs, and certain breeds have specific phenotypes of the disease.

Boxers have a particular variant called arrhythmogenic right ventricular cardiomyopathy (ARVC), characterised by predominantly right-sided disease with a fibrofatty infiltration of the myocardium and severe ventricular tachyarrhythmias that are usually right ventricular in origin (Basso et al, 2004).

In human patients with idiopathic DCM, pedigree analysis suggests a familial component in 30 to 50 per cent, mostly with an autosomal dominant inheritance (Seidman et al, 2008). These patients are further divided into isolated DCM with and without conduction system disease, and DCM with extracardiac manifestations. Mutations have been discovered that affect a wide variety of myocyte
functions, including force generation and transmission, metabolism, calcium homoeostasis and transcription regulation. Isolated DCM without conduction system disease can be caused by mutations involving sarcomere proteins or calcium handling proteins.

Examples include actin, beta myosin heavy chain, titin and cardiac troponin C and T. Isolated DCM with conduction system disease is associated with mutations of the nuclear envelope protein, lamin A/C. Extracardiac manifestations of DCM often include skeletal myopathies such as mutations of the protein components of the dystrophin-associated complex, for example delta sarcoglycan. A naturally occurring recessive DCM phenotype has been identified in the Syrian hamster caused by a homozygous delta sarcoglycan mutation (Nigro et al, 1997). This was followed by research in canine patients for a genetic basis for dilated cardiomyopathy. Certain breeds have an increased tendency to develop DCM, and it is known to be present with increased frequency in certain lines.

Dobermann pinschers have a particularly aggressive form of the disease with mean survival times of 52 days after diagnosis (Petric et al, 2002). A genetic evaluation of an extended family of Dobermann pinschers suggested an autosomal dominant mode of inheritance (Meurs et al, 2007a). Great Dane DCM has a high incidence of sudden death and may be inherited as an x-linked recessive trait, although this was based on 17 cases and was not conclusively proved (Meurs, 2001a).

Portuguese water dogs, beloved of US presidents, have a juvenile form of the disease (Dambach et al, 1999; Sleeper et al, 2002). This suggests an inherited component. In the Dobermann breed, all the dogs in the United States descend from seven German dogs; three of which died of heart disease. Studies using oligonucleotide microchip arrays allow analysis of 23,851 genes. A total of 173 genes were found to be up regulated and 305 down regulated following analysis of two Dobermans with DCM (Oyama and Chittur, 2005).

**Cellular energy production**

Pathways involved in cellular energy production, signalling and communication, and cell structure were down regulated, whereas cellular defence and stress response pathways were up regulated.

This type of information can give clues as to which individual genes are likely to be involved in canine DCM and help target more detailed analysis of genes. Evaluation of genes and their associated proteins has been used to try to identify a mutation associated with canine DCM. In Dobermanns, actin, troponin C and T, lamin A/C, beta myosin heavy chain and protein 3 have all been examined and found to be normal (Meurs, 2001b; Meurs et al, 2008). Unfortunately, a study involving 372 microsatellite markers covering the 38 autosomal chromosomes was unsuccessful in identifying a suitable linkage site for the disease in Dobermanns (Meurs et al, 2007a). Samples from seven dogs with DCM were analysed for abnormalities of dystrophin and its associated proteins, delta sarcoglycan and beta dystroglycan. The results were normal (Spier et al, 2001). In boxers with ARVC, examination of the desmosomal genes did not identify an abnormality (Meurs et
However, a calstabin-2 deficiency was identified in boxers with ARVC (Oyama et al., 2008). Calstabin-2 is a protein associated with the ryanodine receptor (RyR2), the principal intracellular calcium release channel in the heart. Calstabin-2 stabilises RyR2 in a closed state, preventing diastolic calcium ion leak from the sarcoplasmic reticulum, which could trigger ventricular arrhythmias. A study identified calstabin-2 and triadin expression abnormalities in great Danes with DCM (Oyama et al., 2009). In this breed, calstabin-2 was up regulated and triadin, another regulatory component of RyR2, was down regulated.

At the American College of Veterinary Internal Medicine (ACVIM) forum in June, Meurs described the identification of a mutation of the striatin gene associated with boxer ARVC. The exact role of the striatin protein is currently uncertain. While a test for this mutation is available commercially (www.vetmed.wsu.edu/deptsVCGL/Boxer/test.aspx), it would appear that not all ARVC boxers in the UK are affected by this mutation. As a result, the test must be interpreted with caution.

However, there may be geographical differences, as North American boxers present with minimal chamber enlargement and hypokinesis and European boxers have congestive heart failure and more classic features of DCM (Dukes-McEwan et al., 2003).

One of the requirements of a breed scheme to eliminate a disease is early identification of that disease, so that affected dogs are not used for breeding. A genetic test would be ideal, but clearly not available in the majority of cases. There have been advances in two fields: tissue Doppler imaging (TDI) and Holter monitoring. TDI uses software to analyse the Doppler signal for high amplitude, low velocity signals that originate from the muscle (Figure 3).

Both colour and pulsed-wave modes are available, and technological advances have permitted speckle tracking where individual grey spots in the myocardium are tracked throughout the cardiac cycle.

Radial and longitudinal systolic velocity gradients of the left ventricular free wall are decreased and post-systolic shortening, a sign of left ventricular asynchrony, may be present (Chetboul et al., 2007).

In a colony of golden retrievers with muscular dystrophy caused by an x-linked dystrophin mutation, TDI was able to identify affected dogs at the preclinical stage of the disease, even when there was no notable ventricular dilatation or alteration in inotropism with conventional echocardiography (Chetboul et al., 2004a). Holter monitoring has become the gold standard for the early detection of ARVC in boxers.

Indeed, the use of an in-hospital ECG (Figure 4) was insensitive at detecting ventricular premature complexes (VPCs) and the lack of a VPC did not suggest the dog did not have a substantial
number of VPCs (Meurs, 2001a) More than 50 VPCs per 24 hours is thought to be abnormal in boxers (Meurs, 1999). The same figure is probably true for Dobermanns (Calvert et al, 2000). It should be remembered, when evaluating Holter recordings, the number can vary by up to 83 per cent on a day-to-day basis.

Several boxer breed clubs in the UK have obtained Holter monitors, and veterinary surgeons in the UK can refer to their nearest cardiologist for advice or use a loan service (such as www.holtermonitoring.co.uk). Heart rate variability has not proved useful.

However, signal-averaged ECGs can identify the presence of ventricular late potentials, which have been associated with sudden death in some, but not all, Dobermanns with occult DCM (Spier and Meurs, 2004). The Tei index is a Doppler-derived assessment of global myocardial performance, which has been applied to Newfoundland dogs with DCM (Lee et al, 2002). This is applicable to dogs with DCM as both systolic and diastolic abnormalities are present. Differences were found not only between normal and DCM dogs, but also between overt and occult DCM dogs. However, this has not proved useful in boxers with ARVC (Baumwart, 2008).

Diagnosis of early, subtle DCM has proved problematic. The European Society of Veterinary Cardiology has proposed guidelines for the diagnosis of DCM (Dukes-McEwan et al, 2003). A scoring system is used where a score of six points or more suggests the presence of disease.

Criteria are divided into major (score of three points) and minor (score of one point). Major criteria include increased left ventricular (LV) systolic or diastolic dimensions (Figure 5), increased sphericity and reduced LV fractional shortening or ejection fraction. Minor criteria are atrial fibrillation, increased E-point septal separation, increased systolic time intervals, an arrhythmia in a predisposed breed, equivocal M-mode value and atrial enlargement. The values obtained should be compared to breed-specific reference values, where available. The guidelines need prospective evaluation and may need further refinement before they are fully adopted.

Prognostic indicators in dogs with DCM would be useful to predict those dogs with poorer prognosis and may help guide treatment. Atrial fibrillation has been associated with premature death in Dobermanns. In other breeds, shorter survival times are associated with increased severity of heart failure, presence of ascites, low ejection fraction (less than 25 per cent), an end systolic volume index of more than 140ml/m² or a restrictive transmural filling (RTMF) pattern on Doppler echocardiography (Borgarelli et al, 2006). An RTMF pattern is associated with a tall, short E-wave and small A-wave, suggesting high filling pressure and a short E-wave deceleration time. A RTMF pattern was the most important negative prognostic indicator. Vasovagal tonus index, a time domain indicator of heart rate variability, is positively correlated to survival times in dogs with DCM in class two and three failure with a cut off of 7.59 (Pereira et al, 2008).

**Preclinical treatment**
Preclinical treatment of DCM has been controversial, as the only published data was from an ACVIM abstract (O’Grady et al, 1997). However, a retrospective study has been published of 91 Dobermanns with occult DCM, of which 57 received benazepril (O’Grady et al, 2009).

Time to onset of failure was 425 days for dogs receiving benazepril versus 339 days for those not receiving an ACE inhibitor, and this difference was statistically significant. Beta blockers have been advocated in the treatment of DCM in both the occult and overt phases (Tidholm, 2006). Survival figures were similar to the larger ACE inhibitor trials. Carvedilol, a third-generation non-selective beta blocker with vasodilatory and antioxidant properties, failed to improve echocardiographic or neurohormonal parameters over three months of treatment (Oyama et al, 2007).

Once overt failure develops, diuretics, ACE inhibitors and positive inotropes are commonly prescribed. Frusemide is indicated to control failure. The evidence for spironolactone, an aldosterone antagonist, is less convincing, although the prevention of the myocardial fibrosis, remodelling and neurohormonal dysregulation is promising. ACE inhibitors are accepted as standard therapy based on large-scale trials. Pimobendan, a calcium inodilator with positive inotropic and vasodilatory properties, is a logical addition to the treatment regime. It was supported by a small-scale trial involving Dobermanns with DCM (Luis Fuentes et al, 2002). However, a prospective randomised, placebo-controlled trial involving Dobermanns with DCM in heart failure was terminated early because of the significant improvement in time-to-treatment failure of pimobendan-treated dogs (140 days) compared to placebo dogs (14 days; O’Grady et al, 2008).

Arrhythmias require treatment to reduce clinical signs or to prolong life. While digoxin has traditionally been used to slow the heart rate of dogs in atrial fibrillation, the addition of diltiazem has been shown to provide better rate control than digoxin alone, with the rate decreasing from a median of 164bpm to 126bpm (Gelzer et al, 2009). The use of anti-arrhythmics to improve survival times has been suggested in a study in Dobermanns (Calvert and Brown, 2004). Perhaps more interestingly, it has been shown that use of omega-3 fatty acids in boxers with ARVC can reduce the frequency of ventricular arrhythmias (Smithet al, 2007).

References

Figure 1. Right parasternal long axis echocardiogram of a Dobermann with dilated cardiomyopathy, showing rounded dilated left ventricle with thin walls.
Figure 2. Lateral chest radiograph of a Dobermann with congestive heart failure and pulmonary oedema secondary to dilated cardiomyopathy. Note cardiomegaly and perihilar distribution.
Figure 3. TDI image from the interventricular septum in a dog showing E, A and S waves.
Figure 4. ECG from a boxer with ARVC showing ventricular bigeminy. The VPCs are positive – suggesting right ventricular origin.
Figure 5. M-mode obtained from the right parasternal short axis view at the level of the chordae tendineae. The left ventricular lumen is dilated and the free wall virtually immobile.