European Society of Veterinary Cardiology

ESVC Pre-congress day August 31st 2022, Gothenburg, Sweden

CANINE AND FELINE CARDIOMYOPATHIES: AN UPDATE

E-proceeding

Table of contents

European Society of Veterinary Cardiology (ESVC) thanks speakers and sponsors for their support to the ESVC pre-congress day 2022

European Society of Veterinary Cardiology

ESVC Pre-congress day August 31st 2022, Gothenburg, Sweden

CANINE AND FELINE CARDIOMYOPATHIES: AN UPDATE

Program

Time	Title	Speaker
09.00-09.30	Registration	
09.30-10.10	Classification of feline cardiomyopathies: imaging and pathology	V.L. Fuentes
10.15-10.55	Genetics of feline and canine cardiomyopathies	J Häggström
11:00-11.30	Coffee break	
11.30-12.10	Feline cardiomyopathies: incidence, risk, survival and therapy	V.L. Fuentes
12.15-12:55	Cardiac biomarkers in dogs and cats	J Häggström
13:00-14:00	Lunch	
14:00-14:40	Dilated cardiomyopathy in different dog breeds: diagnosis and therapy	G Wess
14:45-15:25	Arrhythmogenic right ventricular cardiomyopathy and tachycardia induced cardiomyopathies: diagnosis, assessment and treatment	R.A. Santilli
15.30-16:00	Coffee break	
16:00-16.40	Myocarditis: diagnosis and treatment	R.A. Santilli
16.45 18.00	Panel discussion – cases	V.L. Fuentes J Häggström G Wess R.A. Santilli
18.00	End of the meeting	

Classification of feline cardiomyopathies: imaging and pathology

Virginia Luis Fuentes DipACVIM, DipECVIM (Cardiology)

Royal Veterinary College, United Kingdom

Cardiomyopathy is a disease of the myocardium in which the heart muscle is structurally and/or functionally abnormal in the absence of any other cardiovascular disease sufficient to cause the observed myocardial abnormality.[1] Classification of feline cardiomyopathies has traditionally followed human classification, as there is considerable species overlap in myocardial disorders. Unfortunately there are multiple human classifications currently in use, all of which differ from one another in important ways.[1-4] Most retain the traditional morphofunctional descriptions of 'hypertrophic' (HCM), 'dilated' (DCM), and 'restrictive' (RCM), but there are differences in how genomics, systemic diseases and channelopathies are incorporated into the various classification systems.

The ACVIM consensus statement on feline cardiomyopathies[5] provided a classification system most closely resembling the 2008 European Society of Cardiology classification.[1] Both are a clinical classification based on phenotype (hypertrophic, dilated etc), and subdivided according to aetiology (eg. genetic/familial; dietary; thyroid disease, etc). This type of classification acknowledges that the phenotype can usually be described by imaging, but the aetiology is not usually evident without further testing. By far the most common cardiomyopathy in cats is HCM. A sarcomeric mutation is identified in approximately 50% of people with HCM, but in around a third of HCM patients an aetiology is not identified. Although a genetic basis for HCM may be suspected in closely-related cats, the aetiology is never identified in the majority of cats with an HCM phenotype.

Cardiomyopathy phenotype definitions*

Phenotype	Echocardiography	Pathology
HCM	Increased LV wall thickness (focal or diffuse) with a nondilated LV chamber.	Myofibre disarray, with interstitial fibrosis and small vessel disease (arteriosclerosis)[6]
End-stage HCM	Transition from the above typical HCM phenotype to a phenotype with focal or global LV systolic dysfunction, increased LV dimensions, and LA dilation	
RCM: myocardial	Normal LV dimensions (including wall thickness) with LA or biatrial enlargement	Normal LV wall thickness and diameter with biatrial enlargement Areas of myofibre disarray and patchy replacement fibrosis[7]
RCM: endomyocardial	Mid-LV obstructed by hyperechoic and often apical LV thinning or aneurysm; LA or biatrial enlargement is generally present.	Prominent endocardial scar that usually bridges the interventricular septum and LV free wall[8]

DCM	LV systolic dysfunction associated with increased ventricular dimensions, normal / reduced LV wall thickness, and biatrial dilation.	Relative lack of histopathological lesions
ARVC	Severe RA and RV dilatation ± RV systolic dysfunction and RV wall thinning, sometimes extending to the left heart	Moderate-severe RV cavity enlargement with histopathological evidence of myocyte injury and repair with fibrofatty replacement
Non-specific	A cardiomyopathic phenotype that is not adequately described by the other categories; a description of cardiac morphology and function should be provided	

*Based on ACVIM feline cardiomyopathy consensus statement.

HCM: hypertrophic cardiomyopathy; RCM: restrictive cardiomyopathy; DCM: dilated cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; LV: left ventricle/ ventricular; LA: left atrium/atrial; RA: right atrial; RV: right ventricular

Imaging controversies and problems

No biological classification system is perfect but classifying cardiomyopathies in cats is particularly challenging. Although widely available, radiography lacks sensitivity and specificity for identifying cardiomyopathy in cats. Cardiac magnetic resonance imaging has many advantages in human phenotyping, but the requirement for general anaesthesia in cats is a major disadvantage. Echocardiography is the most common imaging technique for phenotyping cats with cardiomyopathy as in people, but a number of factors complicate echocardiographic interpretation.

Inter- and intra-observer agreement is poor in applying the traditional classification system

An online survey showed that there was poor agreement between even cardiology specialists in selecting a phenotypic category based on echocardiographic findings. Worryingly, there was also poor intra-observer agreement when participants were asked to phenotype the same cats twice. Poor agreement may result from poorly defined criteria for the different categories, failure to adhere to the reported criteria, or inappropriate criteria. There is certainly overlap between the different feline phenotypic categories, making it difficult to assign a single phenotypic category to some cats. It is important to recognise that the various phenotypic categories are unlikely to each represent a single condition.

One phenotype can have different causes

The ACVIM consensus statement phenotypic system is not based on aetiology. Instead, the phenotypic classification is intended to be a shorthand for describing a group of morphological or

functional characteristics that often occur together. Cats with thickened LV walls on echocardiography have an 'HCM phenotype', and this could be a result of a sarcomeric mutation, acromegaly, hyperthyroidism, or transient myocardial thickening, etc. It is not always possible to identify the specific cause of LV wall thickening.

One aetiology can result in different phenotypes

We know that in people, the same genetic variant can cause an HCM phenotype in one individual, and an RCM phenotype in another. In many cats with an HCM phenotype there is a change in phenotype as they age, so that time also affects cardiac phenotype. A classic HCM phenotype can evolve into an end-stage HCM that has little resemblance to the original phenotype.

Wide phenotypic spectrum

With HCM there is a particularly wide phenotypic spectrum, which is easy to recognise at its most extreme, but at the milder end of the spectrum there is overlap with a normal cardiac phenotype. Factors such as body weight, body condition score and breed influence normal LV wall thickness, making dependence on a single cut-off value for wall thickness unreliable. Presence of other imaging features typical of HCM should improve reliability. These include papillary muscle hypertrophy, presence of systolic anterior motion of the mitral valve, and end-systolic cavity obliteration. For other phenotypic categories such as RCM or arrhythmogenic cardiomyopathy (ARVC), the imaging criteria are less well-defined. Our understanding of the aetiology in these cardiomyopathy phenotypes is poorly defined, and a gold standard is not available for validating imaging phenotypic criteria.

Echocardiographic measurement variability

When screening for subclinical HCM, relying on cut-off values for LV wall thickness increases the importance of standardised measurements. M-mode and 2D echocardiographic measurements of wall thickness are not interchangeable, and including one or more endocardial layers in the septal wall thickness can mean the difference between normal or affected.

Pathology controversies and problems

Histopathology is often thought of as the gold standard for identification of feline cardiomyopathy phenotypes. The classic histopathological findings in HCM are myofibre disarray, myocyte hypertrophy, interstitial and replacement fibrosis, and abnormal intra-mural coronary arteries.[9] However, inter- and intra-observer agreement on phenotype classification does not appear to be any better than for imaging criteria (unpublished data). As with LV wall thickness measured with echocardiography, there is probably no single cut-off value for heart weight that will reliably identify cats with HCM. There is no consensus on an appropriate standardised protocol for selecting locations for histopathological sections, although the region where the interventricular septum joins the right ventricular free wall often demonstrates myocyte disarray even in normal cats. There is inherent variation in the location and extent of myofibre disarray, and in some cats with an HCM

phenotype on echocardiography, no myofibre disarray will be evident.[10] Myocyte disarray is not unique to HCM, as it can also be documented in cats with RCM.[7]

Conclusions

Cardiomyopathies are complex, and the number of different classification systems for human cardiomyopathies suggests that there is no perfect classification system. In the future more sophisticated genomic analysis may help classification, but this still depends on accurate phenotyping in the first place. We should avoid viewing phenotypic labels as definitive categories, and acknowledge that there is wide variation, and a phenotype only describes a 'snapshot' in time of cardiac morphology and/or function.

1. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2008;29(2):270-276.
2. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation.* 2006;113(14):1807-1816.
3. Arbustini E, Narula N, Dec GW, et al. The MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation. *J Am Coll Cardiol.* 2013;62(22):2046-2072.
4. Lipshultz SE, Law YM, Asante-Korang A, et al. Cardiomyopathy in Children: Classification and Diagnosis: A Scientific Statement From the American Heart Association. *Circulation.* 2019;140(1):e9-e68.
5. Luis Fuentes V, Abbott J, Chetboul V, et al. ACVIM consensus statement guidelines for the classification, diagnosis, and management of cardiomyopathies in cats. *J Vet Intern Med.* 2020;34(3):1062-1077.
6. Fox PR. Hypertrophic Cardiomyopathy. Clinical and Pathologic Correlates. *Journal of Veterinary Cardiology.* 2003;5(2):39-45.
7. Fox PR, Basso C, Thiene G, Maron BJ. Spontaneously occurring restrictive nonhypertrophied cardiomyopathy in domestic cats: a new animal model of human disease. *Cardiovasc Pathol.* 2014;23(1):28-34.
8. Fox PR. Endomyocardial fibrosis and restrictive cardiomyopathy: pathologic and clinical features. *Journal of Veterinary Cardiology.* 2004;6(1):25-31.
9. Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J.* 1958;20(1):1-8.
10. Khor KH, Campbell FE, Owen H, Shiels IA, Mills PC. Myocardial collagen deposition and inflammatory cell infiltration in cats with pre-clinical hypertrophic cardiomyopathy. *Vet J.* 2015;203(2):161-168.

Update on the genetics of feline and canine cardiomyopathies

Jens Häggström, DVM, PhD, DECVIM-CA (Cardiology)

Professor Internal Medicine, Companion Animals

Swedish University of Agricultural Sciences, Uppsala, Sweden.

Cardiomyopathies are a heterogeneous group of myocardial diseases with varied phenotype and prognosis. Cardiomyopathy is defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of any other cardiovascular disease sufficient to cause the observed myocardial abnormality. The condition is the most common cardiac disease in cats, and cardiovascular disease is among the 10 most common causes of feline death. In dogs, cardiomyopathy is the second most common cardiac disease after myxomatous mitral valve disease. Classification of cardiomyopathies has previously been based on schemes that were applied to human cardiomyopathy, but currently there are several competing human classification systems, highlighting the difficulties inherent in cardiomyopathy classification (Figure 1).

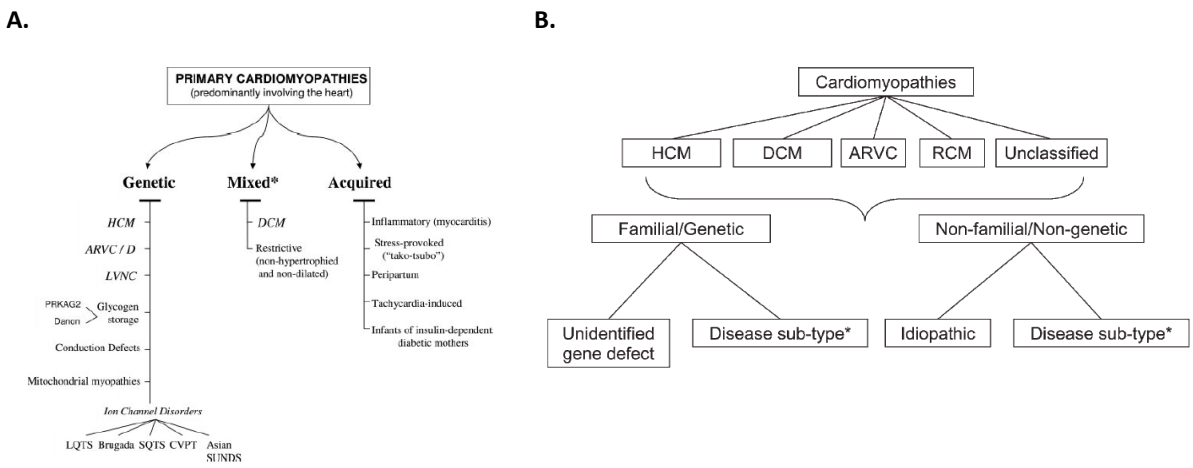

Figure 1. Two commonly used human classification schemes for cardiomyopathy. A. The American College of Cardiology (Circulation 2006;113:1807-1816) and B. The European Society of Cardiology (Eur Heart J 2008;29:270-276) Abbrevations: ARVC, arrhythmogenic right ventricular cardiomyopathy; CVPT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy;HCM, hypertrophic cardiomyopathy; LVNC, left ventricular non-compactation; LQTS, long Q-T syndrome;RCM, restrictive cardiomyopathy; SQTS, short Q-T syndrome; SUNDS, sudden unexplained nuctural death syndrome

In humans, there is comparably large volume of information concerning the genetic background of cardiomyopathy and the cause of cardiomyopathy can often be determined, which is illustrated by the classification scheme by the American college of cardiology, where several types of

cardiomyopathy are grouped under “genetic” (Figure 1A). Much less is known in dogs and cats, which means that classification based on genetic background is currently not ideal. Therefore, the cardiomyopathies are recommended, for the time being, to be classified by to their phenotype, according to the European Society of Cardiology classification scheme (Figure 1B). In dogs, the predominant form of cardiomyopathy is the dilated cardiomyopathy (DCM) phenotype, and in cats the hypertrophic (HCM) phenotype is by far the most common type. Not all cases of cardiomyopathy are likely to be genetic in origin. In dogs, there is emerging evidence that the DCM phenotype may be in some “non-traditional” breeds be food associated, and in cats, there are several diseases that can cause a phenotype similar to HCM. In cats, the distinction between different phenotypes is not always clear and a patient may have more than one cardiomyopathy feature. This document is aimed at summarizing the current knowledge concerning the genetical background of cardiomyopathy in dogs and cats.

Genetic aspects of canine cardiomyopathy

In people, DCM appears to be genetically comparably heterogeneous, with mutations in genes encoding cytoskeletal, nucleoskeletal, mitochondrial, and calcium-handling proteins. Private mutations account for most DCMs, with few hotspots or recurring mutations. More than 50 single genes are linked to inherited DCM in people, including many genes that also link to HCM. There are still many human DCM forms, where the causative mutation remains unknown. Dilated cardiomyopathy has been described to be inherited as an autosomal dominant trait in most dog breeds where it has been studied, the exceptions being Irish Wolhounds, Portuguese Water dogs and Standard and Giant Schnauzers, where it has been described to be inherited as an gender-dependent dominant (Irish Wolfhound) and autosomal recessive (Portuguese water dogs and Schnauzers) traits. At present date, only 5 mutations have been suggested causative of canine DCM, two in Dobermann Pinschers, a 16 base pair deletion in the mitochondrial enzyme pyruvate dehydrogenase kinase 4 (PDK4) gene and a single base-pair (missense) mutation the titin gene, one in Boxer dogs, a 8 base pair deletion in the striatin gene, one in Welsh Springer Spaniels, a single base-pair (missense) mutation in the phospholamban gene, and one in Giant and Standard Schnauzers, a 22-bp deletion resulting in a frameshift mutation in RNA-binding motif protein 20. The mutation in the Dobermann PDK4 gene was tested in a cohort of European dogs from Germany and the UK, but the association could not be replicated in this population of dogs. This is suggestive of other causative genes in European dogs and/or geographic stratification of the breed. Publication is currently pending concerning new data of genetic background to DCM in a large cohort of European

Dobermann dogs. For the Boxer dogs, an attempt has been made to replicate the association between the striatin mutation and arrhytmogenic right ventricular cardiomyopathy (ARVC) in UK Boxer dogs, but failed to do so. The results showed that the striatin mutation was very common in this population of UK Boxer. However, the proportion of dogs in the phenotypically normal and phenotypically affected dogs was not significantly different. Furthermore, in contrast to the Boxers from USA, the genotype was not correlated to the number of VPCs recorded over 24 hours in the UK population. Finally, genome wide association analyses have also been performed in Irish Wolfhounds, Portuguese Water dogs, Newfoundlands and Great Dane dogs, and preliminary results of significant genome wide associations have been presented, but no candidate genes have yet been brought forward in these breeds.

So how can the information of the genetic background of DCM in dogs be used in the real world? Currently, there is no Consensus recommendation of how the suspected disease-causing variants should be used for breeding purposes and for assessing the risk for hetero-and homozygous dogs to develop the DCM phenotype. The PDK4 and the striatin variants are common in European Dobermanns and Boxers, but do not appear to confer an increased risk of developing the DCM or ARVC phenotype. As for the other variants, too little is known to allow general recommendations.

Genetic aspects of feline cardiomyopathy

The familial HCM phenotype has been shown an inherited trait in some cat breeds, such as American Shorthair, Maine Coon, and Persian cats. The disease is suspected to be inherited also in other breeds, such as the Sphynx, Siamese, Siberian and Norwegian Forest cat. In American Shorthair and Maine Coon cats it has been suggested that familial HCM is inherited as an autosomal dominant trait with variable penetrance. In humans, over 1500 mutations have been associated with the HCM phenotype. They are mainly located in sarcomeric genes, although pathogenic variants in non-sarcomeric genes have also been described, such as those encoding Z-disc proteins or calcium signaling proteins. Mutations in the genes encoding the thick filament components myosin heavy chain (MYC) and myosin binding protein C (MBPC) together explain 75% of inherited cases of HCM, which is suggestive of that HCM is mainly a disease of the sarcomere. In cats, only two mutations in the MYBPC3 gene have been associated with the HCM phenotype: One in Maine Coon (A31P) and one in Ragdoll cats (R820W). Genetic tests for the HCM phenotype in both breeds are available to the public. There is a third mutation described in the MYPC3 gene and this variant is entitled A74T, but this variant does not seem to be associated with the HCM phenotype. The proportion of gene test positive cats for the A31P mutation appears to be very high in the Maine Coon population both

in the USA and in Europe with a prevalence range from 34% to 41%. Approximately 10% of the cats with the A31P mutation are homozygous and 90% are heterozygous for the mutation. A percentage of Maine Coon cats with HCM do not have the A31P mutation, which suggests that there must be at least one more cause in this breed. Conversely, not all cats with the mutation, even homozygous cats for the A31P, do not develop the HCM phenotype, although, in a recent meta-analysis, homozygous cats appear to have an approximately 3-fold increased risk compared to combined groups of wildtype and heterozygous cats of developing the HCM phenotype (Figure 2). Concerning the R820W mutation in Ragdoll cats, 27.4% of Ragdoll cats sampled in the UK was reported to carry the mutation (26% heterozygous, 1.4% homozygous). The current information concerning the R820W variant in Ragdoll cats is not sufficient to allow robust risk assessments in hetero-and homozygous cats, but it appears as if that homozygous cats are at risk for developing the HCM phenotype compared to heterozygous and wildtype cats, a situation similar to the A31P mutation in Maine Coon cats. An intronic variant in cardiac muscle troponin T gene (TNNT2, c.95-108G>A), was recently suggested as the cause of HCM in one Maine Coon cat, but a subsequent study failed to replicate these findings.

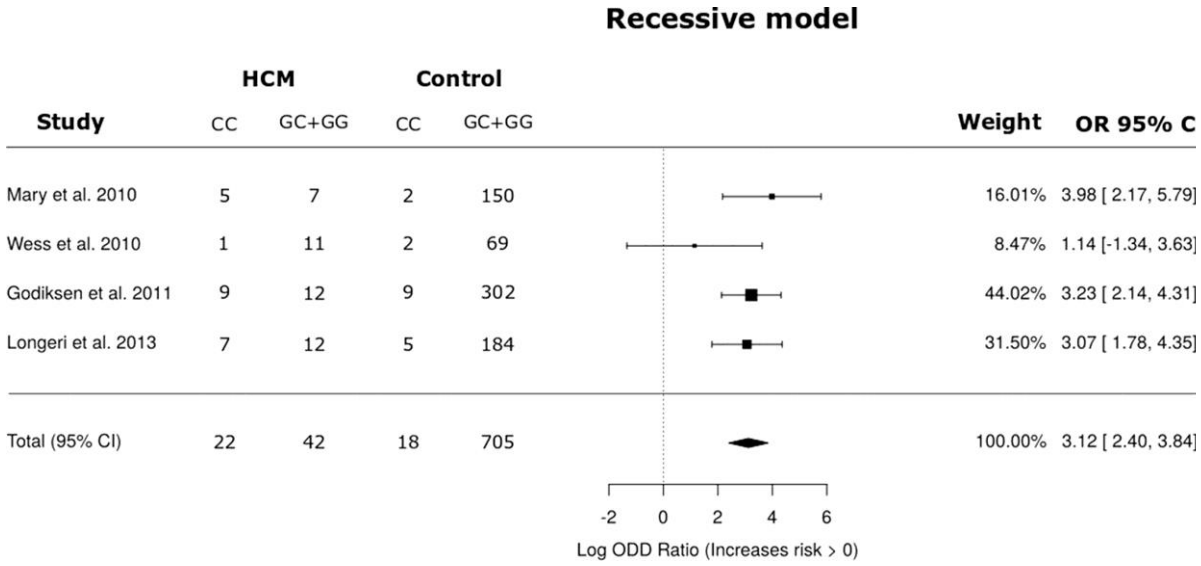

Figure 2. Forest plot of feline hypertrophic cardiomyopathy (HCM) and A31P variant in MYBPC3 compares homozygous carriers vs heterozygous and wild-type carriers (CC vs GC + GG). The horizontal lines correspond to the study specific OR and 95% CI. The diamond represents the pooled results. The pooled incidence of risk HCM was 3.12 (95% CI, 2.40-3.84). From Gil-Ortuño, et al. Clin Genet 2020;98:203-214.

In Sphynx cats with HCM, a mutation in the Alstrom syndrome 1 *(ALMS1)* gene has been identified. Mutations in the *ALMS1* gene in people is, among other things, associated with the development of the DCM and/or the RCM phenotype. Of the Sphynx cats with HCM examined, 87% had this variant

(44% heterozygotes and 56% homozygotes), so not all affected cats had the variant and no Sphynx cats without HCM were examined for this variant. Consequently, the study did not provide conclusive evidence that this variant is responsible for the development of the HCM phenotype in this breed.

The vast majority of cats presenting with the HCM phenotype are domestic or cross breeds with no or unknown family history of cardiomyopathy. It is widely suspected that these cats have a genetic cause of their HCM too, but intensive efforts aimed at identifying such mutations have not been successful. Consequently, it is likely there is some other unknown cause of feline HCM. A case of a domestic mixed-breed cat with HCM carrying a heterozygous variant in the MYH7 gene was recently published. This variant, p.E1883K; rs121913652, has also been reported to be associated with cardiomyopathy in humans. Although there is currently not enough data to support mutation as disease causative in cats, it is the first reported variant in the MYH7 gene in a mixed-breed cat with the HCM phenotype.

So how can the information of the genetic background of HCM be used in the real world? The 2020 ACVIM Consensus statement concerning classification, diagnosis and management of feline cardiomyopathy recommends genetic testing for the MyBPC3-A31P mutation and the MyBPC3 R820W mutation in Maine Coon and Ragdoll cats (respectively) intended for breeding, with the aim of reducing the incidence of these mutations and HCM phenotype in these specific breeds. It is recommended that cats homozygous for either mutation not be used for breeding, but heterozygous cats can be bred to genotype-negative cats if they have other outstanding characteristics. Maine Coon and Ragdoll cats that are heterozygous or test negative for these MYBPC3 mutations are recommended to undergo regular echocardiographic screening. Genetic testing for the A31P and R820W MYBPC3 mutations in non-Maine Coon or non-Ragdoll cats is not recommended, as these two variants are almost completely specific to Maine Coon and Ragdoll cats. As for the other mutations in the other cat breeds, too little is known to allow general recommendations.

Selected references

Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-276.

Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and

Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006;113:1807-1816.

Meurs KM, Lahmers S, Keene BW, et al. A splice site mutation in a gene encoding for PDK4, a mitochondrial protein, is associated with the development of dilated cardiomyopathy in the Doberman pinscher. Hum Genet 2012;131:1319-25.

Owczarek-Lipska M, Mausberg TB, Stephenson H, et al. A 16-bp deletion in the canine PDK4 gene is not associated with dilated cardiomyopathy in a European cohort of Doberman Pinschers. Anim Genet 2013;44:239.

Meurs KM, Mauceli E, Lahmers S, et al. Genome-wide association identifies a deletion in the 3' untranslated region of striatin in a canine model of arrhythmogenic right ventricular cardiomyopathy. Hum Genet 2010;128:315-24.

Cattanach BM, Dukes-McEwan J, Wotton PR, et al. A pedigree-based genetic appraisal of Boxer ARVC and the role of the Striatin mutation. Vet Rec 2015;176:492.

Yost O, Friedenberg SG, Jesty SA, et al. The R9H phospholamban mutation is associated with highly penetrant dilated cardiomyopathy and sudden death in a spontaneous canine model Gene 2019;697:118-122.

Leach SB , Briggs M, Hansen L, et al. Prevalence, geographic distribution, and impact on lifespan of a dilated cardiomyopathy-associated RNA-binding motif protein 20 variant in genotyped dogs. J Vet Cardiol 2021;40:119-125

Meurs KM, Friedenberg SG, Kolb J, et al. A missense variant in the titin gene in Doberman pinscher dogs with familial dilated cardiomyopathy and sudden cardiac death. Hum Genet 2019;138:515-524

Philipp U, Vollmar A, Haggstrom J, et al. Multiple Loci are associated with dilated cardiomyopathy in Irish wolfhounds. PLoS One.7(6):e36691.

Kittleson MD, Meurs KM, Munro MJ, et al. Familial hypertrophic cardiomyopathy in maine coon cats: an animal model of human disease. Circulation 1999;99:3172-3180.

Meurs KM, Sanchez X, David RM, et al. A cardiac myosin binding protein C mutation in the Maine Coon cat with familial hypertrophic cardiomyopathy. Hum Mol Genet. 2005 Dec 1;14(23):3587-93.

Meurs KM, Norgard MM, Ederer MM, et al. A substitution mutation in the myosin binding protein C gene in ragdoll hypertrophic cardiomyopathy. Genomics 2007;90:261-264.

Wess G, Schinner C, Weber K, et al. Association of A31P and A74T polymorphisms in the myosin binding protein C3 gene and hypertrophic cardiomyopathy in Maine Coon and other breed cats. J Vet Intern Med 2010;24:527-532.

Meurs KM, Williams BG, DeProspero D, et al. A deleterious mutation in the ALMS1 gene in a naturally occurring model of hypertrophic cardiomyopathy in the Sphynx cat. Orphanet J Rare Dis 2021; 16: 108.

Gil-Ortuño C, Sebastián-Marcos P, Sabater-Molina M, et al.Genetics of feline hypertrophic cardiomyopathy. Clin Genet. 2020 Sep;98(3):203-214

O'Donnell K, Adin D, Atkins CE, DeFrancesco T, Keene BW, Tou S, Meurs KM. Absence of known feline MYH7 and MYBPC3 variants in a diverse cohort of cats with hypertrophic cardiomyopathy. Anim Genet. 2021;52:542-544

Fuentes VL, Abbott J, Chetboul V, Côté E, Fox PR, Häggström J, Kittleson M, Schober K, Stern J. Guidelines for the classification, diagnosis and management of feline cardiomyopathies. J Vet Intern Med 2020;34:1062–1077

Feline cardiomyopathies: prevalence, risk, survival and therapy

Virginia Luis Fuentes DipACVIM, DipECVIM (Cardiology)

Royal Veterinary College, United Kingdom

Prevalence

Cardiomyopathy is extremely common in cats, and hypertrophic cardiomyopathy (HCM) is by far the most common phenotype, affecting around 15% of the general cat population.[1,2] This is much more common than in people, where current best estimates of human HCM prevalence are around 0.2% to 0.5%, with the prevalence of non-ischaemic dilated cardiomyopathy (DCM) probably quite similar.[3] The prevalence of DCM in cats decreased substantially following the discovery of the importance of taurine in commercial cat foods,[4] and this is now considered an uncommon condition. Other cardiomyopathy phenotypes appear to be much less common than HCM in both people and cats, although epidemiological studies of other cardiomyopathy phenotypes in the general cat population have not been reported. The prevalence of other cardiomyopathy phenotypes appears to be higher among cats with cardiac complications such as congestive heart failure (CHF) or arterial thromboembolism (ATE) than in asymptomatic cats.[5]

HCM is more prevalent in male cats, and prevalence also increases with age.[2] HCM is widespread in non-pedigree cats but it is more difficult to establish the prevalence in pedigree cats, as echocardiographic screening for HCM is highly dependent on breeder motivation. Screening is also often limited to younger breeding cats, so can miss cases where HCM develops later in life. Genetic testing is only possible where a causal mutation has already been identified (eg. in Maine coons and Ragdolls), and constitutes a different measure of prevalence as some genotype positive cats have a normal phenotype. Maine coons homozygous for the *MYBPC3* A31P mutation are more likely to have an HCM phenotype than heterozygous cats. Prevalence of the A31P mutation in Maine coons varies geographically, with prevalence reports ranging from 22% to 46%.[6-8] Prevalence of the *MYBPC3* R820W mutation in UK Ragdolls has been reported at around 27%.[9] Genetic testing is also at risk of selection bias, as sampling is difficult to randomize.

Risk and survival

Outcome in cats with HCM is very variable, with some cats remaining asymptomatic throughout a normal lifespan, and others dying at a young age. The most common adverse events associated with cardiomyopathy are CHF, ATE and sudden death (SD). The REVEAL study followed 1008 asymptomatic cats with HCM, and over the study period documented CHF in 24.2%, ATE in 11.6%, and sudden death in 2.2%.[10] A smaller prospective study of first opinion cases of preclinical HCM reported a similar event rate of 31.9% over a median follow-up period of 3.1 years.[11] Cardiac disease is one of the top 10 causes of death in cats.[12,13]

Prognostic factors

A number of factors associated with adverse events have been identified, and fortunately there is probably better inter-observer agreement on which cats are at high risk of CHF /ATE than agreement on phenotypic classification. Cats that have already experienced CHF or ATE are at greatly increased risk of further cardiac events. [13,14,15] Prognosis has been studied mostly in cats with HCM, and some studies of other cardiomyopathy phenotypes have tended to report a particularly poor prognosis.[16,17] There is some overlap in prognostic factors between different cardiomyopathy phenotypes, with left atrial enlargement being an important risk factor in most cardiomyopathies.[14,18]

Among cats with HCM, auscultation of a murmur is not a poor prognostic factor, but presence of a gallop sound or arrhythmia is related to a worse prognosis. Other than previous episodes of CHF or ATE, the majority of other prognostic factors are based on echocardiography. The association of left atrial (LA) size and function with clinical signs has long been recognized as one of the most important prognostic factors, and appears particularly important as a risk factor for ATE.[14,15,19-21] Although systolic dysfunction has not traditionally been associated with HCM, left ventricular (LV) systolic function is an independent predictor of cardiac mortality in cats with HCM, particularly with respect to risk of CHF.[14,15] Extreme LV hypertrophy is also an independent predictor of cardiac death.[15] Other factors associated with increased risk of cardiac mortality include a restrictive diastolic filling pattern, spontaneous echo-contrast, and regional wall motion hypokinesis.[15] Risk factors for sudden death are less well-established, but potentially include presence of arrhythmias and a history of syncope.[15]

Therapy

Prognosis worsens and therapeutic indications change as the severity of cardiomyopathy progresses. For this reason, the ACVIM consensus statement on feline cardiomyopathies proposes a staging system to help guide therapy. As with myxomatous mitral valve disease, stages A, B1, B2, C through to D indicate progression of disease. Stage A indicates cats at risk of developing cardiomyopathy. Stage B indicates cats with subclinical cardiomyopathy, and this is divided into B1 (subclinical cardiomyopathy but no/mild atrial enlargement), and B2 (subclinical cardiomyopathy with moderate/severe atrial enlargement). Stage C indicates the onset of clinical signs (CHF or ATE), and stage D indicates persistence of clinical signs/ CHF despite appropriate therapy.

Stage B1

Many cats remain in this stage for the rest of their lives, and no treatment is indicated. There is still some controversy over management of dynamic LV outflow tract obstruction (DLVOTO), as this can cause myocardial ischaemia and symptoms of chest pain or a sensation of breathlessness in affected people. It is hard to evaluate whether the same occurs in cats. Human symptoms can sometimes be relieved by beta-blockade, and there are anecdotal reports that beta-blockers can prevent or reduce open-mouth breathing associated with exertion in cats. In a prospective study of cats with DLVOTO vs healthy controls, the cats with DLVOTO had poorer quality of life scores. However, there was no effect on quality of life scores or activity levels in cats treated with atenolol 6.25 mg/cat q12h PO.[22] Cats at this stage are considered at low risk for CHF or ATE, but might still progress over time.

Although no treatment is indicated at this stage, they should be monitored with annual echocardiograms.

Stage B2

This stage includes cats with cardiomyopathy (mostly HCM) with significant LA enlargement and/or signs of poor LA function (eg. LA FS% < 24%). Presence of other poor prognostic findings would also be consistent with stage B2, but LA enlargement would be one of the most common findings. Such cats are likely to be at higher risk of CHF or ATE, and clopidogrel is indicated. The evidence base for other antithrombotics is less well-established. Owners should be monitoring resting/ sleeping respiratory rate, and any persistent increase in respiratory rate should be reported to the primary care vet.

Stage C

The onset of clinical signs (such as CHF or ATE) indicates progression to stage C, even if clinical signs resolve with treatment. Signs of CHF should be treated with furosemide to effect at diagnosis. Clopidogrel should be added once the owner is confident about being able to administer medications, as this is often a difficult medication to administer. The evidence base in cats for other CHF treatments is less convincing than in dogs. ACE inhibitors have not been shown to influence outcome[23], and in cats with CHF only a pilot study has been published on the use of spironolactone.[24] Several retrospective studies of pimobendan in cats with CHF have indicated a beneficial effect[25,26], but in a randomised, placebo-controlled study of pimobendan in cats with CHF, there appeared to be different effects on outcome in cats with and without DLVOTO, with better results in cats with non-obstructive HCM.[27] Loop diuretic dose should be titrated to resting/sleeping respiratory rate, and renal function and electrolytes should be checked.

Stage D

For cats with persistent CHF despite appropriate therapy, the first approach is to increase the dose of furosemide, or switch from furosemide to torasemide and titrate to effect. If the cat is not already receiving spironolactone, this can be added. If there is no DLVOTO, it is reasonable to add pimobendan. Renal function and electrolytes should be monitored if diuretic doses are increased.

Future therapies

New treatment options for people with HCM include the myosin inhibitors, such as mavacamten. This is primarily targeted at DLVOTO, but studies are likely to be extended to people with non-obstructive HCM. Mavacamten has been studied in anaesthetized cats with obstructive HCM, but clinical trials in pet cats have not been reported.[28]

1. Paige CF, Abbott JA, Elvinger Fo, Pyle RL. Prevalence of cardiomyopathy in apparently healthy cats. *Journal of the American Veterinary Medical Association.* 2009;234(11):1398-1403.
2. Payne JR, Brodbelt DC, Luis Fuentes V. Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centres (the CatScan study). *Journal of Veterinary Cardiology.* 2015;17, Supplement 1:S244-S257.
3. McKenna WJ, Maron BJ, Thiene G. Classification, Epidemiology, and Global Burden of Cardiomyopathies. *Circ Res.* 2017;121(7):722-730.
4. Pion PD, Kittleson MD, Rogers QR, Morris JG. Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. *Science.* 1987;237:764-768.
5. Ferasin L, Sturgess CP, Cannon MJ, Caney SMA, Gruffydd-Jones TJ, Wotton PR. Feline idiopathic cardiomyopathy: a retrospective study of 106 cats (1994-2001). *Journal of Feline Medicine & Surgery.* 2003;5(3):151-159.
6. Wess G, Schinner C, Weber K, Kuchenhoff H, Hartmann K. Association of A31P and A74T polymorphisms in the myosin binding protein C3 gene and hypertrophic cardiomyopathy in Maine Coon and other breed cats. *J Vet Intern Med.* 2010;24(3):527-532.
7. Fries R, Heaney AM, Meurs KM. Prevalence of the Myosin-Binding Protein C Mutation in Maine Coon Cats. *Journal of Veterinary Internal Medicine.* 2008;22(4):893-896.
8. Mary J, Chetboul V, Sampedrano CC, et al. Prevalence of the MYBPC3-A31P mutation in a large European feline population and association with hypertrophic cardiomyopathy in the Maine Coon breed. *Journal of Veterinary Cardiology.* 2010;12(3):155-161.
9. Casamian-Sorrosal D, Chong SK, Fonfara S, Helps C. Prevalence and demographics of the MYBPC3-mutations in ragdolls and Maine coons in the British Isles. *J Small Anim Pract.* 2014;55(5):269-273.
10. Fox PR, Keene BW, Lamb K, et al. International collaborative study to assess cardiovascular risk and evaluate long-term health in cats with preclinical hypertrophic cardiomyopathy and apparently healthy cats: The REVEAL Study. *J Vet Intern Med.* 2018;32(3):930-943.
11. Ironside VA, Tricklebank PR, Boswood A. Risk indictors in cats with preclinical hypertrophic cardiomyopathy: a prospective cohort study. *J Feline Med Surg.* 2020:1098612X20938651.
12. Egenvall A, Nodtvedt A, Haggstrom J, Strom Holst B, Moller L, Bonnett BN. Mortality of life-insured Swedish cats during 1999-2006: age, breed, sex, and diagnosis. *J Vet Intern Med.* 2009;23(6):1175-1183.
13. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Longevity and mortality of cats attending primary care veterinary practices in England. *J Feline Med Surg.* 2015;17:125-133.
14. Payne JR, Borgeat K, Connolly DJ, et al. Prognostic Indicators in Cats with Hypertrophic Cardiomyopathy. *Journal of Veterinary Internal Medicine.* 2013;27(6):1427-1436.
15. Payne JR, Borgeat K, Brodbelt DC, Connolly DJ, Luis Fuentes V. Risk factors associated with sudden death vs. congestive heart failure or arterial thromboembolism in cats with hypertrophic cardiomyopathy. *Journal of Veterinary Cardiology.* 2015;17, Supplement 1:S318-S328.
16. Locatelli C, Pradelli D, Campo G, et al. Survival and prognostic factors in cats with restrictive cardiomyopathy: a review of 90 cases. *J Feline Med Surg.* 2018;20(12):1138-1143.
17. Karp SI, Freeman LM, Rush JE, et al. Dilated cardiomyopathy in cats: survey of veterinary cardiologists and retrospective evaluation of a possible association with diet. *J Vet Cardiol.* 2022;39:22-34.
18. Chetboul V, Passavin P, Trehiou-Sechi E, et al. Clinical, epidemiological and echocardiographic features and prognostic factors in cats with restrictive cardiomyopathy: A retrospective study of 92 cases (2001-2015). *Journal of Veterinary Internal Medicine.* 2019;33(3):1222-1231.

19. Linney CJ, Dukes-McEwan J, Stephenson HM, Lopez-Alvarez J, Fonfara S. Left atrial size, atrial function and left ventricular diastolic function in cats with hypertrophic cardiomyopathy. *J Small Anim Pract.* 2014;55(4):198-206.
20. Smith S, Dukes-McEwan J. Clinical signs and left atrial size in cats with cardiovascular disease in general practice. *Journal of Small Animal Practice.* 2012;53(1):27-33.
21. Rush JE, Freeman LM, Fenollosa NK, Brown DJ. Population and survival characteristics of cats with hypertrophic cardiomyopathy: 260 cases (1990-1999). *Journal of the American Veterinary Medical Association.* 2002;220(2):202-207.
22. Coleman AE, DeFrancesco TC, Griffiths EH, et al. Atenolol in cats with subclinical hypertrophic cardiomyopathy: a double-blind, placebo-controlled, randomized clinical trial of effect on quality of life, activity, and cardiac biomarkers. *J Vet Cardiol.* 2020;30:77-91.
23. King JN, Martin M, Chetboul V, et al. Evaluation of benazepril in cats with heart disease in a prospective, randomized, blinded, placebo-controlled clinical trial. *J Vet Intern Med.* 2019.
24. James R, Guillot E, Garelli-Paar C, Huxley J, Grassi V, Cobb M. The SEISICAT study: a pilot study assessing efficacy and safety of spironolactone in cats with congestive heart failure secondary to cardiomyopathy. *J Vet Cardiol.* 2018;20(1):1-12.
25. Hambrook LE, Bennett PF. Effect of pimobendan on the clinical outcome and survival of cats with non-taurine responsive dilated cardiomyopathy. *Journal of Feline Medicine and Surgery.* 2012;14(4):233-239.
26. Reina-Doreste Y, Stern JA, Keene BW, et al. Case-control study of the effects of pimobendan on survival time in cats with hypertrophic cardiomyopathy and congestive heart failure. *Journal of the American Veterinary Medical Association.* 2014;245(5):534-539.
27. Schober KE, Rush JE, Luis Fuentes V, et al. Effects of pimobendan in cats with hypertrophic cardiomyopathy and recent congestive heart failure: Results of a prospective, double-blind, randomized, nonpivotal, exploratory field study. *Journal of Veterinary Internal Medicine.* 2021;35(2):789-800.
28. Stern JA, Markova S, Ueda Y, et al. A Small Molecule Inhibitor of Sarcomere Contractility Acutely Relieves Left Ventricular Outflow Tract Obstruction in Feline Hypertrophic Cardiomyopathy. *Plos One.* 2016;11(12):e0168407.

Cardiac biomarkers in dogs and cats

Jens Häggström, DVM, PhD, DECVIM-CA (Cardiology)

Professor Internal Medicine, Companion Animals

Swedish University of Agricultural Sciences, Uppsala, Sweden.

Biomarkers are commonly regarded as a biochemical characteristic that can be used to measure the progress of disease or the effects of treatment. However, the biomarker concept is much broader and refers to a physical, functional, or biochemical indicator (e.g. the presence of a particular metabolite) of a physiological or disease process. This broader definition includes most of the diagnostic methods we currently use in veterinary medicine from cardiac auscultation to measurement of specific molecules in body fluids. This document is aimed at reviewing the current knowledge that is relevant in the clinical setting of commonly used cardiac biochemical biomarkers in dogs and cats. An update on genetic tests in dogs and cats is presented in a separate presentation.

Much research has been conducted in veterinary medicine concerning different cardiac biomarkers, especially concerning the natriuretic peptides (NP) and the cardiac troponins, which both represent cardiac specific molecules that can be measured in blood. Once it was established that these substances could be measured reliably in dogs and cats, much focus was placed on how the concentrations were changed with different types of heart disease and then how severity of disease impacted test results. Many of these studies included only dogs and cats with heart disease and the result was contrasted against normal healthy dogs. Accordingly, these biomarkers performed remarkably well to identify dogs and cats with heart disease, because the populations of comparison were very different. The reality in the clinical setting is that dogs and cats that are likely to be tested present some form abnormal clinical signs and are suspected of having disease. Many of them turn out to have disease, not only cardiac, and some might event have multiple disease. Many of non-cardiac disease may impact cardiac health and thereby biomarkers, which inevitably means that these tests perform less well in the clinical setting, compared to the studies. Furthermore, the clinician is usually not restricted to have to make decisions based on one laboratory result. Usually, much more is known about the patient and information concerning the case history and findings at the physical examination is available. The information is often obtained starting with the case history and then moving on to physical examination findings and along this journey of gathering

information, the clinician makes several decisions to proceed with cardiac working diagnosis or to change direction. The decision of biochemical testing of a biomarker is often taken at a stage comparably far into this process, the exception being emergencies. Information obtained from the analysis of the cardiac biochemical biomarker may accordingly often be regarded as “add-on” information, and these tests may be particularly useful at sites where echocardiography and cardiology expertise are not available. Comparably many recent studies have studied the add-on value of the cardiac biomarkers in this setting.

The most commonly used cardiac biomarkers used in dogs and cats are N-terminal pro B-type natriuretic peptide (NT-proBNP) and cardiac specific Troponin I (cTnI). The NT-proBNP is released in response to cardiac volume expansion and pressure overload, i.e. in response to myocardial stretch. Therefore, NT-proBNP is likely to be increased in any form of cardiac or non-cardiac condition leading to myocardial stretch. The release of cTnI into the blood is different than NT-proBNP, because cTnI is a leakage marker, meaning that its concentration in blood reflects myocardial cell integrity. Therefore, cTnI is expected to be increased in any condition leading to myocyte injury because of cardiac or non-cardiac disease. Furthermore, cTnI leakage does not necessarily reflect myocyte death, because, although most cTnI within the myocyte is bound to the troponin complex, there is also a pool of non-bound cTnI in the cytoplasm (approximately 5%) that can leak.

Both NT-proBNP and cTnI have been shown to be increased in dogs with myxomatous mitral valve disease (MMVD) and dilated cardiomyopathy (DCM) when dogs have reached the clinical phase of the disease, i.e. American College of Veterinary Medicine (ACVIM) MMVD consensus statement stage C. Some, but not all, dogs in the preclinical phase (ACVIM stage B) of MMVD or DCM have increased NT-prBNP or cTnI concentrations. Dogs that are more likely than others at stage B are the ones that are classified as ACVIM stage B2, meaning that they have the disease and they have increased cardiac size in response to impaired cardiac function but they have no current or previous history or signs of congestive heart failure (CHF). Likewise, most cats with feline cardiomyopathy have increased NT-proBNP and cTnI concentrations when they have reached the clinical phase of the disease (ACVIM stage C), some, but not all cats in the preclinical phase have increased concentrations of the biomarkers, and of these cats, the ones with left atrial dilatation (Stage B2) are more likely than the ones without (stage B1) to have increased biomarkers concentrations. In dogs, the NT-proBNP test is not as reliable is it is in cats owing the potential breed differences and other factors leading to false positive test results. In cats, the likelihood for false positive test is less, and

there seems to be little influence of breed and sex. Furthermore, a point-of-care (POC) test is available for emergencies and other situations. This POC test leads to binary results, i.e. positive or negative, and is limited unfortunately limited by the comparably low NT-proBNP threshold at which the test becomes positive, leading to false positive test results. In both dogs and cats, the value of the test lies in making the diagnosis of significant heart disease much less likely by a negative test, and in to consider heart disease in test positive patients. The cTnI test does not appear to be limited by effect of breed or gender in dogs and cats. The amino acid sequence of cTnI is conserved over mammalian species, which means that many (most) human tests can be used in dogs and cats. Because the test to large extent has been developed for use in people to assess presence and severity of coronary artery disease and presence and severity of myocardial infarcts, the test has been refined and improved and is now available as a high-sensitivity assay. The test is, however, limited by the fact that many systemic or organ related diseases have an impact on the myocardium leading to cTnI leakage and increased test results. In addition to assessment of different cardiac disease, cTnI has proven a valuable test for making the diagnosis of myocarditis more or less likely and as a compliment test to echocardiography in identifying cardiac tumours in cases of pericardial effusion. Furthermore, the test is also valuable in monitoring treatment including cardiac toxic drugs, i.e. doxorubicin, and identifying doxorubicin induced cardiomyopathy.

So, how are these tests most commonly used in veterinary practise? A recently published large study from the UK for reasons to test for NT-proBNP showed that presence of a heart murmur and/or cough were the most common reasons in dogs, and presence of a heart murmur, suspected thromboembolism and/or weight loss the most common reasons in cats. Dyspnea and/or tachypnea were infrequently recorded as reasons for testing in both species. This is suggestive that a large proportion of NT-proBNP testing is performed in dogs and cats with heart murmurs in the preclinical phase (Stage B), most likely aiming at aid in staging the animal for diagnostic (referring the animal for echocardiography), therapy and prognostic reasons. In dogs, there is a large proportion of old dogs with or without heart murmurs that presents with coughing and it appears as if testing is performed to aid in differentiating between cardiac or non-cardiac reasons for coughing (i.e. tracheobronchial instability). In cats, the test is used partly to differentiate motion disturbances and weight loss from thromboembolism caused by cardiac disease from non-cardiac disease. Similar data on how the cTnI test is used in the general veterinary practise is currently not available. A master thesis investigated the reasons for cTnI testing over a 3-year period at a academic teaching hospital (where cardiac expertise was available) in Sweden and the majority of tests were performed in dogs and cats with non-cardiac disease, such as snake bite, gastric torsion, pyometra.

So, what is the add-on value of the NT-proBNP test to signalment and physical findings I predicting stage in dogs and cats with preclinical disease? Some publications have addressed this question recently, particularly in dogs with MMVD. The HAMLET study investigated prospectively the value of combined case history, signalment and NT-proBNP variables in distinguishing MMVD stage B1 from stage B2 in a large number of dogs. The study found that NT-proBNP was the strongest predictor, but prediction was most accurate when combining this test with information on the dog's appetite, body condition score (BCS), creatinine concentration, murmur intensity, and NT-proBNP concentration. Appetitite, BCS and creatinine, a loss of appetite, decreased BCS and creatinine concentration are all likely to reflect cardiac cachexia in development and a low intensity murmur makes stage B2 unlikely, whereas a loud thrilling murmur stage B2 more likely. The results of the analysis in the HAMLET study showed that the NT-proBNP alone was a slightly more powerful predictor than VHS alone, but the combination of the above mentioned variables provided the best prediction. Recently a study including cavaliers only was presented and the results showed that although NT-proBNP is a powerful predictor to distinguish ACVIM stage B2 from Stage A and B1 dogs, murmur intensity, presence of cough, radiographic heart size (vertebral heart score), ECG PQRS duration and murmur intensity could generate prediction models without NT-proBNP that performed marginally less well compared to have NT-proBNP included. In a comparably large group of Dobermann dogs, both NT-proBNP and cTnI had good clinical utility as the only diagnostic tests for discriminating between preclinical DCM (Stage B2) and all other dogs (Normal, MMVD and Stage B1), with NTproBNP slightly outperforming cTnI. Prediction models performed best using the combination of physical exam findings (murmur, arrhythmia) and biomarker result. However, the increase in discriminatory ability derived from the use of both biomarkers was marginal. It was concluded that, screening for preclinical DCM in the Dobermanns should likely include a thorough physical examination, 3-min ECG and NT-proBNP to provide the best determination of dogs most likely to benefit from advanced diagnostic tests such as an echocardiogram and Holter evaluation. Similar studies to these in MMVD and DCM dogs are currently not available in cats, but considering the available literature, the NT-proBNP and the cTnI tests are useful test in cats presenting with a moderate to loud murmur and/or with physical examination findings indicative of CHF to identify significant feline cardiomyopathy (stages B2 and C).

The overall impression in the current veterinary literature is that information from the case history and physical examination can allow a comparably accurate prediction of stage B2 versus stage B1 in

dogs with MMVD, and to some extent in dogs with DCM and in cats with feline cardiomyopathy. Auscultation in particular is useful in this context and adding findings from thoracic radiography increases the prediction performance further. There is currently a problem with many clinicians feeling uncertain when interpreting auscultatory and radiographic findings. In the case of thoracic radiography, there are currently automated systems to aid the clinician when measuring heart size (VHS) under evaluation. Likely, these systems will be available to the public the near future. As for auscultation, there are also systems in development that analyzes heart sounds and murmurs in dogs digitally. These systems will also be available to the public in the near future. It remains to evaluate how these automated systems perform in a mixed population of dogs prospectively.

In summary, the cardiac biomarkers NT-proBNP and cTnI are useful in dogs and cats in detecting significant acquired preclinical disease from normal or less diseased individuals. In the case of cTnI, the test is also very useful for assessing severity of cardiac damage in non-cardiac disease and for assessing presence of cardiac tumors and/or myocarditis. The predictive performance of these biomarkers increases if information from case history and physical examination is included in the prediction. Auscultatory findings are of particular value for this purpose.

Selected references

Keene BW, Atkins C, Bonagura JD, et al. ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. J Vet Intern Med 2019;33:1127-1140

Fuentes VL, Abbott J, Chetboul V, et al. Guidelines for the classification, diagnosis and management of feline cardiomyopathies. J Vet Intern Med 2020;34:1062–1077.

Oyama MA, Boswood A, Connolly DJ, et al. Clinical usefulness of an assay for measurement of circulating N-terminal pro-B-type natriuretic peptide concentration in dogs and cats with heart disease. J Am Vet Med Assoc. 2013;243:71-82.

Hertzsch S, Roos A, Wess G. Evaluation of a sensitive cardiac troponin I assay as a screening test for the diagnosis of hypertrophic cardiomyopathy in cats. J Vet Intern Med. 2019;33:1242-1250.

O'Shaughnessy S, Crawford I, Arsevska E, et al. Clinical findings associated with N-terminal pro-B-type natriuretic peptide measurement in dogs and cats attending first opinion veterinary practices. Vet Rec. 2022;191:e945.

Sidsten A. Clinical use of Troponin I in dogs and cats. Master of Science Thesis Swedish University of Agricultural Sciences, 2012, Uppsala, Sweden.

Wilshaw J, Rosenthal SL, Wess G, et al. Accuracy of history, physical examination, cardiac biomarkers, and biochemical variables in identifying dogs with stage B2 degenerative mitral valve disease. J Vet Intern Med. 2021;35:755-770

Gordon SGG, Wesselowski S, Estrada AH, et al. Prospective evaluation of the combined value of physical examination, electrocardiographic and biomarker variables in screening for preclinical dilated cardiomyopathy in Doberman Pinschers. J Vet Cardiol 2022:40:69-83.

Wesselowski SR, Gordon SGG. Prediction of Stage B2 Mitral Valve Disease in Cavaliers with Longitudinal Follow-Up (abstract). 2022 ACVIM Hybrid Forum, 21-25 June, Austin TX.

Dilated cardiomyopathy in different dog breeds: diagnosis and therapy

Affiliations: Clinic for small animal medicine, LMU university, Munich, Germany

Qualifications: Gerhard Wess, Dipl. ACVIM/ECVIM-CA (Cardiology), Dipl. ECVIM-CA 8Internal Medicine); gwess@lmu.de

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. In most cases DCM is a genetic disease, even if the disease has a slow onset and is usually detected later in life, 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. Here is a suggested staging for DCM (1):

Stage A is characterized by a morphologically and electrically normal heart and no evidence of clinical signs of heart disease. Dogs in this stage have only a high predisposition to develop DCM, such as Doberman Pinscher, Irish Wolfhound, Great Dane or other predisposed breed).

Stage B 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. Stage B1 include dogs with electrical abnormality supposedly caused by DCM. This arrhythmogenic stage without cardiac enlargement includes ventricular premature contractions (VPCs) in certain breeds such as Doberman Pinschers or Boxers, or atrial fibrillation in other breeds such as Irish Wolfhound or other giant breeds.

Stage B2 include dogs without symptoms, but cardiac enlargement detectable on echocardiography. The morphologic and electrical abnormalities may coexist in stage B2.

Stage C is characterized by the previous or acute presence of clinical signs of heart failure and is referred to as the overt stage of DCM. Stage D refers to dogs with end-stage DCM, in which clinical signs of heart failure are refractory to standard treatment.

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 oedema or ascites and pleural effusion, respectively, is

comparatively easy, this is only the tip of an iceberg, as the recognition of the recognition of the occult phase of the disease (stage B1 and B2) is challenging.

Dog Breeds with a known prevalence to develop DCM:

Doberman Pinschers are one of the most commonly affected breeds (prevalence 58%).(2) DCM in this breed is an inherited, slowly progressive primary myocardial disease. The occult stage of the disease is characterized by evidence of morphologic or electrical derangement in the absence of clinical signs of heart disease. The morphologic abnormality consists of LV enlargement in systole and later in diastole. VPCs are a common finding in the occult phase of DCM in Doberman Pinschers. Sudden death, caused by ventricular tachycardia/-fibrillation, occurs during the occult phase in at least 25 to 30% of affected dogs. These abnormalities, morphologic or electrical, can coexist or can be of predominantly one form at any time during this occult stage.

Irish Wolfhounds

In Irish Wolfhounds, the incidence of DCM reaches approximately 24%. Irish Wolfhounds often develop atrial fibrillation, which can be detected sometimes years before the dogs develop the classical DCM type with systolic dysfunction. However, not all dogs with atrial fibrillation will develop the classical DCM.

Boxer dogs

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a familial primary myocardial disease in the boxer dog, characterized by the progressive replacement of ventricular myocardium (primarily right ventricular myocardium) with fatty or fibrofatty tissue which leads to right ventricular failure, arrhythmias and sudden cardiac death.

The disease therefore shows a variable clinical picture with a long occult phase of the disease, in which the dogs appear to be unremarkable to their owners, but despite this the affected dogs have usually ventricular arrhythmias, which can lead to syncope or sudden cardiac death.

Great Danes

A recent study reported a prevalence of 35.9% for DCM and suspects an autosomal dominant mode of inheritance. In the pre-clinical phase Great Danes can have ventricular arrhythmias. Similar to Irish

Wolfhounds some Great Danes develop atrial fibrillation before they develop the classical DCM type, but this appears less common compared to ventricular arrhythmias.

Cocker Spaniels

A special feature of DCM in Cocker Spaniels is that many affected dogs have a taurine-induced cardiomyopathy, which is potentially reversible. The clinical picture is that of a classical DCM.

Besides the breeds already described above, other breeds commonly affected were German Shepherd, Saint Bernard, Labrador, Golden Retriever, Newfoundland and Old English Sheepdog.

Diagnosis:

The disease can be detected by cardiac ultrasound or/and by a 24-hours-ECG. On ultrasound the cardiologist will detect that heart is too large and not pumping sufficiently. Additionally, arrhythmias, specifically ventricular premature complexes (VPCs) are a common finding in the occult stage of DCM in Dobermans. These can be detected by a 24-hours-ECG (Holter monitoring), or sometimes by a short time ECG.

In House-ECG

An in-house ECG cannot be used to replace a Holter examination. However, if at least 1 VPC is detected during the ultrasound or an in-house ECG, this is highly suggestive that there will be more VPCs recorded in 24 hours if a Holter is performed. Therefore, one or more VPCs are detected, the dogs should get a Holter ECG.

Holter Criteria

It is essential that the Holter recording be of sufficient duration (at least 20 hours of readable recording), good quality and have an accurate analysis verified by a cardiologist. Holter reports generated by automated Holter analysis software are notoriously inaccurate and manual adjustments are always necessary. Inaccurate Holter reports can lead to both false positive and false negative results both of which can have a significant negative impact on breeders and pet owners.

Fewer than 50 single VPCs in 24 hours is considered to be normal in Dobermans and other breeds.(2)

Echocardiography:

There are now several ultrasound parameters established, which allow an earlier diagnosis and on which the disease is diagnosed. The preferred echocardiographic method by the author is the measurement of the left ventricular volume by Simpson's method of discs (SMOD), which basically measures the size of the heart during the filling and the pumping phase. Reference ranges have been published now for several breeds and studies using allometric scaling enabling to use this method all breeds are under print. M-mode measurements can also be used if SMOD is not feasible, but it should be combined with EPSS measurements, as this is a very good parameter to detect systolic dysfunction.(3)

Alternative screening tests

When Holter and/or echocardiography are not available, or an owner wants to first have other tests performed, in order to be more convinced that further examinations (Holter, echocardiography) are necessary, a combination of the following tests should be performed. However, it should be emphasized that these tests are not validated as sole screening tests, do not represent the gold standard screening tests and cannot be used to establish a diagnosis with which to make recommendations to begin treatment.

Clinical examination:

A veterinarian could hear a systolic murmur with a stethoscope over the left side of the thorax, indicating that one of the heart valves is not closing properly – this could be because the heart is enlarged, but there are also other underlying diseases being responsible for the murmur. Also, an audible gallop sound on auscultation could be heard, the pulse quality could be weak. An arrhythmia or pulse deficits are all suspicious findings and represent a strong indication to proceed with additional tests.

Biomarker (blood tests):

- NTproBNP result > 500 pmol/L (for Dobermans to predict cardiac enlargements); > 900 pmol/l in other large breed dogs
- cTnI > 0.22 ng/mL (first generation) or > 0.113 ng/ml using a high-sensitivity cTNI test) (4)

- ECG: 1 VPC/5 minutes (or more) or atrial fibrillation are considered abnormal

Treatment

There are now different drugs available, which are prescribed to delay the onset of heart failure and prevent the sudden cardiac death. Not all arrhythmias need to be treated. The chosen drug depends on the Holter and echocardiographic results and will be discussed during the lecture, as well as new and future directions concerning treatment such as aptamer treatments.(5)

1. Wess G. Screening for dilated cardiomyopathy in dogs. J Vet Cardiol. 2022;40:51-68.
2. Wess G, Domenech O, Dukes-McEwan J, Haggstrom J, Gordon S. European Society of Veterinary Cardiology screening guidelines for dilated cardiomyopathy in Doberman Pinschers. J Vet Cardiol. 2017;19(5):405-15.
3. Holler PJ, Wess G. Sphericity index and E-point-to-septal-separation (EPSS) to diagnose dilated cardiomyopathy in Doberman Pinschers. J Vet Intern Med. 2014;28(1):123-9.
4. Kluser L, Maier ET, Wess G. Evaluation of a high-sensitivity cardiac troponin I assay compared to a first-generation cardiac troponin I assay in Doberman Pinschers with and without dilated cardiomyopathy. J Vet Intern Med. 2019;33(1):54-63.
5. Werner S, Wallukat G, Becker NP, Wenzel K, Muller J, Schimke I, et al. The aptamer BC 007 for treatment of dilated cardiomyopathy: evaluation in Doberman Pinschers of efficacy and outcomes. ESC Heart Fail. 2020.

Arrhythmic-induced cardiomyopathy: diagnosis, assessment and treatment

Roberto A. Santilli DMV, PhD, D.E.C.V.I.M.-C.A. (Cardiology)

Adjunct Professor of Cardiology - Cornell University – Cardiology Department – New York - USA

Clinica Veterinaria Malpensa – Samarate – Varese – Italy

Introduction

The presence of uncontrolled tachycardias, either supraventricular or ventricular, can induce an impairment of left ventricular (LV) function defined tachycardia-induced cardiomyopathy (TICM). Tachycardia-induced cardiomyopathy is characterized by different degree of chambers dilation with systolic and diastolic ventricular dysfunction and congestive heart failure. Systolic dysfunction is usually transitory with complete recovery after controlling the rhythm disorder. Lately the term TICM has been modified to arrhythmia-induced cardiomyopathy (AIC) to include atrial and / or ventricular dysfunction secondary to rapid, asynchronous or irregular rate that can be completely or partially reversible after treatment of causative arrhythmia. In AIC should also be included cardiomyopathies caused by asynchronous myocardial contraction, resulting from premature ventricular contractions (PCV) or right apical ventricular pacing, that can lead to a completely or partially reversible myocardial dilatation and symptoms of congestive heart failure.

Arrhythmia-induced cardiomyopathy may finally be divided in a pure form in which ventricular dysfunction is present in normal hearts and is characterized by a complete recovery, and in an impure form in which ventricular dysfunction is present in patients with underlining cardio-structural disease, for whose recovery is often incomplete.

Rate-dependent changes

Several experimental studies have investigated the pathogenesis AIC during of rapid, asynchronous or irregular pacing.These experiments have provided valuable information on the effects of rapid atrial or ventricular stimulation, resulting in systolic and diastolic dysfunction. The systolic and diastolic dysfunction was more pronounced when induced by ventricular pacing, while its severity was linked to the duration of tachyarrhythmias. A pacing continues with more than 240 beats / min for 3 weeks induced a decrease in cardiac output, a dilation of the left ventricle, reduced systolic

function and diastolic dysfunction, and neurohumoral abnormalities similar to those present in the course of human dilated cardiomyopathy. After the cessation of stimulation, there has been a rapid recovery of systolic function, and diastolic function remained abnormal. Rapid, irregular or asynchronous pacing induces changes in myocardial structure and function, neurohumoral disorders, and changes at the microscopic level, with depletion of energy reserves (creatine phospho-creatine and adenosine triphosphate) and myocardial ischemia. They also highlighted lower levels of Na - K activity - ATPase, as a result of increased activity of the enzymes of the Krebs cycle. Ischemia is induced by structural and functional alterations of the capillary network of the myocardium, with impaired blood flow reserve. A form of myocardial hibernation may be the reason why these changes are partially or fully reversible after termination of the arrhythmia. Other assumptions include a decrease in the density of B-receptors, the occurrence of an oxidative stress, which contributes to myocardial damage through an imbalance between pro- and anti -oxidants and a decrease in the density of the T-tubules and L - Ca channels, which contribute to the coupling abnormality. The myocardial hypertrophy in the course of rapid stimulation seems to be associated with activation of some mechanosensors (Icirc). Once developed AIC induces an electrical remodelling of ion channels (Ito, Ikr, Iks and Ca2 +) that promotes ventricular arrhythmias.

Asynchronous contraction

The asynchronous contraction of the myocardium as in the case of bundle branch block or right ventricular pacing alters the normal activation of the myocardium by the His- Purkinje system. During asynchronous contraction workload is redistributed with loss of contractile strength. During right ventricular pacing adrenergic innervation of the ventricle is altered in the vast majority (89.7%) of patients particularly in regional area of the lower portion (92.3%) and apical portion (38.5%) of the LV wall. Myocardial perfusion defects have been proven in up to two thirds of patients with chronic right ventricular apical pacing. The same mechanisms seem to be the cause of PVC-induced cardiomyopathy. The number of PVC, expressed as a percentage of PVC on the total number of QRS complexes or as a sum PVC per day are used as criteria to define cardiomyopathy PVC - induced. Many studies have identified the percentage of ectopies that can induce the PVC-induced cardiomyopathy (> 24% or > 20% if LV originating PCV and > 10 if right ventricular originating PCV), or the prevalence of cardiomyopathy related to the absolute number: 1000/24 hours (4%), 1000-10 000/24 hours (12%), and >10000/24 10 hours (34%). Another cause of asynchrony is atrial fibrillation which induces a loss of atrial contraction and a reduction of 15 - 20% of the cardiac output with a concomitant alteration of LV filling times. It has been shown that even a sequence of irregular RR

intervals has the hemodynamic consequences independently of heart rate. Implicated mechanisms are alterations of myofibers length and the force of contraction relationship.

Atrial myopathy

During incessant tachycardias also the atrium remodels electrically and anatomically. During the high rates an alteration of calcium handling occurs, which induces a deficiency of L-type channels, together with phenomena of apoptosis, cell death and inflammatory infiltration.

Diagnosis of arrhythmia-induced cardiomyopathy

The hemodynamic changes begin as early as 24 hours post-stimulation at rapid rates with a decrease in blood pressure and cardiac output and increased in right atrial and wedge pressure. These variations will last for at least 3 weeks, and the size of the left ventricle remain altered with a slow reverse remodelling which can last 3 months.

A definitive diagnosis of AIC is difficult. The suspected diagnosis can only be confirmed by a normalization or improvement of impaired LV function after the control of tachyarrhythmias. However, it is also true that the tachyarrhythmia control does not always contribute to the improvement of left ventricular function in patients with AIC, and may simply reflect the irreversible stage of a pure AIC or an impure AIC. Some authors have proposed the following criteria for the diagnosis of AIC: 1) dilation or heart failure, 2) chronic cardiac arrhythmias or very frequent with incessant behaviour emphasizing the concept that if chronic tachycardia is not constant but lasts more than 10-15% of the day, with an atrial rate of over 150% of that expected for age, may also cause AIC.

The echocardiographic data obtained in humans with AIC have shown that LV cavitary diameters are smaller than in the case of dilated cardiomyopathy, and rhythm control induced an improvement of at least 15% compared to 5% in the case of dilated cardiomyopathy.

Treatment

The basic concept for the treatment of AIC is heart rate and asynchrony control respectively with antiarrhythmic drugs, ablation techniques and re-sinchronization therapy with biventricular pacemaker. The most common antiarrhythmic drugs used for supraventricular tachycardias are

diltiazem, verapamil, digoxin and sotalol, for ventricular sotalol and amiodarone. The advent of radiofrequency catheter ablation in veterinary medicine allowed to control permanently many rhythm disturbances both supraventricular (focal atrial tachycardia, typical and atypical atrial flutter, and bypass tract-mediated tachycardia) and ventricular tachycardias.

Reference

1- Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol* 1997;30:1039 – 1045.
2- Chugh SS, Shen WK, Luria DM, et al. First evidence of premature ventricular complex-induced cardiomyopathy: a potentially reversible cause of heart failure. *J Cardiovasc Electrophysiol* 2000;11:328 –329.
3- Coleman HN, Taylor RR, Pool PE, et al. Congestive heart failure following chronic tachycardia. *Am Heart J* 1971;81:790-798.
4- Cruz F, Cheriex E, Smeets JL, et al. Reversibility of tachycardia induced cardiomyopathy after cure of incessant supraventicular tachycardia. *J Am Coll Cardiol* 1990;16:739-744.
5- Fenelon G, Wijns W, Andries E, et al. Tachycardiomyopathy:mechanisms and clinical implications. *PACE* 1996;19:95-106.
6- Gallagher JJ. Tachycardia and cardiomyopathy:the chicken-egg dilemma revisited. *J Am Coll Cardiol* 1985;6:1172 – 1173.
7- Hanna N, Cardin s, Leung TK, Nattel S. Differences in atrial versus ventricular remodeling in dogs with ventricular tachypacing-induced congestive heart failure. *Cardiovasc Res* 2004;63:236–244.
8- Kanei Y, Friedman M, Ogawa N, et al. Frequent premature ventricular complexes originating from the right ventricular outflow tract are associated with left ventricular dysfunction. *Ann Noninvasive Electrocardiol* 2008;13:81–85.
9- Khasnis A, Jongnarangsin K, Abela G, et al. Tachycardia-induced cardiomyopathy: a review of literature. *Pacing Clin Electrophysiol* 2005;28:710 –721
10- Jeong YH, Choi KJ, Song JM, et al. Diagnostic approach and treatment strategy in tachycardia-induced cardiomyopathy. *Clin Cardiol* 2008; 31:172 – 178.
11- Moe GW, Stopps TP, Angus C, et al. Alterations in serum sodium in relation to atrial natriuretic factor and other neuroendocrine variables in experimental pacing-induced heart failure. *J Am Coll Cardiol* 1989;13: 173 –9-34.
12- Olgun H, Yokokawa M, Baman T, et al. The role of interpolation in PVC-induced cardiomyopathy. *Heart Rhythm* 2011;8:1046 –1049.
13- Packer DL, Bardy GH, Worley SJ, et al. Tachycardia-induced cardiomyopathy: a reversible form of LV dysfunction. *Am J Cardiol* 1986;57:563-570.
14- Prinzen FW, Hunter WC, Wyman BT, et al. Mapping ofregional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol 1999;33:1735 – 1742.*
15- Rakovec P, Lajovic J, Dolenc M. Reversible congestive cardiomyopathy due to chronic ventricular tachycardia*. PACE*, 1989;12:542-545.
16- Santilli RA, Bontempi LV, Perego M *et al*. Outflow tract segmental arrhythmogenic right ventricular cardiomyopathy in an English Bulldog. *J of Vet Cardiol* 2009;11:47-51.
17- Santilli RA, Spadacini GM, Moretti P. et al. Radiofrequency catheter ablation of concealed accessory pathways in two dogs with symptomatic atrioventricular reciprocating tachicardia. *J Vet Cardiol* 2006;8:157-165.

18- Santilli RA, Spadacini GM, Moretti P et al. Anatomic distribution and electrophysiologic properties of accessory atrioventricular pathways in dogs. *J Am Vet Med Assoc*. 2007;231(3):393-398.
19- Santilli RA, Perego M, Perini A, et al. Radiofrequency catheter ablation of cavo-tricuspid isthmus as treatment of atrial flutter in two dogs. *J Vet Cardiol* 2010;12:59-66.
20- Santilli RA, Perego M, Perini A, et al. Electrophysiologic characteristics and topographic distribution of focal atrial tachycardias in dogs. *J Vet Intern Med* 2010;24:539-545.
21- Santilli RA, Bontempi LV, Perego M. Ventricular tachycardia in English bulldogs with localized right ventricular outflow tract enlargement. *J Small Animal Pract* 2011;52(11):574-80.
22- Santilli RA, Santos LFN, Perego M. Permanent junctional reciprocating tachycardia in a dog. *J Vet Cardiol* 2013;15:225-230.
23- Santilli RA, Ramera L, Perego M, et al. Radiofrequency catheter ablation of atypical atrial flutter in five dogs. *J Vet Cardiol* 2014;16:9-17.
24- Santilli RA, Mateos Panero M, Porteiro Vazquez DM, Perini A, Perego M. Radiofrequency catheter ablation of accessory pathways in the dog: the Italian experience (2008-2016). J Vet Cardiol 2018;20;384-397.
25- Battaia S, Perego M, **Santilli R.** Radiofrequency catheter ablation of cranial vena cava flutter in four dogs. J Vet Cardioline 2021;36:123-130.
26- Shinbane JS, Wood MA, Jensen N, et al. Tachycardia-induced cardiomyopathy:a review of animal models and clinical studies. *J Am Coll Cardiol* 1997;29:709-715.
27- Skalidis EI, Kochiadakis GE, Koukouraki SI, et al. Myocardial perfusion in patients with permanent ventricular pacing and normal coronary arteries. *J Am Coll Cardiol* 2001;37:124 – 129.
28- Simantirakis EN, Prassopoulos VK, Chrysostomakis SI, et al. Effects of asynchronous ventricular activation on myocardial adrenergic innervations in patients with permanent dual-chamber pacemakers. *Eur Heart J* 2001;22:323 – 332.
29- Spinale FG, Tanaka R, Crawford FA, et al. Changes in myocardial blood flow during development of and recovery from tachycardia-induced cardiomyopathy. *Circulation* 1992;85:717–29-33.
30- Tanaka R, Fulbright BM, Mukherjee R, et al. The cellular basis for the blunted response to beta-adrenergic stimulation in supraventricular tachycardia-induced cardiomyopathy. *J Mol Cell Cardiol* 1993;25: 1212 –1233.
31- Zellner JL, Spinale FG, Eble DM, et al. Alterations in myocyte shape and basement membrane attachment with tachycardia-induced heart failure. *Circ Res* 1991;69:590 –600.
32- Zupan I, Rakovec P, Budihna N, et al. Tachycardia-induced cardiomyopathy in dogs; relation between chronic supraventricular and chronic ventricular tachycardias. *Int J Cardiol* 1996;56:75 –81.

Myocarditis: diagnosis and treatment

Roberto A. Santilli DMV, PhD, D.E.C.V.I.M.-C.A. (Cardiology)

Adjunct Professor of Cardiology - Cornell University – Cardiology Department – New York - USA

Clinica Veterinaria Malpensa – Samarate – Varese – Italy

Introduction

Myocarditis is an inflammatory disease of the heart muscle, diagnosed by histology, immunology and immunohistochemistry. Myocarditis is the result of RNA and DNA virus infections that induce a post-viral immune-mediated response or chronic myocarditis due to viral persistence. In humans myocarditis is considered a precursor of dilated cardiomyopathy with systolic dysfunction development in approximately 21 % of patients over a period of about three years after the acute event. Myocarditis is also a cause of sudden death in approximately 12 % of young adults.
The viral myocarditis has a triphasic pattern that includes an acute onset with viremia, a subacute phase with the host response and a chronic immune-mediated or with viral persistence characterized by varying and progressive degrees of ventricular dysfunction. The acute phase is predominantly characterized by necrosis with loss of myocytes induced by the virus, the cytotoxic effects of inflammatory mediators and oxidative stress products that induce endothelial dysfunction and ischemia. The viral activity induces, in addition, a complex immune response characterized by a remarkable infiltration of inflammatory cells such as natural killer cells and macrophages and the production of cytokinin. Neutralizing antibodies are not detectable until the fourth day after the viral infection begins when the virus titres are extremely high. The immunoresponses reached peak levels on the fourteenth day and correlate with viral elimination from cardiac tissues. The subacute phase lasts from day 4 to day 14 post-infection and it is characterized by the infiltration of T-lymphocytes. The biggest myocardial cell damage occurs during this time when it starts also the infiltration of B-lymphocytes. The humoral immune response plays an important role in myocardial injury process with the release of anti-chain antibodies heavy myosin. The chronic phase extending from days 15 to 90 days post-infection and is characterized by intense deposition of interstitial myocardial collagen, myocardial fibrosis and the progression of myocardial damage with cardiac dilatation, systolic dysfunction and congestive heart failure. New studies have suggested that the progression to the stage of dilated cardiomyopathy is induced by the persistence of RNA viruses in myocytes beyond 90 days before the event, with cell apoptosis and infiltrate of T-lymphocytes.
In humans myocarditis is preceded by flu-like symptoms, and gastrointestinal symptoms such as decreased appetite, nausea, vomiting and diarrhea. Cardiac manifestations of myocarditis appear a few hours to a few days after the first symptoms and are represented by heart failure, chest pain due to irritation pericardial, and arrhythmias such as the transient heart block (16% of patients) and ventricular arrhythmias. In the acute phase, it follows a monophasic clinical course, and the majority of patients recover spontaneously after a few days. On the other hand, some patients with acute myocarditis progressing rapidly in cardiogenic shock. Some patients progress to subacute or chronic forms, which induces chronic heart failure.

Although certain blood markers such as troponin I can help in the suspected diagnosis of myocarditis, the gold standard for diagnosis remains the endomyocardial biopsy. The progressive

increase of troponin in 24 hours with peak one or more days after the first upward may aid in differentiating myocarditis from acute coronary syndrome. There are several clinical and histopathologic criteria for classifying myocarditis. According to the Dallas criteria, the acute myocarditis is characterized by lymphocytic infiltrates in association with myocyte necrosis, while the borderline myocarditis is characterized by inflammatory infiltrates without evidence of myocyte necrosis. The Dallas criteria are limited by the high variability of biopsy interpretation and why inflammatory processes non-cellular samples cannot be detected. Immunohistochemistry is gaining consensus in the diagnosis of myocarditis. The monoclonal antibodies allow the characterization and the localization of the infiltrating mononuclear cell: for example, CD3 for T cells, PGM1 (CD68) for activated macrophages, and human leukocyte antigen (HLA) - DR - can evaluate HLA class II.
Another method of classification definable with endomyocardial biopsy involves the division of myocarditis in acute, subacute and chronic progressive. Acute forms are characterized by extensive necrosis with lympho-plasmacellular infiltration, the rapidly progressive forms are characterized by extensive cell damage and marked fibrosis, in chronic forms the cell damage is minimal and focal.
One last classification method combines the histological findings to clinical and divides in fulminant myocarditis, giant cell, eosinophilic, chronic, pediatric and neonatal. Endomyocardial biopsy is a safe procedure is performed through the skin with a bioptome with predetermined curvature and is guided by fluoroscopy. Is usually done by passing through the jugular from the right ventricle, although some studies have shown that performing endomyocardial biopsies sinister may increase the diagnostic power especially if the right ventricular systolic dysfunction on echocardiography shows. In the acute phase, endomyocardial biopsy is usually not necessary, but virological diagnosis is possible using some techniques such as PCR and in situ hybridization. PCR techniques have positive results in 20% of patients with clinically suspected myocarditis or dilated cardiomyopathy. The frequency is much higher in the first phase of the disease. The in situ hybridization technique detects viral genome in 35% of affected patients. The sub-acute phase of the disease, where the immune activation occurs, it can be definitely diagnosed by endomyocardial biopsy. The diagnosis is safer when made a few days or a few weeks after the resolution of a viral infection, and in this phase many lymphocytic infiltration outbreaks can be detected with histology.

The data coming from a large survey involving 4000 patients suggest that the frequency of positive biopsy in patients with myocarditis or dilated cardiomyopathy is low (10%), and increases with increasing the number of samples.
The risks of endomyocardial biopsy can be divided into immediate or delayed. The immediate risks include cardiac perforation with cardiac tamponade, ventricular or supraventricular arrhythmias, heart block, pneumothorax, puncture of central arteries , pulmonary embolism , hematoma at the venous access site , damage to the tricuspid valve , and the creation of a arteriovenous fistula within the heart. The use of an introducer along which runs through the tricuspid valve may decrease the risk of trauma induced by bioptome. Delayed complications include bleeding in the venous access site, damage to the tricuspid valve, pericardial tamponade , and deep vein thrombosis. In humans, the complication rate in of endomyocardial biopsy varies from 1 to 1.5 % with very rare cases of death caused by myocardial perforation.

Myocarditis in dogs and cats

In dogs, there are only case reports describing clinical pictures of myocarditis caused by different viral, bacterial and protozoan agents. The clinical pictures of dogs suffering from myocarditis include myocardial disorders with hypokinetic - dilatation, acute heart failure, ventricular arrhythmias and transient atrioventricular block.

One study evaluated the presence of viral genome histological specimens fixed with formalin in 18 dogs with dilated cardiomyopathy and 9 dogs with myocarditis. In this study only one dog with dilated cardiomyopathy showed the presence of an adenovirus type 1.

Our group has been study myocarditis and endomyocardial biopsy in the last 3 years. We evaluated the prevalence of infectious cardiotropic pathogens in the myocardium of adult dogs with unexplained myocardial and rhythm disorders (UMRD). Biopsy specimens were obtained from 25 dogs with non familial dilated cardiomyopathy, 6 dogs with atrioventricular block, 4 dogs with non familial ventricular and 2 with supraventricular arrhythmias. This group was compared with a control group of dogs undergoing right ventricular catheterization for congenital heart disease correction. For each cases histology and molecular biology throughout PCR (12 pathogens) were run. We obtained a total of 197 specimens and we found positive for viral persistence 21/37 (57%) of the cases with UMRD and 1/10 of cases in the control group. Most common pathogen found in dogs with dilated cardiomyopathy were Distemper virus, Parvovirus and Bartonella Spp., while in dogs with atrioventricular block was enteric Coronavirus. Concurrent PCRs on blood samples were negative in all dogs with positive myocardial PCR. In 3 out of 37 dogs self-limiting minor complication were observed following the endomyocardial biopsy. After we documented the presence of parvoviral myocarditis in adult dog post-mortem with myocardial fibrosis, another study confirmed this finding testing viral replication in the myocardium and in the small intestine in dogs with myocardial necrosis. The same authors found lately the presence of cardiotrophic agents post-mortem also in dogs without cardiac involvement but an increase of ionized calcium binding adpter molecule I (IbaI), major histocompatibility complex class II (MHCII) and cluster of differentiation 3 (CD3) in sample of paraffin-embedded myocardial tissue of dog with juvenile myocarditis to confirm the presence of viral myocarditis.

A recent study described 64 cases of presuntive antemortem diagnosis of myocarditis confirmed then post-mortem in 26 dogs. Confirmed infectious etiologies included bacterial sepsis, extension from endocarditis, toxoplasmosis and neosporosis, parvovirus, bartonellosis, trypanosomiasis, leptospirosis and dirofilariosis. Median survival time was 4 days for all dogs and 82 days for the ones that survived at least 2 weeks post-diagnosis.

Few case reports described myocarditis in cats. Recent case series suggested myocarditis as a possible cause of transient left ventricular hypertrophy and trifascicular block in the cat. Both alterations lasted around 1 month from the presentation and a complete recovery was noted. In one case with transient atrioventricular block and left ventricular hypertrophy Bartonella Spp was considered a causative agent.

Myocarditis should be treated with supportive drugs to control congestive heart failure, and pacemaker in case of high grade atrioventricular block. Despite the fact that in around 16 % of the case conduction disturbances are transient, pacemaker is still indicate due the instability of the idioventricular rhythm and the risk of sudden cardiac death in these patients. Treatment direct against cardiotrophic agents can be used if the pathogens are isolated. No data regarding the use of antiviral drugs (e.g. interferon) are available in dogs and cats.

References

1. Aretz HT, Billingham Me, Edwards WD et al. Myocarditis. A histopatologic definition and

classification. Am J Cardiovasc Pathol 1987;1:3-14
2. Breitschwerdt EB, Atkins CE, Brown TT, et al. Bartonella vinsonii subsp. berkhoffii and related members of the alpha subdivision of the proteobacteria in dogs with cardiac arrhythmias, endocarditis, or myocarditis. *J Clin Microbiol* 1999;37:3618–3626.
3. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;34:2636-2648.
4. Costagliola A, Piegari G, Otrocka-Domagala I, et al. Immunopathological Features of Canine Myocarditis Associated with Leishmania infantum Infection. *Biomed Res Int*. 2016; article ID 8016186;1-6.
5. Cooper LT, Baughman KL, Feldman AM, et al. The Role of Endomyocardial Biopsy in the Management of Cardiovascular Disease: A Scientific Statement From the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation* 2007;116:2216-2233.
6. Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: A seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol* 1992;19:43-47.
7. Ford J, McEndaffer L, Renshaw R et al. Parvovirus infection is associated with myocarditis and myocardial fibrosis in young dogs. *Vet Pathol* 2017;54:964-971.
8. Guedes PMM, Veloso VM, Afonso LCC, et al. Development of chronic cardiomyopathy in canine Chagas disease correlates with high IFN-g, TNF-a, and low IL-10 production during the acute infection phase. *Vet Immunol and Immunopathol* 2009; 130:43–52.
9. Janus I, Noszczyk-Nowak A, Nowak M, et al. Myocarditis in dogs: etiology, clinical and histopathological features (11 cases: 2007–2013). *Ir Vet J* 2014;67:28-35.
10. Kaneshige T, Mda N, Nakao S, et al. Complete atrioventricular block associated with lymphocytic myocarditis of the atrioventricular node in two young adult dogs. *J Comp Path* 2007;137:146-150.
11. Keene BW, Kittleson ME, Atkins CE, et al. Modified transvenous endomyocardial biopsy technique in dogs. *Am J Vet Res* 1990;51:1769-1772.
12. Kimura Y, Fukushima R, Hirakawa A, et al. Epidemiological and clinical features of the endomyocardial form of restrictive cardiomyopathy in cats: a review of 41 cases. *J Vet Med Sci* 2016;78:781-784.
13. Kühl U, Pauschinger M, Seeberg B, et al. Viral Persistence in the Myocardium Is Associated With Progressive Cardiac Dysfunction. *Circulation* 2005;112:1965-1970.
14. Kühl U, Pauschinger M, Noutsias M, et al. High Prevalence of Viral Genomes and Multiple Viral Infections in the Myocardium of Adults With “Idiopathic” Left Ventricular Dysfunction. *Circulation* 2005;111:887-893.
15. Lakhdhir S, Viall A, Alloway E, et al. Clinical presentation, cardiovascular findings, etiology, and outcome of myocarditis in dogs: 64 cases with presumptive antemortem diagnosis (26 confirmed postmortem) and 137 cases with postmortem diagnosis only (2004-2017). J Vet Cardiol. 2020;30:44–56.
16. Martínez-Hernández L, Casamian-Sorrosal D, Barrera-Chacón R, et al. Comparison of myocardial damage among dogs at different stages of clinical leishmaniasis and dogs with idiopathic chronic kidney disease. *Vet J* 2017;221:1-5
17. Maxson TR, Meurs KM, Lehmkuhl LB, et al. Polymerase chain reaction analysis for viruses in paraffin-embedded myocardium from dogs with dilated cardiomyopathy or myocarditis. *Am J Vet Res* 2001;62:130–135.
18. Meurs KM, Fox PR, Magnon AL, et al. Molecular Screening by Polymerase Chain Reaction Detects Panleukopenia Virus DNA in Formalin-Fixed Hearts from Cats with Idiopathic Cardiomyopathy and Myocarditis. *Cardiovasc Pathol* 2000;9:119–126
19. Molesan A, Goodman L, Ford J, et al. The causes of canine myocarditis and myocardial fibrosis are

elusive by targeted molecular testing: retrospective analysis and literature review. Vet Pathol. 2019;56:761–777.
20. Oxford E, Joseph J, Santilli R. Transient myocardial thickening in a Bartonella henselae positive cat. J Vet Cardiol 2018;20:198-212.
21. Oxford E, Giacomazzi F, Moise NS, Santilli RA. Clinical and electrocardiographic presentation of trifascicular block in three cats. J Vet Cardiol 2018;20:204-212.
22. Rush JE, Keene BW, Eicker SW. Endomyocardial biopsy in cats. *Am J Vet Res* 1990;51(11):1765-1768.
23. Santilli RA, Porteiro Vazquez DM, Vezzosi T, et al. Long-term Intrinsic Rhythm Evaluation in Dogs with Atrioventricular Block. *J Vet Intern Med* 2016;30:58–62.
24. Santilli RA, Battaia S, Perego M, et al. Bartonella-associated inflammatory cardiomyopathy in a dog. *J Vet Cardiol* 2017;19:74-81.
25. Santilli RA, Grego E, Battaia S et al. Prevalence of infectious cardiotropic pathogens in the myocardium of adult dogs with unexplained myocardial and rhythm disorders. J Am Vet Med Assoc 2018 (in press)
26. Simpson KE, Devine BC, Gunn-Moore D. Suspected toxoplasma-associated myocarditis in a cat. *J Feline Med Surg* 2005;7(3):203-208.
27. Vu K, Wikel V, Molesan A, et al. Myocardial Iba1, MHC class II, and CD3 are diffusely increased in canine myocarditis: A step toward antemortem myocarditis diagnostics. Vet Pathol 2022; doi.org/10.1177/03009858221098433

Bibliographies of the speakers

Virginia Luis Fuentes DipACVIM, DipECVIM (Cardiology).

Virginia Luis Fuentes graduated from the Cambridge Veterinary School and then spent 5 years working as a small animal vet in general practice before returning to academia. She is a Diplomate in cardiology with the RCVS, ACVIM and ECVIM, and has worked as a veterinary cardiologist at the Royal (Dick) School of Veterinary Studies, Edinburgh; the University of Missouri-Columbia, US; the Ohio State University, US; and since 2004, the Royal Veterinary College, where she is a Professor of Veterinary Cardiology. She is a past Chair of the ECVIM Cardiology Specialty, and was Chair of the ACVIM Feline Cardiomyopathy Consensus Statement group. She is currently a member of the leadership group of the American Society of Echocardiography Veterinary Special Interest Group, and is the feline lead author for the ASE /ACVIM/ ECVIM guidelines currently in preparation on canine and feline transthoracic echocardiography.

Jens Häggström, DVM, PhD, DECVIM-CA (Cardiology)

Jens Häggström was born and brought up in Uppsala, Sweden, where he also completed his basic veterinary training 1990. He earned his Doctorate degree in 1996 with a thesis concerning myxomatous mitral valve disease in dogs. He became an Associate Professor in Internal Medicine, in Uppsala the year 2000, 2003 Promoted Professor, 2012 Professor (Chair) in the same subject, and in 2014 Section Head for Small Animal Medicine and Surgery. Jens Häggström is author and co-author of a large number of original papers in Internationally distributed peer-viewed Journals, Congress abstracts and Textbook chapters. Jens Häggström is Lead Investigator of the SVEP, QUEST and the EPIC trials, all investigating the effect of different drugs in Myxomatous Mitral Valve Disease in dogs. He a panelist for the 2009 and 2019 ACVIM Consensus statements concerning Myxomatous Mitral Valve Disease in dogs and for the 2020 ACVIM Consensus statement concerning Feline Cardiomyopathy. In addition to therapy of heart failure, his main interests in research concerns acquired heart disease in dogs and cats (MMVD, DCM and Feline Cardiomyopathy), pathophysiology, and genetic risk factors for heart disease in dogs and cats. Jens Häggström is a Diplomate of ECVIM since 1998 and past President of ESVC. He enjoys running, racquet sports, golf and skiing in his spare time.

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

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. 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 Director of the ESAVS cardiology modules (I-V) and contributed to the veterinary literature with a vast number of articles, abstracts and book chapters.

Roberto Santilli DMV, PhD, Dipl.E.C.V.I.M.-C.A. (Cardiology)

Roberto Santilli graduated from the College of Veterinary Medicine of the University of Milan in 1990. He became a diplomate of the European College of Veterinary Internal Medicine - Companion Animals (Specialty of Cardiology) in 1999. Between 2004 and 2006, he completed a Master in Electrophysiology and electrical stimulation at the University of Medicine of Insubria. He then obtained a PhD at the University of Turin – College of Veterinary Internal medicine in 2010. Roberto Santilli is the head of the cardiology departments of the Clinica Veterinaria Malpensa, Anicura in Samarate, Varese (Italy) and of the Ospedale Veterinario I Portoni Rossi, Anicura, Bologna (Italy). Since 2014, he has been an Adjunct Professor of Cardiology at the Cornell University College of Veterinary Medicine, where he is actively involved in the activities of the cardiac electrophysiologic laboratory. He's co-author of the book: Electrocardiography of the dog and cat", now translated into 9 languages. His main research activities include the diagnosis and treatment of arrhythmias in dogs and cats.


NEW CC CARDIOCARE™
PROTECTS THEIR HEART
FROM THE START
Introducing new PURINA® PRO PLAN®
VETERINARY DIETS CC CardioCare™.
A life changing blend of nutrients with the power
to support cardiac function.
PURINA
PRO PLAN
VETERINARY DIETS
CC CARDIOCARE
NEW

ACT NOW,

BEFORE IT'S TOO LATE.

Boehringer Ingelheim

vetmedin®

(pimobendan)


Together beyond animal health
Ceva Cardiology
Solutions for life