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Programme VCS MEETING
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Speakers:

Gerhard Wess DVM Dr. med. vet. Dr. habil. PhD Priv.-Doz. Dipl ECVIM-CA (Cardiology, Internal Medicine) Dipl ACVIM (Cardiology)

Gerhard Wess received his D.V.M. from the Ludwig Maximilians University in Munich, Germany. He completed an internship at the Clinic of Small Animal Medicine in Zurich, Switzerland, and subsequently a residency in Internal Medicine at the Clinic of Small Animal Medicine in Zurich (ECVIM). He also completed his doctoral thesis in Zurich during this time. During his residency he also spent one year at the veterinary teaching hospital at the University of Georgia, USA. Subsequently Gerhard completed a residency in Cardiology at UC Davis, California, USA with his mentors Bill Thomas and Mark Kittleson. Since 2003 Gerhard is the head of the cardiology department at the Clinic of Small Animal Medicine at the LMU University Munich, Germany and has built up a cardiology team consisting of up to 12 persons (doctoral students/residents). His residency program is recognized by both the ECVIM and ACVIM.

His clinical and research interests include the diagnosis and medical management of cardiac disease and failure. He has a particular interest in cardiomyopathies in dogs and cats, including genetic research, basic research and clinical trials to evaluate new echocardiographic methods, biomarkers, Holter-ECGs among others as well prospective drug trials. Gerhard is the course Master of the ESAVS cardiology modules (I-V) and contributed to the veterinary literature with a vast number of articles, abstracts and book chapters.

Virginia Luis Fuentes MA VetMB PhD CertVR DVC MRCVS DipACVIM DipECVIM MRCVS

Virginia Luis Fuentes graduated from Cambridge and spent 5 years in small animal practice before returning to academia. She has worked as a cardiologist at the University of Edinburgh, University of Missouri-Columbia, the Ohio State University, and since 2004, the Royal Veterinary College (London, UK), where she is a Professor of Veterinary Cardiology. She is a Diplomate of the American and European Colleges of Veterinary Internal Medicine, and is Chair of the ECVIM Cardiology Specialty.

Antonis Pantazis

Dr Antonis Pantazis has joined the Inherited Cardiovascular Disease Unit at The Heart Hospital in 2004, immediately after completing his training in Cardiology. He had had an early interest in Cardiomyopathies and worked in the field during his training. As a Consultant Cardiologist, he is leading a dedicated ARVC clinic. He also has an additional interest in advanced non-invasive Cardiac Imaging and management of left ventricular outflow tract obstruction in Hypertrophic Cardiomyopathy. Beyond his clinical commitments, he is active in research and training of medical students and young doctors. He is an Honorary Clinical Senior Lecturer at UCL. He is a member of the nucleus of the Myocardial and Pericardial Disease Working of the European Society of Cardiology.
Paul Wotton BVSc PhD DVC MRCVS

Paul graduated from Bristol University in 1975, followed by a short spell in practice then a year as a House Physician. Subsequently, 2.5yrs clinical work and research at Bristol lead to a PhD in small animal electrocardiology. After 4yrs teaching small animal and equine cardio-pulmonary medicine at the RVC, he returned to Bristol in 1983 as a Lecturer in Small Animal Medicine, with particular interests in cardiothoracic medicine and diagnostic imaging, and research interests in cardiomyopathy (extracellular matrix changes in DCM), achieving the RCVS Diploma in Veterinary Cardiology in 1996. In 1998 he moved to Glasgow Veterinary School as a Senior Lecturer in Cardio-Pulmonary Medicine. He worked at Davies Veterinary Specialists, Hertfordshire, from 2001-2007 before returning to Glasgow as a Senior University Clinician (from 2012 an Honorary Clinical Fellow) in Veterinary Cardiology.

Nuala Summerfield BSc BVMS DipACVIM DipECVIM-CA(Cardiology)

After graduating from the University of Edinburgh Veterinary School, Nuala undertook a residency in Cardiology at the University of Pennsylvania, USA. In 2002 she obtained her ACVIM Diploma in Veterinary Cardiology. After returning to UK, Nuala was awarded RCVS specialist status in Cardiology in 2006 and became recognised as a European Specialist in Cardiology in 2010. Nuala has lectured both nationally and internationally and published widely in the field. She currently works part time as a cardiologist in specialty referral practice in UK and at the University of Zurich veterinary school, Switzerland. Her areas of particular interest are canine dilated cardiomyopathy, heart failure and cardiac arrhythmias.

Tom Lewis BSc MDip PhD

Tom gained his PhD investigating multiple aspects of quantitative genetics (including genotype by environment interactions, heterosis and recombination loss effects, and modelling inherited and non-inherited components of traits) at the Roslin Institute and Nottingham University. He joined the Animal Health Trust in 2008, where his research focusing on genetic analysis of complex inherited disease and population structure in pedigree dog breeds resulted in multiple publications, several conference presentations and many talks to breed clubs. He was also heavily involved in implementing the Kennel Club’s ‘Mate Select’ web tool. In 2014 he joined the Kennel Club to provide ‘in-house’ genetics expertise.

Dave Dickson BVetMed CertAVP(VC) MRCVS

Dave is a member of HeartVets and holds the RVCS Certificate in Advanced Veterinary Practice (Cardiology). Despite growing up in “God’s-own county” (Yorkshire), living for a while in “Godzone country” (New Zealand) and residing in “God’s-own country” (Wales), he remains agnostic. He is currently working towards his RCVS Diploma in Veterinary Cardiology and is undertaking research into echocardiographic assessment of canine myocardial function. He believes he has recently discovered the cure for curiosity.
Introduction

DCM is an important cause of cardiac morbidity and mortality in dogs and is the most commonly acquired cardiac disorder in medium sized, large and giant breed dogs.\textsuperscript{1,2} In most cases DCM is a genetic disease, even if the disease has a slow onset and is usually detected later in live, in middle-aged or older dogs. DCM is the most common cause of congestive heart failure (CHF) and sudden cardiac death in mid-size and large breed dogs. The natural progression of DCM can be described by 3 distinct stages.\textsuperscript{1,3-6} Stage I is characterized by a morphologically and electrically normal heart and no evidence of clinical signs of heart disease. Stage II is characterized by evidence of morphologic or electrical derangement in the absence of clinical signs of heart disease. This stage has also been called “the occult stage” of DCM, or “silent disease stage”. The term “occult” refers to the owner’s perspective. That is, from the owner’s point of view, the dog appears normal despite evidence of abnormality on cardiac examination. The morphologic abnormality consists of left ventricular (LV) enlargement in systole, diastole, or both. The electrical abnormality consists of the occurrence of ventricular premature contractions (VPCs). These abnormalities, morphologic or electrical, may coexist or be of predominantly one form at any time during the occult stage.\textsuperscript{1,7-10} Stage III is characterized by the presence of clinical signs of heart failure and is referred to as the overt stage of DCM. Whereas the first and second stage can persist for years, stage III has often a comparatively short duration of several months, after the development of CHF.\textsuperscript{11}

Detection of early stages of the disease is important for each specific dog as well as for all dogs of a particular breed, because of the desire to perpetuate breeding programs that result in healthy dogs. Whereas detecting the clinical stage of the disease, where the dogs
develop symptoms of left or right heart failure, consisting of pulmonary edema or ascites and pleural effusion, respectively, is comparatively easy, this is only the tip of an iceberg, as the recognition of the occult phase of the disease is much more challenging.

For breeding purposes as well as for the initiation of drugs in order to delay the progression of the disease, it is mandatory to detect and identify the early stages of the disease. In order to raise the awareness that a specific dog might be in the occult phase of the disease, it is necessary to know the prevalence of DCM and possible early clinical signs of specific dog breeds in the occult phase of DCM.

Dobermans Pinschers are one of the most commonly affected breeds, and DCM in this breed is an inherited, slowly progressive primary myocardial disease.\textsuperscript{1,12} The occult stage of the disease is characterized by evidence of morphologic or electrical derangement in the absence of clinical signs of heart disease.\textsuperscript{1} The morphologic abnormality consists of left ventricular (LV) enlargement in systole and later in diastole. Ventricular premature contractions (VPCs) are a common finding in the occult phase of DCM in Doberman Pinschers.\textsuperscript{12} Sudden death, caused by ventricular tachycardia-fibrillation, occurs during the occult phase in at least 25 to 30\% of affected dogs.\textsuperscript{7} These abnormalities, morphologic or electrical, can coexist or can be of predominantly one form at any time during this occult stage.\textsuperscript{1,7}

Existing prevalence information’s on cardiomyopathy in Doberman Pinschers is from dogs in the US or Canada where prevalence ranges between 45 and 63 \%.\textsuperscript{13} A recent study from Europe showed a similar prevalence with 58 \% of the dogs being affected.\textsuperscript{14} This European study showed that 37 \% of the dogs had only VPCs without echocardiographic changes and that arrhythmias often were the first abnormality detected. Only a few dogs (13 \%) presented with only echocardiographic changes and no arrhythmias on Holter examination. Another interesting finding was that although there was no overall difference in the occurrence of cardiomyopathy between male and female dogs, there was a difference between sex concerning disease manifestation.\textsuperscript{14} Female dogs had significantly more VPCs without echocardiographic changes than male dogs and this difference became more apparent with increasing age. On the other hand, male dogs developed earlier echocardiographic changes than did female dogs. Some older studies concerning Doberman Pinscher cardiomyopathy found a higher prevalence of the disease in male dogs. However, the prevalence study from Europe found an equal sex distribution, which supports the
suspected autosomal dominant mode of inheritance. The different findings concerning the sex distribution may be explained by the results of the study that showed an equal sex distribution but different disease progression between male and female dogs. Female dogs seem to experience a more slowly progressive disease with VPCs as the only abnormality found even in the older age groups. Male dogs, on the contrary, showed echocardiographic changes earlier than did female dogs. These changes are easier to detect because no 24-hour-ambulatory-ECG (Holter) examination is necessary, and male dogs therefore are also more likely to develop CHF at an earlier age than female dogs and also die earlier from their disease.

**Recommendations by the author concerning screening for DCM in Doberman Pinschers**

The average age of detection of occult DCM is between 5-7 years, but some dogs are affected as young as 2 years of age. Therefore, screening for occult DCM should be started in Dobermans at two years of age and include Holter monitoring and echocardiography. Given the disease can develop over time in combination with the known rate of progression, screening should ideally be repeated on a yearly basis. In high-risk breeds, yearly screening over the life of the dog is recommended but can be cost prohibitive and requires a devoted owner.

Early detection of occult DCM can facilitate timely removal of affected dogs from active breeding programs and early treatment for all dogs leading an increase in symptom free survival. Removal of affected dogs from breeding programs should over time reduce the prevalence of DCM in Dobermans.

**Screening Age:** screening should be started at 2 - 4 years of age. An isolated screen is not sufficient to rule out DCM in the future, because the disease may develop with increasing age. Yearly screening should be performed ideally in both, male and female dogs, but if for financial reasons this is not possible, at least male Doberman Pinschers should be screened yearly due to their higher impact on the dog population and female dogs every two years.

**Screening Tests:** Screening should ideally be started at 2 years of age in both males and females.

**Screening Frequency:** A one-time screening is not sufficient as in many dogs the disease can only be detected with increasing age. Yearly screening should be performed ideally in both,
male and female dogs. However, given male dogs that are being used for breeding have a greater potential to pass on the disease if they are affected and not diagnosed emphasis should be on annual screening in male dogs that are being used for breeding. Female dogs, pets and non-breeding dogs could be screened once every 2 years if budgetary restrictions prevent annual screening.

**Holter Criteria:** < 50 single VPCs/24-hrs is considered to be normal in Dobermans. Some dogs will have VPCs in a range between 50 – 300 VPCs/24-hrs and sometimes at the next Holter examination they will have < 50 VPCs. These dogs remain a challenge. A recent study evaluated the best cut-off values for number of VPCs on Holter recordings in Dobermans and concluded that dogs with two Holter recordings within one year showing between 50-300 VPCs/24-hrs is diagnostic of having DCM. Dogs with a single count > 300 VPCs/24-hours is also diagnostic of occult DCM in Doberman Pinschers (Gerathy and Wess, 2013) regardless of the echocardiographic findings. Complexity should also be considered as diagnostic criterion, as couplets, triplets or single short runs of VPCs with a fast rate (>260/min measured from the R-R interval) are potentially dangerous and are less likely caused by systemic diseases.

Note: the Holter reading must be good quality and an accurate analysis verified by a cardiologist is mandatory, as automatic analysis by a Holter software is not accurate and manual adjustments are always necessary. Systemic diseases that could potentially cause VPCs must be excluded.

**Echocardiographic Criteria:**

In general, the accuracy of the echocardiographic results will depend on the quality of the examination. Basic guidelines should be followed including all measurements being made in triplicate.

The Simpson method of disc (SMOD) is more sensitive than M-Mode to detect early echocardiographic changes in Doberman Pinschers. SMOD should be measured in the right parasternal long axis view, with the aorta not visible, and in the left apical window (aorta also closed). EDV (End Diastolic Volume) frame is selected at the onset of QRS-complex at the time of mitral valve closure and ESV (End Systolic Volume) frame is chosen to the last frame before mitral valve opening at the end of the T wave, where the volume is smallest.
Cut-off values that indicate the presence of occult DCM based on echo (gold standard):

EDV/BSA: > 95ml/m²

ESV/BSA: > 55 ml/m²

M-Mode variables:

As M-Mode is still commonly measured, the authors recommend to use the following reference values if SMOD is not available. However, if M-Mode is normal, but SMOD enlarged, the authors recommend to trust the SMOD values, as they are more sensitive than M-Mode.

M-Mode Wess¹⁸:

LVIDd (male any weight) > 48 mm

LVIDd (female any weight) > 46 mm

LVIDs (male and female any weight) > 36 mm

Or:

M-Mode O’Grady¹⁶:

LVIDd was >0.1749 x (kg) + 40.3 mm or

LVIDs was > 0.1402 x (kg) + 26.7 mm

EPSS > 6.5 mm¹⁹

Anxillary tests, currently not recommended for screening purposes:

The following tests are currently not recommended for screening purposes, but may have some utility when ideally tests are not available or financially untenable on an annual basis:

In-house ECG

Ventricular premature contractions (VPCs) are common in the occult stage of cardiomyopathy in Doberman Pinschers. Electrocardiography (ECG) is widely available, whereas the gold standard to detect arrhythmias, the 24-hour ambulatory ECG (Holter), is more expensive, time-consuming and often not readily available. A recent study compared
911 ECG-Holter examination pairs to evaluate the value of a 5-minute ECG. The results were, that a 5-minutes ECG is a rather insensitive method to detect arrhythmias in Doberman Pinschers. However, the presence of at least 1 VPC in a 5-minutes ECG is a strong indication for further workup of the dog, as specificity (96.7 %) and positive predictive value (86.8 %) are high to predict occult cardiomyopathy.

**Biomarker**

Screening for occult disease stages is one of the most promising areas of blood sample-based biomarker research. In one study including 328 Doberman Pinschers, plasma NT-proBNP concentration was significantly higher in Doberman Pinchers with DCM, including those with occult DCM diagnosed through left ventricular systolic dysfunction or both left ventricular systolic dysfunction and arrhythmias, than in healthy dogs. The NT-proBNP assay was not clinically useful to detect disease in those dogs solely with ventricular arrhythmias. NT-proBNP values > 500 pmol/L can predict echocardiographic changes. In a second study, the combined use of an NT-proBNP cutoff value > 457 pmol/L and a Holter recording led to detection of ODCM with a sensitivity of 94.5%, specificity of 87.8%, and overall accuracy of 91.0%. Similar to the aforementioned study, NT-proBNP concentration was most accurate for detection of occult DCM when Doberman Pinchers had echocardiographic changes, but had poor accuracy for identification of dogs that only had ventricular arrhythmias. Both of these studies were performed without use of the protease inhibitor tubes for sample collection, and ideally, these studies should be repeated with the most current recommended collection and handling methods. Despite its reported usefulness, the NT-proBNP assay does not replace recommended diagnostic procedures such as echocardiographic examination wherein the sensitivity and specificity of detecting left ventricular dysfunction can be as high as 97%.

A recent study showed that cTnI was significantly elevated in Doberman Pinschers with cardiomyopathy. Dogs in the more advanced stages of the disease had the highest cTnI levels. cTnI was not only elevated in Doberman Pinschers with echocardiographic changes, but also in dogs that had only VPCs. This study was also able to show, that cTnI was elevated in a very early stage of the disease ("last normal group"). Dogs in this stage were classified as “normal” according to echocardiographic and Holter examinations - but cardiomyopathy was diagnosed within 1.5 years. Dogs in the “last normal” group had significantly higher cTnI values compared to control dogs. A cut-off value of >0.22 ng/ml
had a sensitivity of 79.5 % and a specificity of 84.4 % to detect all forms of cardiomyopathy. cTnI is therefore a valuable additional diagnostic test to screen for cardiomyopathy in Doberman Pinschers, but it should not replace conventional methods such as echocardiography and Holter examination.

**Recommendations (personal opinion) for less ideal situations:**

When Holter and/or Echocardiography are not available, or an owner wants first to have other tests being performed, in order to be more convinced that further examinations (Holter/Echocardiography) are necessary a combination of the following tests could be performed. However, it should be mentioned that these tests are not validated as sole screening tests and that they do not represent the ideal screening tests:

**Clinical examination:**

Suspicious is a systolic murmur over the left apex, a gallop rhythm on auscultation, a weak pulse quality or an arrhythmia or pulse deficit

**Biomarker:**

NT-proBNP result > 500 pmol/l

cTNI > 0.22

**ECG:** 1 VPC (or more) or atrial fibrillation is considered abnormal

**If any of the above tests are abnormal, a further work-up including Holter examination and echocardiography is strongly recommended**

Genetic tests that are available in Doberman Pinschers:

PDK4 might be useful in the US, but currently not in Europe, as one study showed no association between PDK4 and DCM in a European study.
References:

Hypertrophic cardiomyopathy (HCM) is very common in both pedigree and non-pedigree cats, and is thought to be familial in many cats. A demand has arisen amongst pedigree cat breeders for HCM screening in breeding cats, with the hope that identifying affected cats will allow selective breeding to reduce the prevalence of HCM in affected breeds. As is common with inherited heart disease in small animals, our ability to meet this demand is confounded by a number of complicating factors.

Defining HCM
The traditional human definition of HCM is ‘hypertrophy of a non-dilated left ventricle in the absence of abnormal loading conditions capable of producing the magnitude of wall thickening evident’. A similar definition is used in cats, although the left ventricle can become dilated with advanced HCM in both species. HCM has a wide phenotypic spectrum, so hypertrophy may be mild/severe, focal/diffuse, and accompanied or not by abnormalities of the papillary muscles or mitral leaflets. For severe cases, provided alternative causes of hypertrophy are excluded (hypertension, hyperthyroidism, acromegaly), the diagnosis is straightforward. Borderline cases can be extremely challenging to differentiate from normal. A similar spectrum of severity exists on a histopathological level, although HCM is typically recognised by the presence of myofibre disarray, particularly if combined with interstitial fibrosis and medial hypertrophy of small coronary arteries.

Population screening for HCM in people has not generally been undertaken, as increased LV wall thickness can be associated with athleticism (false positives) and LV wall thickness can be normal even in individuals with a known pathogenic HCM mutation (false negatives).
Instead, the most common situation is for relatives of people with newly diagnosed HCM to be screened. As genomic knowledge of human HCM advances, genetic screening for known sarcomeric mutations has become standard practice. To date, over 1,400 human HCM mutations have been identified, in predominantly sarcomeric genes. Nevertheless, no mutation is identified in up to 40% of human HCM patients, even though the disease may still be familial. Whether there are non-genetic causes of HCM in people is not known. Only two mutations have been identified in feline HCM (in Maine coons and Ragdolls), both in the myosin binding protein C gene (MYBPC3). Nevertheless, there are reports of familial HCM in both pedigree and non-pedigree cats.

In people, a left ventricular (LV) wall thickness of ≥15mm is used to define LV hypertrophy. In cats, there is less agreement on which (essentially arbitrary) cut-off value is used. The degree of accuracy required for diagnosing HCM in cats is much greater than in human HCM, as measurement differences of 0.5mm can make the difference between a judgement of ‘normal’ and ‘affected’. While image resolution and frame rates have improved, there has been little standardization of image acquisition or measurement technique.

**Measurement of LV wall thickness**

Two-dimensional echocardiography allows for greater sampling of wall thickness than M-mode, and there is less risk of inadvertently including false tendons, but M-mode is still commonly used in screening protocols. There is no consensus in whether ‘leading edge to leading edge’, ‘leading edge to trailing edge’ or ‘trailing edge to leading edge’ should be used when measuring 2D images of the septum (figure 1).

**Figure 1**

Leading edge to trailing edge  Leading edge to leading edge  Trailing edge to leading edge
There is no consensus on the upper limit of normal for LV thickness. There is general agreement that 6 mm or greater is abnormally thick in the absence of preload depletion, but some cardiologists believe 5.5mm is abnormal and have suggested 5mm should be the upper limit for cats weighing <6kg. There may be differences between breeds, and wall thickness is also affected by body weight. Subjective impressions are permitted in some screening schemes (such as the PawPeds scheme). Cats with borderline measurements are usually classed as "equivocal".

Qualitative findings suggestive of HCM include dynamic LV outflow tract obstruction (DLVOTO), which is present in many cats with preclinical HCM. When DLVOTO is present with increased LV wall thickness, a diagnosis of HCM is strongly supported. However, some cats demonstrate systolic anterior motion of the mitral valve in the absence of LV hypertrophy, and it is not clear whether these cats are also part of the HCM spectrum, whether they have a congenital. There is controversy as to whether SAM can be a normal finding, is associated with congenital malformations, or whether SAM is an indicator of HCM even in the absence of LV hypertrophy. Papillary muscle hypertrophy is also associated with HCM, and may be the only indicator of HCM in some cats. Abnormal papillary muscle position and morphology have been linked to outflow tract obstruction in human HCM. Elongated anterior mitral leaflets appear to be common in both people and cats with HCM.

Cardiac biomarkers
NT-proBNP may have some role in stratifying disease severity in asymptomatic cats, but it may not be sufficiently sensitive as a test for identifying subtle HCM in breeding cats. Troponin-I is even less likely to be useful as a screening tool.

Genetic testing
Breeders of Maine coon and Ragdoll cats have the option of commercial genetic testing when making breeding decisions. Two specific mutations have been identified in the MYBPC3 gene: the A31P mutation in Maine coon cats, and the R820W mutation in Ragdoll cats. HCM in Maine Coon cats has also been associated with another single nucleotide polymorphism (SNP) (A74T) of the MYBPC3 gene. The A31P mutation is relatively common in Maine Coon cats, with heterozygous cats at lower risk of developing an HCM phenotype.
than homozygous cats.\textsuperscript{16} A similar pattern of disease expression in homozygous cats has been described in Ragdolls with the R820W mutation.\textsuperscript{17} It is evident that not all cats testing positive for these mutations will be obviously affected with HCM, but they may still produce affected offspring even though the mode of inheritance is considered autosomal dominant. Sarcomeric mutations have not been identified in other breeds of cat with HCM, so echocardiography remains the principal method used in screening for HCM.
References:


Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder characterized by disruption of the myocytic architecture resulting in electrical instability and increased risk for life-threatening ventricular arrhythmias in some patients (1). The disease is pathologically characterized by a fibrofatty replacement of myocytes predominantly in the right ventricle (2).

Human patients usually present with symptoms such as palpitations, syncope, atypical chest pain, dyspnea and more rarely right ventricular failure (3). Most commonly palpitations or syncope are manifestations of ventricular arrhythmias, usually sustained or nonsustained ventricular tachycardia (VT) (4,5). Sudden cardiac death may be the first presenting symptom (4).

In humans, we base the diagnosis on diagnostic criteria, which were defined by the European Society of Cardiology Task Force in 1994 (6) and revised in 2010 (7). The current criteria include structural changes indentified by cardiac MRI, echocardiography or right ventricular (RV) angiography, characteristic ECG-changes, documentation of arrhythmias, histopathology, and family history. In all the aforementioned categories major and minor criteria have been defined (7).

Imaging with echocardiography and MRI is used to analyse structural changes in both ventricles. Although changes may be observed in both ventricles, the diagnostic criteria include only right ventricular changes. If either RV size is increased or function reduced in combination with RV wall motion abnormality, it is considered as a major criterion (7). A diagnosis based on fatty infiltrates in MRI has been found to be misleading and has therefore not been included in the task force criteria (8,9).

Histological analysis of specimens obtained by right ventricular endomyocardial biopsy and transmural tissue acquired at necropsy are utilized for evidence of fibrous or fatty replacement of myocytes (7).
Repolarization abnormalities are early and sensitive markers of disease expression (7). Since T-wave inversion is very uncommon in healthy individuals beyond the age of 14 years their presence is suggestive of ARVC (10).

In the original diagnostic criteria from 1994 ECG Epsilon waves were considered a major criterion (6) and late potentials were considered a minor criterion (6). Terminal QRS activation duration prolongation, reflecting RV activation delay, has been shown to be a specific and sensitive early sign of ARVC (11,12).

Ventricular ectopic beats appear more frequent with increasing age in normal individuals (13). Higher volume than 200 ventricular premature beats in 24 hours in a subject of <50 years may suggest an underlying myocardial disease (7). The current task force criteria apply a cut-off of >500/24h as a minor criterion (7). In order to discriminate idiopathic VT originating from the RVOT from ARVC, both of which typically have a LBBB-morphology, the axis has shown to be diagnostically valuable, with a superior axis appearing only in patients with ARVC, but inferior axis being possible in both ARVC and idiopathic RVOT-VT (11).

Identification of disease-causing genes has contributed to the awareness of a broader variability in the phenotype within families, which also includes individuals with predominantly LV disease characterised by inferolateral T-wave changes, ventricular ectopy or tachycardia with right bundle-branch block morphology and epicardial or midmyocardial late enhancement in the MRI (14–18). A positive diagnosis in a family member increases the probability of the disease in an individual with suspected ARVC from 1:1000-5000 to 1:2. Therefore, confirmed disease in a first degree relative has been included as a major criterion (7,19).

Changes of ECG features during follow up in comparison to baseline examinations have been noted as a possible precursor of structural changes (20,21).

Risk stratification remains imperfect. Patients with syncope appear to have the poorest prognosis (22,23). Non-sustained VT has been shown as a predictor for ICD discharges, but not for potentially life threatening arrhythmias such as VF (23). No other clear predictor for arrhythmias has been found to date.
The disease in humans is comparable to the disease in Boxer dogs. Similarly, Boxer dogs present with syncope, breathlessness and exercise intolerance (24,25). Structurally, the disease is characterised by fibrofatty replacement of myocardiocytes, moderate RV chamber dilatation and more rarely infundibular aneurysms (26,27). There is marked arrhythmia typically in the sense of large numbers of single VPCs, but also increased complexity such as couplets, triplets or VT (24,26,28). Boxer dogs with ARVC are at risk for sudden cardiac death (29).

In conclusion, ARVC has a diverse phenotype. Arrhythmic manifestations may not always be consistent with the structural changes. The disease may lead to sudden cardiac death and risk stratification remains complex.

### Diagnostic criteria for ARVC in humans

<table>
<thead>
<tr>
<th>Global or regional dysfunction or structural alterations:</th>
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<tbody>
<tr>
<td><strong>MAJOR:</strong></td>
</tr>
<tr>
<td><strong>By 2D echo:</strong></td>
</tr>
<tr>
<td>- Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole):</td>
</tr>
<tr>
<td>— PLAX RVOT 32 mm (corrected for body size [PLAX/BSA] 19 mm/m²)</td>
</tr>
<tr>
<td>— PSAX RVOT 36 mm (corrected for body size [PSAX/BSA] 21 mm/m²)</td>
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<tr>
<td>— or fractional area change 33%</td>
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<tr>
<td><strong>By MRI:</strong></td>
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<tr>
<td>- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:</td>
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<tr>
<td>— Ratio of RV end-diastolic volume to BSA 110 mL/m² (male) or 100 mL/m² (female)</td>
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<tr>
<td>— or RV ejection fraction 40%</td>
</tr>
<tr>
<td><strong>By RV angiography:</strong></td>
</tr>
<tr>
<td>Regional RV akinesia, dyskinesia, or aneurysm</td>
</tr>
<tr>
<td><strong>MINOR:</strong></td>
</tr>
<tr>
<td><strong>By 2D echo:</strong></td>
</tr>
<tr>
<td>Regional RV akinesia or dyskinesia and 1 of the following (end diastole):</td>
</tr>
<tr>
<td>— PLAX RVOT 29 to 32 mm (corrected for body size [PLAX/BSA] 16 to 19 mm/m²)</td>
</tr>
<tr>
<td>— PSAX RVOT 32 to 36 mm (corrected for body size [PSAX/BSA] 18 to 21 mm/m²)</td>
</tr>
</tbody>
</table>
or fractional area change 33% to 40%

**By MRI:**

- Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
  - Ratio of RV end-diastolic volume to BSA 100 to 110 mL/m² (male) or 90 to 100 mL/m² (female)
  - or RV ejection fraction 40% to 45%

**Tissue characterization of walls**

**MAJOR:**

- Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

**MINOR:**

- Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

**Repolarization abnormalities**

**MAJOR:**

Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals > 14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)

**MINOR:**

- Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6
- Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block

**Depolarization/conduction abnormalities**

**MAJOR:**

- Epsilon wave (reproducible low amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)

**MINOR:**

- Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
- Filtered QRS duration (fQRS) ≥114 ms
- Duration of terminal QRS <40 uV (low-amplitude signal duration) ≥38 ms

- Root-mean-square voltage of terminal 40ms ≤20mV

- Terminal activation duration of QRS ≥55 ms measured from the nadir of the S-wave to the end of the QRS, including R’, in V1, V2, or V3, in the absence of complete right bundle-branch block

**Arrhythmias**

**MAJOR:**

- Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)

**MINOR:**

- Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis

- > 500 ventricular extrasystoles per 24 hours (Holter)

**Family history**

**MAJOR:**

- ARVC/D confirmed in a first-degree relative who meets current Task Force criteria
- ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
- Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation

**MINOR:**

- History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
- Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative
- ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

Table 1: Current Task Force Criteria for the diagnosis of ARVC (7)
References:


15. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. Clinical and genetic characterization of families with arrhythmogenic right ventricular
Diagnosis of, and screening for, ARVC in dogs and cats

Paul Wotton
University of Glasgow

Cardiomyopathy in boxers: Since the first published description of ‘boxer cardiomyopathy’ (BCM) from the USA\textsuperscript{13} in 1983, the condition has become widely recognised and there have been several clinical and pathological descriptions of this disease from Europe and the USA.\textsuperscript{1,2,6,18,22,23,31,40} Three clinical categories of disease are described:

- **Cat. 1 ‘Concealed’** (occult or pre-clinical) disease: no signs, but arrhythmias present;
- **Cat. 2 ‘Overt’ disease**: episodic syncope (usually with exertion or excitement) with arrhythmias; occasionally sudden death. Various arrhythmias are seen, but VPCs with a “left bundle-branch block (LBBB) pattern” (implying RV origin\textsuperscript{16}) are common;
- **Cat. 3 ‘Myocardial dysfunction’ stage**: congestive heart failure, esp. involving the left ventricle, resembling the phenotype of ‘classical’ dilated cardiomyopathy (DCM).\textsuperscript{2,24,40}

It was not known for certain whether these three categories represent three phases in a continuum of the same disease, different variants of the same disease or different diseases altogether (the latter being very unlikely), but progression from Cat. 1 to Cat. 2 and sometimes Cat. 2 to Cat. 3 is seen (see next paragraph). Cat. 3 BCM has been reported more frequently in the UK (although this may no longer be the case, probably due to changes in breeding practice), and carries a poorer prognosis.\textsuperscript{31,40} In contrast, Boxers with Cat. 1 & Cat. 2 disease may be long-lived.\textsuperscript{23} The age of diagnosis varies widely, but tends to be in the older age groups, except in severely affected cases in Cat. 3, which has been reported in younger animals.\textsuperscript{31,40}

BCM has long been recognised to be familial.\textsuperscript{22,40} Recent pedigree studies suggest that BCM in the UK has the same genetic basis as that in the USA, a single dominant gene mutation with incomplete (probably very low) penetrance, and that the different severity categories and variable age of presentation are varying expressions of the one disease (with or without modifying factors such as physical activity and myocarditis) rather than being attributable to different forms of cardiomyopathy.\textsuperscript{7} Boxer cardiomyopathy is often referred to as arrhythmogenic right ventricular cardiomyopathy (ARVC) because of its resemblance,
clinically and pathologically, to this condition in humans.\textsuperscript{1,40} There is an unresolved debate as to whether all BCM is ARVC, or whether boxers also suffer from a form/forms of idiopathic DCM. However, ARVC in humans may be very variable in clinical presentation, and there is increasing recognition that there can be biventricular or predominantly left ventricular involvement.\textsuperscript{32} Therefore any case of “DCM” in a boxer may still be (and is probably most likely to be) a form of ARVC.

**ARVC in cats:** The first published description of ARVC in 12 cats was in 2000.\textsuperscript{11} There are three subsequent published case reports\textsuperscript{8,12,14} describing 4 cats, and most veterinary cardiologists have seen sporadic cases, but it seems to be uncommon. Of the published cases, 10 were Domestic Shorthaired cats, 4 were Birmans and 2 were Burmese, with a wide age range. Clinical features included marked right ventricular (RV) and atrial enlargement, tricuspid regurgitation, significant tachy- and bradyarrhythmias, congestive heart failure and a short survival time. Gross pathological features included apical aneurisms and RV wall thinning, with histopathological changes similar to those described in boxers (see below). The clinical presentation is reasonably characteristic, but is most likely to be confused with congenital tricuspid dysplasia, given the marked right-sided enlargement and tricuspid regurgitation.

**ARVC in other dog breeds and other species:** ARVC has been described in other breeds of dog,\textsuperscript{10,26} especially English bulldogs,\textsuperscript{33} where a segmental, right outflow tract form is described, and also in two young related chimpanzees,\textsuperscript{39} but as ARVC is most commonly seen in, and is best characterised in, Boxer dogs, this presentation will concentrate on BCM.

**Diagnosis of ARVC:** As discussed by various authors, the diagnosis of BCM may be challenging, and may often be a diagnosis of exclusion, in particular the exclusion of other causes of ventricular arrhythmias (cardiac and non-cardiac causes). Changes in the criteria for the diagnosis of ARVC in humans have recently been made due to a number of factors, including increasing recognition of the familial nature of the disease, the need to screen asymptomatic family members and early left ventricular involvement in some cases.\textsuperscript{17,32,35} Six categories are included in the revised 2010 task force criteria: cardiac anatomy and function, histological changes, ECG abnormalities, arrhythmias, family history and genetic markers (see previous presentation), but even so, “no gold standard to establish or exclude the diagnosis of ARVC exists”.\textsuperscript{32}
In Boxers:

- **Echocardiographic** findings will often be unremarkable, except in Cat. 3 cases (“DCM” phenotype), as echocardiography is insensitive for the recognition of early changes in RV anatomy and function.

- **24hr ECG recordings** are often regarded as a gold standard for clinical diagnosis and are useful for prognosis, but considerable variability (~80% day-to-day) in arrhythmia frequency has been found. The threshold used for the diagnosis of ARVC varies in different publications. In her 1999 paper, Meurs used >50 VPCs/24hrs, but in a recent paper ARVC was defined as having ≥300 VPCs/24hrs in the absence of other disease and “unaffected” was defined as being ≥6 years of age and having <50 VPCs/24hrs. Thus 50-300 VPCs/24hrs is something of a “grey zone”. Arrhythmia complexity is also used.

- **Signal-averaged ECG (SAECG)** recordings, which detect high frequency, low amplitude signals in the terminal portion of the QRS complex, may have some value in detecting potential substrates for arrhythmias, and have been included in the criteria used in humans, but the technique is technically demanding.

- Serum levels of **cardiac troponin I** (cTnI) appeared to be a better marker for BCM than plasma BNP concentrations in work performed by Meurs’ group. cTnI is a sensitive and specific marker of myocardial damage, including hypoxia secondary to arrhythmias of any cause, and can be reasonably sensitive as a screening test for BCM, especially if used to pick out the best dogs to target for closer examination (e.g. a 24hr ECG). However, although cTnI is specific for myocardial damage it is not specific for cause, so non-cardiac causes of secondary myocardial damage leading to cTnI elevation must be ruled-out.

- In the one study published, magnetic resonance imaging (important for diagnosis in humans) was found to be of limited value in boxers, at least in the earlier stages of disease. RV ejection fraction was found to be significantly lower in Boxers with ARVC cf. controls, but gross fatty changes were not observed in the myocardium of either group, suggesting that “arrhythmias and myocardial dysfunction precede the development of morphological abnormalities in dogs with ARVC”. This imaging technique clearly needs more investigation in veterinary patients (see previous presentation).

- **Family history** should always be reviewed where possible.
Pathological changes in ARVC: *Post mortem* examination and a complete histological examination of the myocardium may be regarded as the “gold standard” diagnostic test! Whereas in ‘classical’ (primary, idiopathic, non-ischaemic) DCM, histological changes in the myocardium are often mild or non-specific, out of proportion to the marked functional disturbances seen (although “attenuated wavy fibres” are reported in a proportion of cases⁴⁸), in ARVC the pathological and histological findings are striking, and involve:¹

- Right ventricular enlargement or aneurisms;
- Early focal, later widespread, severe RV myocyte atrophy with replacement by fatty and fibro-fatty tissue, especially in the cranio-lateral and infundibular RV;
- Focal fibro-fatty lesions are also present in both atria and the left ventricle;
- Evidence of myocarditis may be seen especially in dogs that die suddenly, with patchy lysis, necrosis, haemorrhage and a mononuclear response.

However, replacement of RV myocardium by fatty tissue may not be specific for ARVC (it is a matter of degree and distribution) and these changes are probably secondary to myocardial damage and/or changes in cell signalling consequent to changes in desmosomal function (see below).

Screening for ARVC/BCM: Screening apparently healthy individuals to try to assess freedom from disease prior to breeding is particularly problematic with a late-onset, low penetrance disease, such as ARVC in Boxers appears to be. Added factors are the variability of the clinical signs and often a lack of specific findings: there is no BCM/ARVC equivalent of the typical murmur found in patients with DMVD or PDA!

- The most commonly used approach is 24hr ECG screening, and some Boxer breed clubs have their own Holter monitors.
- This could be combined with regular assessment of serum cTnl to pick out those dogs to target for closer examination.
- Consideration of the family history alongside clinical testing is the most powerful approach, as used in humans.³⁵ An individual dog carrying the gene would be expected to show evidence of this somewhere in their ancestry or offspring if a sufficiently wide timespan is examined, whereas they might appear to be completely normal when examined by 24hr ECG on only one or two occasions. However, examining a sufficiently
wide timespan is not always possible, practical or opportune for screening potential breeding animals.

- The ideal screening tool should be a **reliable genetic marker**, which unfortunately is not yet available. It is possible that more than one genetic mutation might be involved.

**The search for a genetic cause/marker for ARVC in boxers**: Much research effort, particularly by Kate Meurs and associates, has been put into trying to identify a mutation or genetic abnormality linked to BCM, targeting especially the genes implicated in humans: those encoding proteins of the intercalated disk, mutations of which can lead to electromechanical instability.

- One research group at Cornell University has used immunofluorescence to look at the molecular composition of the intercalated disk structure in boxers with ARVC. They have also demonstrated ultrastructural changes in the desmosomes and gap junctions of affected dogs and changes in a key signaling pathway, but have not been able to identify associated genetic mutations.

- Meurs & others found differences in cardiac ryanodine receptor (RyR2) protein & RNA expression (implicated in ARVC2 in humans) between normal and ARVC dogs. However, subsequent work again failed to identify any genetic linkage with the RyR2 gene in cases of ARVC.

- Oyama and others found that calstabin2 mRNA expression is significantly down-regulated in myocardium from ARVC boxers compared with healthy controls and dobermanns with DCM.

With all of the above findings it is possible that these molecular changes might be secondary rather than primary.

**Striatin**: In what initially seemed to be a very promising development, a mutation of the Striatin gene (STRN) was identified by Meurs and associates that was associated with Boxer ARVC. This gene was a likely candidate, as the protein had been shown to localise to the intercalated disc. However, 4 of 61 cases investigated in this study did not have the STRN mutation and it was present in 9 of 38 controls (the authors attributed the latter to incomplete penetrance). The identification of this striatin gene mutation resulted in widespread screening of affected and apparently normal boxers. However, subsequent published reports indicated further exceptions and anomalous results were also obtained in veterinary practices with the commercially-available ARVC test based on this
STRN mutation. Striatin genotype does not appear to correlate with phenotype in UK dogs, with similar findings in other countries, including the USA.

A recent pedigree-based study by Bruce Cattanach of ARVC in UK Boxers found that all cases traced back to a small number of imported American dogs deriving from the group of Boxers studied by Harpster in 1983 to define the disease, strongly suggesting that the disease is the same in the two countries. Dogs with and without the STRN mutation were found in both ARVC-affected and normal Boxers showing that the mutation is not responsible for the disease. Evidence was found that the STRN mutation is, however, genetically linked with the, as yet undiscovered, ARVC mutation, lying on the same chromosome. The linkage implies that the two genes can separate by meiotic recombination such that both ARVC-affected and unaffected lines of dogs may carry either the STRN mutation or its wild type allele; these have been found. Homozygotes for the STRN mutation tended to be severely affected at early ages suggesting there is an interaction between the effects of the STRN mutation on the cardiomyocyte and ARVC. Thus it appears that the striatin gene mutation may enhance or modify expression of an ARVC gene (the STRN mutation has recently been shown to be associated with the Cat. 3 phenotype), but that further searches for a primary causative mutation are still needed.

Acknowledgments: Dr. Bruce Cattanach & other co-authors of reference 7 for permission to use some details and diagrams from this paper.
References:


PROTECT and its implications: treating pre-clinical DCM

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PROTECT stands for Pimobendan Randomized Occult DCM Trial to Evaluate Clinical symptoms and Time to heart failure. The PROTECT study was a prospective, randomized, double-blinded placebo-controlled multicenter clinical trial, published in the Journal of Veterinary Internal Medicine in 2012.  

STUDY BACKGROUND AND RATIONALE

In humans with preclinical left ventricular systolic dysfunction, ACEI or ARBs and beta adrenergic receptor blockers are routinely recommended. However, there was an absence of published data to guide treatment recommendations in dogs with preclinical dilated cardiomyopathy (DCM). Prior to PROTECT, no previous prospective study had evaluated the effectiveness of any medication for the treatment of preclinical DCM in dogs. Pimobendan treatment had been proven to significantly reduce mortality and morbidity in dogs with CHF secondary to DCM, but the potential benefit of pimobendan therapy in delaying the progression of preclinical DCM in dogs had not previously been evaluated. After the initiation of PROTECT, one retrospective study was published and reported that benazepril might delay the progression of preclinical DCM in Dobermanns.

The Dobermann breed was chosen as the study population for PROTECT, as this breed has a well documented high predisposition for DCM and represents a uniform population of dogs with a relatively predictable disease phenotype and rate of disease progression.

STUDY HYPOTHESIS

The PROTECT study hypothesis was that the administration of pimobendan to Dobermanns with preclinical DCM would delay the onset of congestive heart failure or sudden cardiac death and in doing so prolong the period between diagnosis and the death of the patient.
**STUDY RESULTS**

The PROTECT study showed that the administration of pimobendan to Dobermanns with preclinical DCM (i.e. Dobermanns with echocardiographic evidence of DCM but free from clinical signs of disease) prolongs time to onset of clinical signs and extends survival.

Interestingly, dogs treated with pimobendan demonstrated a significant reduction in heart size after 30 days.

**SAFETY**

Pimobendan therapy was not associated with an increase in frequency or perceived severity of ventricular arrhythmia. Pimobendan was not associated with an increased tendency for sudden death.

**BROADER OUTCOMES**

The PROTECT study is the first prospective study in veterinary cardiology to show a convincing benefit of therapy in the preclinical stage of heart disease.

It is also the first veterinary cardiology study to demonstrate that a population identified through screening benefits from an early medical intervention.

**NEW VETMEDIN INDICATION**

As a result of the PROTECT study, Vetmedin is now licenced for the treatment of DCM in the preclinical stage (asymptomatic with an increase in left ventricular end-systolic and end-diastolic diameter) in Dobermanns following echocardiographic diagnosis of cardiac disease.

**CAN THE RESULTS OF PROTECT BE EXTRAPOLATED TO OTHER BREEDS?**

Further studies are required to assess the benefit of pimobendan therapy in other breeds with preclinical DCM as well as in Dobermanns meeting some of the PROTECT study exclusion criteria.

The left ventricular end systolic size has been shown to be a powerful predictor of outcome in dogs with DCM in another study which included many different breeds. The PROTECT study reported that pimobendan reduced left ventricular size in both diastole and systole, however the reduction in systolic size was more pronounced and was shown to be
associated with an improved outcome. It is plausible that the reduction in heart size induced by pimobendan treatment could confer a similar improved outcome in dogs of other breeds with phenotypically similar preclinical DCM. This is supported by the results from another study (not yet published), which reports improved outcome (survival) in Irish Wolfhounds with preclinical DCM following pimobendan therapy in comparison to either benazepril or digoxin. In summary, although the extrapolation of the PROTECT Study results to other breeds seems reasonable, clinical data in the form of published clinical studies to support this is currently lacking.

DCM SCREENING ALGORITHM

The diagnosis of preclinical DCM can be challenging. For this reason, a simple screening algorithm has been devised by a group of veterinary cardiologists and GP vets. The aim of this algorithm is to assist and encourage vets in practice to screen for DCM appropriately.

(Refer to Screening Algorithm)
EARLY DETECTION OF HEART DISEASE IN LARGE-BREED DOGS.

Identifying dogs with dilated cardiomyopathy (DCM) that are not yet showing obvious clinical signs can be challenging. A diagnosis can be made with echocardiography, but screening every at-risk dog with an echocardiogram (ECHO) is impractical.

Follow this simple screening process to determine which large-breed dogs have early evidence suggestive of DCM and are appropriate for further screening.

**DOGS AT RISK**
- Dog >3 years of age
- Dog >20 kg
- AND/OR
- At-risk breed

If there is a high index of suspicion, proceed directly with ECHO if available.

**PERFORM PHYSICAL EXAMINATION**
- Abnormal pulse or pulse deficits
- OR
- Any arrhythmia
- OR
- Gallop sounds
- OR
- Soft systolic murmur

**NOTE SUBTLE CLINICAL SIGNS**
- History of mild exercise intolerance or syncope
- Increased resting respiratory rate (RRR) or effort (>30 at home or >40 in clinic)
- Inappropriate/unintended weight loss

YES

Proceed with ECHO if available. If not, consider additional tests.

**CONSIDER ADDITIONAL TESTS**
- Electrocardiogram (non-sinus arrhythmia or VPCs = abnormal)
- OR
- Chest radiograph (ventral heart score >10.7 = abnormal)
- OR
- NT-proBNP biomarker (>900 pg/mL = abnormal; >500 pg/mL for Dobermann)

**REEXAMINE IN 1 YEAR**

**NORMAL**
- (DCM possible but less likely)

ABNORMAL
- (High probability of DCM)

**ECHO**

**NORMAL**

**ABNORMAL**

**DIAGNOSIS**

PRE-CLINICAL DCM

**HIGH-RISK BREEDS**

*Select breeds with a higher risk of developing DCM: Great Dane, Boxer, St. Bernard, Rottweiler, Dalmatian, German Shepherd Dog, and Doberman Pinscher.

**REFERENCES**

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4. Vollmar AC, Mohren N, Trötschel C, Fox PR. Comparison of Pimobendan, Benazepril, or Methyldigoxin in Irish Wolfhounds with Occult DCM or Atrial Fibrillation: A 10-year-study. International Cardiology Veterinary Symposium; May 4-6, 2012; Dubai, 30.
Estimated breeding values and their potential use in screening for heart disease

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Where a disease with a genetic basis is prevalent in a breed or population, selection against the disease is the only way to ensure widespread and lasting improvement in welfare, since only genetics is inherited across generations. The response to selection is directly related to the accuracy of selection, i.e. accurately identifying those individuals with the lowest genetic risk for breeding. Traditional selection based on phenotypes is therefore sub-optimal, unless the phenotype is a perfect representation of the underlying genetics.

The use of DNA tests for single autosomal recessive genetic diseases is a good example of improvement in the accuracy of selection. In such cases there are two possible phenotypes (clear or affected) but breeding from two apparently clear animals may result in some affected offspring. However, the DNA test reveals three possible genotypes: clear, carrier and affected, and breeders can more accurately identify breeding animals with the lowest genetic risk, and ensure matings are undertaken that result in no affected offspring.

However, most diseases are under the control of more than one (and usually many) genes meaning that individuals can no longer be categorised as ‘clear’, ‘carriers’ or ‘affected’. The existence of multiple genes influencing a trait or disease, and allelic additivity rather than complete dominance, means there is genetic variation underpinning the phenotype and individual liabilities are estimated on a spectrum of risk. Furthermore, the disease may be under the influence of both genetic and non-genetic, or environmental, effects. This further complicates assessment of genetic risk since the genetics is ‘overlaid’ by environmental influences (‘good’ genetics may be masked by detrimental environment and vice versa). Such diseases do not display a discernible familial pattern of inheritance (as seen with single gene diseases) and identifying and quantifying the effects of the genes involved is very difficult. However, methods do exist which allow estimation of the genetic risk.
Estimated breeding values (EBVs) are a quantitative estimate of the true genetic risk, or breeding value, made using trait information on an individual and *all its relatives*. Pedigree information allows quantification of the relationship between all the dogs therein and statistical techniques known as Residual Estimate Maximum Likelihood (REML) and Best Linear Unbiased Prediction (BLUP) use phenotypic data and the matrix of relationships to estimate the genetic variation and heritability of the trait, and calculate EBVs. The information on relatives, who share genes to a quantifiable degree, enables a better judgement of an individual’s genetics. For example, we may feel very differently about using a stud dog with a poor hip score if we knew that he had over 50 progeny scored with a very good average hip score. The performance of the progeny tells us about the genetics of the parent. In fact, this aspect has been key to the success of EBVs, which have been extensively used in the dairy industry for over 20 years. Here we are concerned with milk production traits – traits that are *only* expressed in females – yet we have very accurate EBVs for dairy bulls based on the milking performance of thousands of their daughters. Somewhat paradoxically, we know more about a bull’s genetics with respect to milking traits than we do for any cow!

As with all estimates, it is useful to know how good an estimate of the true value the EBV really is. It is intuitive that we will have more confidence in the estimate of genetic risk of hip dysplasia of the stud dog mentioned above, with his own hip score and scores of 50 progeny known, than a stud dog with no information on itself or its progeny. Just as EBVs are a quantitatively formal way of taking account of relative information in the assessment of an individual’s genetic liability, so we can formally calculate the accuracy of our estimate of true genetic liability, the EBV.

*Example of EBVs for hip dysplasia*

Studies of the genetics of hip dysplasia as measured by the BVA/KC hip score scheme demonstrate the potential improvements in accuracy of selection for scored dogs and those with parental scores only (Lewis et al, 2013). This study determined that the mean accuracy of EBVs for dogs with their own hip score were up to 24% greater than the accuracy of selection using their phenotypic score, and that the mean accuracy of EBVs of dogs with both parents scored (but without their own score) was up to 47% greater than selection on parental phenotypes. The use of the pedigree to calculate genetic relationships means that all dogs therein will have an EBV, even if they do not have a phenotypic record. Thus EBVs
are not only a more accurate metric for selection than hip scores, but are also more abundant. Up to three times as many animals have an EBV at least as accurate as selection using parental hip scores than the number with both parental scores actually available.

EBVs for hip score in 15 breeds have been publically available on the Kennel Club website (http://www.thekennelclub.org.uk/services/public/mateselect/ebv/Default.aspx) since 2014, with another 13 breed added in 2015. These breeds account for approximately 1/3 of annual registrations with the Kennel Club.

Further possible improvements to the accuracy of selection

The quantitative analysis of traits to estimate genetic variance can be extended to multiple traits and the estimation of the genetic co-variance between them, and so calculation of genetic correlations. This is useful in revealing the effect that selection for one trait will have on the genetic liability of another. Such information can be used in selection indices to determine the optimal combination of trait information that will deliver the greatest response for pre-defined selection objectives.

The importance of continued testing

The development of EBVs may lead to the belief that they are an effective replacement for phenotypes, and that scoring is no longer necessary. It is crucial, however, that participation in screening schemes continues. Phenotypes are the basis of accurate breeding values, and accuracies will rapidly decline if phenotypic information becomes sparse. Moreover, the phenotype is of value to breeders and owners alike in providing an indicator of not only the genetics but the environmental influence on an animal’s welfare. While the EBV should be used to guide breeding decisions, the phenotype is the most useful metric to inform of the appropriate care of the dog, which may ameliorate the severity of disease where it occurs.

REFERENCES

When a trait or disease is described as ‘complex’ it is usually meant that the trait is influenced by both genetic and non-genetic, or environmental, effects. This means that the phenotype (the observable manifestation of the trait) is not necessarily an accurate indicator of the genetics; the genetics is only a part of the picture and is ‘overlaid’ by environmental influences (‘good’ genetics may be masked by detrimental environment and vice versa). Thus, using phenotype to identify breeding individuals may result in sub-optimal accuracy of selection, since only the genetics is inherited across generations. The accuracy of selection is directly related to the response, so lasting and widespread improvements to welfare in selecting against inherited disease can be more quickly achieved using evaluations of genetic risk.

Poss eg of DNA Test?

You are probably all familiar with Mendelian inheritance which Gregor Mendel demonstrated with a 3:1 ratio of yellow to green peas. This ratio allowed him to infer that the trait of pea colour was determined by 2 variants (alleles) at a single gene; the yellow allele (A) being ‘dominant’ and the green allele (a) being ‘recessive’. This meant that the two possible phenotypes of pea colour (yellow and green) were in fact produced by three possible genotypes. Homozygotes (so called as both alleles are the same variety) with two yellow alleles (AA) produced yellow peas and those with two green alleles (aa) produced green peas. Heterozygotes having one green and one yellow allele (Aa) were yellow in appearance (phenotype), the dominant yellow allele masking the recessive green. This is important since it allows phenotypic variations, in this example the green pea colour, to apparently disappear for a number of generations before suddenly reappearing.

Heterozygotes produce half their gametes (sex cells) with the A allele and half with the a allele. Therefore progeny of two heterozygotes will have the genotypes AA : Aa : aa in the ratio 1 : 2 : 1, but because the yellow allele A is dominant the phenotypic ratio is 3:1 (see figure 1). However, this 1 : 2 : 1 ratio is very important – because the ‘dominance’ we have encountered up to this point is not universal or complete across all traits or diseases.

Gametes from parent 1 (Aa)

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Figure 1: Punnett square showing the genotypes and phenotypes from crossing two heterozygote parents.

Consider for a moment (hypothetically) that gene A (with 2 alleles A and a) determines the quantity of peas rather than their colour. So AA might yield 9 peas in each pod, while aa yields only 3. If the A allele is completely dominant, then we expect the heterozygote to show the same phenotype as the
dominant homozygote; so in this hypothetical example $Aa$ yields 9 peas per pod. However, as mentioned above, dominance is not universal or always complete. For example, imagine that instead the heterozygote yielded 6 peas per pod – half way between the two homozygotes. We can begin to look at things more quantitatively, plotting the number of peas per pod against the number of $A$ alleles:

![Chart showing hypothetical examples of complete dominance (L) and completely additive (R) A allele.]

Figure 2: hypothetical examples of complete dominance (L) and completely additive (R) $A$ allele.

These are two important examples; the chart on the left in figure 2 shows **complete dominance**, i.e. the heterozygote ($Aa$) is the same phenotypically as the $AA$ homozygote. The chart on the right shows **no dominance**, or **complete additivity** (i.e. the heterozygote is the intermediate of the two homozygotes, and each $A$ allele adds 3 peas per pod). Additivity is an important concept as we move on to consider ‘genetic variation’.

Complete additivity at a single gene will give us a 1 : 2 : 1 ratio of phenotypes (reflecting the genotype ratio). However, as stated earlier, many quantitative or complex traits are influenced by multiple genes. As we consider perfect additivity over an increasing number of genes (figure 3) we can see the phenotypic distribution (discounting non-genetic effects for a moment) approaching a ‘normal distribution’ (also known as the ‘bell curve’, and very important in statistics). Figure 3 shows (from left to right) the genetic distributions of traits controlled by 1, 3 and 6 genes respectively, followed by a normal distribution on the far right. Hopefully you can see that increasing the number of genes increases the number of phenotypic categories and begins to produce **continuous genetic variation** for the trait or disease in question. Thus, we have moved from thinking in terms of ‘clear’, ‘carrier’ and ‘affected’, to thinking in terms of a continuous scale of liability or risk.

![Chart showing genotype frequency distributions for 1, 3 and 6 completely additive genes, and a normal distribution (far right).]

Figure 3: (L to R) genotype frequency distributions for 1, 3 and 6 completely additive genes, and a normal distribution (far right).
This is probably not as novel a concept as it may appear; think about when you hear news reports about scientists having found a gene for cancer, heart disease, diabetes, Alzheimer’s etc. – it’s always a gene, not the gene. There isn’t a single gene for any of these diseases just as there isn’t a single gene for height or weight. So, for complex diseases like hip dysplasia we will have to deal with the concept of genetic variation and risk.

But the complexity doesn’t end here. As mentioned at the outset complex traits are influenced by both genetic and environmental factors. While the genes (and so the genetic risk) are determined at conception, this risk is subsequently modified by the effects of numerous known and unknown non-genetic or environmental influences. Think of heart disease; I may have a moderate genetic risk, but if I smoke, eat a poor diet, eat too much, take no exercise and have a stressful lifestyle my actual risk creeps up. My actual risk when I’m 50 may be higher than a 50 year old with a higher genetic risk, but who watches their weight, eats healthily, has never smoked and has a low stress lifestyle. The same is true for hip dysplasia, where known environmental effects include diet and early-life exercise regime.

Nevertheless, genetics makes an important contribution to the overall risk. The heritability of a trait tells us how important genetics is relative to non-genetic effects – strictly it is the proportion of phenotypic variation that is due to genetic variation. For hip dysplasia about 40% of the overall observable variation is due to genetic variation. This may not seem much - it is less than half after all - but it is by far the biggest single component.

However, when it comes to breeding, it is only the genetic risk we are concerned with, as it is only genetics that is passed across generations. This presents us with a problem – we are using phenotypes (hip scores) to guide our selections, but we know that they are not necessarily the best guide to genetics. We may unwittingly choose a dog with a good hip score, not knowing that this is actually more to do with a beneficial environment and that the genetic risk, which is passed to the progeny, is actually fairly high. But to date, hip scores are all that breeders have had to guide them.

This is where estimated breeding values, or EBVs, come in. EBVs are a quantitative estimate of the true genetic risk, or breeding value. We make the estimate using trait information, in the case of hip dysplasia using the hip score, on an individual and all its relatives. We are able to do this thanks to the availability of pedigree information, which allows us to quantify the relationship between all the dogs therein. Information on relatives, who share genes to a quantifiable degree, will allow us to make a better judgement on an individual’s genetics. For example, we may feel very differently about using a stud dog with a poor hip score if we knew that he had over 50 progeny scored with a very good average hip score. The performance of the progeny tells us about the genetics of the parent. In fact, this aspect has been key to the success of EBVs, which have been extensively used in the dairy industry for over 20 years. Here we are concerned with milk production traits – traits that are only expressed in females. Yet we have very accurate EBVs for dairy bulls based on the milking performance of thousands of their daughters. Somewhat paradoxically, we know more about a bull’s genetics with respect to milking traits than we do for any cow!

As with all estimates, it is useful to know how good an estimate the EBV really is. It is intuitive that we will have more confidence in the genetics of the stud dog mentioned above, with his own hip score and scores of 50 progeny known, than a stud dog with no information on itself or its progeny. Just as EBVs are a quantitatively formal way of taking account of relative information in the assessment of an individual’s genetic liability, so we can formally calculate the accuracy of our estimate of true genetic liability, the EBV.
So, EBVs are a more accurate indicator of genetics than an individual phenotype – and are more abundant. This means selections made using EBV will be more accurate, and more accurate selection delivers greater genetic progress. I aim to demonstrate this and other improvements in the efficacy of selection in my lecture, using some examples from my research.

Finally, it is important to remember that EBVs are simply a more effective way of using the hip score data in selection – they are NOT a direct replacement! Quality data is critical for the calculation of accurate EBVs. Furthermore, hip scores themselves have significant prognostic value for individual dogs.
Dilated cardiomyopathy (DCM) is the second most common acquired cardiac disease in dogs in the UK. The diagnosis is usually made using a combination of age/sex/breed, history and physical examination findings alongside results of multiple diagnostic tests. However, in most clinical situations the typical echocardiographic findings of a dilated left ventricle with increased end-systolic dimensions are sufficient. When presented with a patient of a typical breed in congestive heart failure with these echo findings, further investigation of the underlying cause is usually unwarranted.\(^1\)

The clinician is presented with more of a challenge when animals demonstrate apparent reductions in systolic function (assessed echocardiographically) without clear evidence of congestive heart failure. Animals often present with non-specific clinical signs such as exercise intolerance or lethargy: the detection of a heart murmur may prompt echocardiographic evaluation and systolic dysfunction may then be suspected. In this scenario, it is useful to review the possible causes for apparent systolic dysfunction before a diagnosis of idiopathic primary myocardial failure (an alternative, nicely descriptive term that has been proposed for DCM\(^1\)) is made.

In order for systolic dysfunction to be diagnosed, subjective and objective echocardiographic assessments are made. When possible, measured cardiac dimensions can be compared against normal tables for the breed. However, of breeds commonly diagnosed with DCM, a third do not yet have published reference intervals.\(^2,3\) When breed reference intervals are not available, weight-based allometric scaling or ratiometric indices may be used.\(^4,5\) However, these often provide wide confidence intervals and do not take into account body condition, making it very difficult to identify mild-moderate ventricular dilatation based on a single examination.\(^6\)

Systolic dysfunction is characterised by a decrease in myocardial contractility and can be defined as impaired emptying of the LV, apparent as a decreased ejection fraction (EF) on
echo. It is tempting to assume that a reduction in EF is synonymous with systolic dysfunction: clearly, this may not always be the case. EF is a load-dependent estimate of systolic function and relates to the animal’s current cardiovascular demand. Cardiac output is highly variable, depending upon the patient’s physical and emotional state and this is reflected in the measured EF. The EF in a fit, relaxed dog will be much lower than in an excited or stressed animal undergoing echocardiography. One of the author’s dogs frequently falls asleep during echo and his FS and EF may go as low as 20% and 40%, respectively.

Furthermore, clinicians mustn’t assume that depressed systolic function means that DCM is present. When making a diagnosis of idiopathic DCM (or primary myocardial failure), other causes of systolic dysfunction need to be excluded. These include (but are not limited to): hypothyroidism; hypertensive disease; tachycardia-induced, toxic, metabolic, infectious, autoimmune and infiltrative myocardial failure; arrhythmogenic and ischaemic cardiomyopathies. Other specific cardiomyopathies such as periparturient and neuromuscular dystrophies have been well-characterised in man yet are rarely (if ever) reported in the veterinary literature.

A challenge for cardiologists is when trying to assess systolic function in the presence of significant mitral regurgitation. Two excellent articles have comprehensively reviewed the use of conventional, Doppler and Tissue-tracking echocardiography in the assessment of systolic function in mitral valve disease. These articles conclude that no single echocardiographic technique has been found to be reliable at identifying systolic dysfunction: all techniques are to some extent load-dependent or cannot be relied upon in the presence of significant mitral regurgitation. Published values for many systolic function indices are lacking in normal animals, let alone values in the presence of disease states. Most authors agree that the presence of low-normal functional indices (FS, EF) and increased left ventricular systolic dimension and/or volume identify systolic dysfunction in the context of significant mitral regurgitation. Other echo parameters such as E/E’, IVRT, Tei index, dP/dt as well as strain and strain-rate imaging may all add information but again published reference ranges are lacking for many.

Another consideration in some dogs’ hearts is the potential for exercise-induced remodelling. This is a well-recognised condition in man, necessitating specialised evaluation of the “athlete’s heart” by experienced cardiologists. In 1975 the Morganroth Hypothesis proposed that endurance training promoted eccentric left ventricular hypertrophy and resistance training (e.g. weight-lifting) promoted concentric LV hypertrophy. This concept gained wide acceptance in the scientific world however a recent review has questioned the hypothesis and concluded that the supporting evidence is weak. There is a reasonable body of evidence to support the theory that endurance
training results in increases in left ventricular dimensions and wall mass but the effects of resistance training are in dispute.

There is some evidence in dogs to suggest that exercise remodelling can be documented with echocardiography in “field” conditions.\textsuperscript{11,12} However, much of the remaining work done in this area was performed prior to the introduction of echo to veterinary research, or by using artificial methods of physically training dogs.\textsuperscript{13-15} An abstract presented at ECVIM in 2005 (Van Israel, N. et al.; Athlete heart or DCM in a Springer spaniel family?; ECVIM proceedings 2005) described a group of Springer Spaniels with apparent exercise remodelling but to the author’s knowledge there are no recent published studies in this field. Athlete’s heart has not been fully characterised in veterinary medicine.

As part of an ongoing research project into English Springer Spaniels, the author would like to offer preliminary reference ranges for the breed, from 40 dogs in a study. These data are preliminary and may change on publication; please only use them as a guide. The range has been “trimmed” removing the lowest and highest outlier from each data set. Clearly some of these are well outside the expected normal range for any dog – all dogs will be scanned twice (at least a year apart) to try to exclude cases of preclinical dilated cardiomyopathy (or other systolic dysfunction). The author is collecting cases of DCM with CHF in English Springer Spaniels. If you have a case please contact me if you are happy to share the case details.
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LV linear dimensions were measured from M-mode imaging

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