

ABSTRACTS OF THESES AUTHORED BY GRADUATE STUDENTS OF THE KORET SCHOOL OF VETERINARY MEDICINE, THE HEBREW UNIVERSITY IN JERUSALEM.

DOPPLER IMAGING OF A SPONTANEOUSLY OCCURRING FELINE DIASTOLIC DYSFUNCTION

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This retrospective clinical study was designed to identify useful indices to discriminate between healthy and cardiomyopathic cats for use in diagnosing borderline cases where findings of traditional diagnostic criteria are equivocal. Cut-off points of selected diastolic parameters were defined, enabling the distinction between healthy cats and cats with diastolic dysfunction.

The study evaluated parameters of trans-mitral flow velocity and duration, pulmonary venous flow into and away from the left atrium, tissue Doppler imaging, and propagation velocity (Vp). Thirty five systolic and diastolic parameters were quantified in 76 non-sedated, non-treated animals. Allocation into study groups was based on structural criteria, as follows: 34 healthy normal cats (N), 31 cats with hypertrophic cardiomyopathy (HCM), and 11 cats with unclassified cardiomyopathy (UCM).

We compared healthy versus diastolic dysfunctional cats (HCM+UCM pooled as one group for some of the tests). Multiple comparisons among all three groups using both non-parametric and parametric statistical tests were applied. Most of the significant parameters were identified when comparing the healthy to the "pooled" diastolic dysfunction group.

Traditional Doppler parameters of diastolic function, namely trans-mitral flow velocities, pulmonary venous flow, and isovolumetric relaxation time, were not useful for the identification of diastolic dysfunction, as their ability to discriminate between the groups was found to be poor.

Conversely, other parameters were statistically different between groups. Preload (or LV compliance) related parameters such as both the ratio and the difference (the "delta") between durations of trans-mitral A-wave and pulmonary venous reversed A-wave diverged: the ratio was lower in the pooled group of sick animals than it was in healthy ones; the difference was smaller in UCM than it was in normal cats. In HCM cats the reversed A-wave duration was longer than the trans-mitral late (and active) inflow wave, in contrast to the situation in both healthy and UCM animals. The E/Em ratio was higher in sick than in normal cats, while the ratio Em/Am in the sick was significantly lower than in the healthy. Left ventricular relaxation related parameters, such as Sm and Em, were slower in the sick than in the healthy, while sick cats had significantly lower Vp values than normal cats.

Tissue Doppler imaging proved the most promising tool in our study, in that it was demonstrated to contribute to the distinction between healthy and sick cats: [A time / AR-time] was found to be a highly sensitive and specific parameter. Similarly, [E/Em] was also found to be a remarkably promising parameter. Based on several types of parameter rank orders, both relaxation-related and preload (or compliance) related parameters were meaningfully different between healthy and cardiomyopathic cats.

The study also demonstrated that spontaneously occurring feline diastolic dysfunction can serve as a model for human diastolic dysfunction. This is a "growing" entity in human cardiology implicated as the underlying etiology in 40-50% of congestive heart failure cases.

PHYSICAL EXAMINATION TO PREDICT THE OUTCOME OF CANINE PULMONARY HYPERTENSION

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Secondary pulmonary arterial hypertension (PHT) is a common (30-40%) complication of acquired mitral valve insufficiency and may trigger clinically identifiable sequels such as right-sided congestive heart failure (R-CHF) and/or syncope. The index of suspicion, however, is not typically high among practitioners when based on the combination of anamnesis and physical examination findings alone. We tested whether selected findings predict the diagnosis of PHT, as confirmed by a Doppler-derived systolic pressure gradient >35 mmHg between the right ventricle and atrium.

Data from 312 consecutive dogs presented to the Cardiology Service between January 2006 and August 2007 (PHT =96; non-PHT =216) were retrospectively analyzed to calculate the correspondence ratio between pairs of non-quantitative (historical and/or physical) versus quantitative (Doppler) variables. Sensitivity, specificity and predictive value indices were computed. The McNemar test was used to seek a trend among cases of disagreement.

Combined or isolated non-quantitative variables reflecting R-CHF, syncope, or a "loud" right apical murmur had a low sensitivity of <57% and a high specificity of >82% as predictors of PHT. While an isolated louder right apical than left apical murmur had a positive predictive value (PPV) of 82% and was 98% specific for PHT, an isolated Grade \geq IV/VI right apical murmur had a PPV of 85% and was 96% specific for PHT. While syncope or acute collapse combined with a louder right apical than left apical murmur had a PPV of 91% and was 96% specific for PHT, syncope or acute collapse combined with a Grade \geq IV/VI right apical murmur had a PPV of 94% and was 96% specific for PHT. The combination of abdominal distention with a Grade $>$ IV/VI right apical murmur had a PPV of 100% and a specificity of 100% for PHT.

A louder than expected right apical systolic murmur combined with R-CHF and/or with syncope should increase the index of suspicion of PHT and help improve patient selection for referral to Doppler diagnostics and disease severity evaluation.

CONGENITAL HEART DISEASE IN THE DOGUE DE BORDEAUX BREED

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Canine subaortic stenosis (SAS) and canine tricuspid valve dysplasia (TVD) are known congenital heart defects in dogs. Between 2003 and 2006, 21 consecutive Dogue de Bordeaux (DdB) dogs were diagnosed with these and other congenital cardiac disorders by our Cardiology Service. Relative to this breed presenting to our hospital over the same period with non-cardiac pathologies, the number seems to reflect an over-representation.

The DdB breed has gone through several population historical "bottle neck"-like effects and its population is relatively small in Israel. According to one unofficial estimate, the national breed "herd" consists of about 600 registered dogs). These circumstances are likely to unintentionally promote frequent, even if unrecognized, inbreeding. It is therefore quite possible that inherited congenital defects in the local DdB population are particularly prevalent. This is probably reflected by the relatively high number of DdB dogs presented to our Cardiology service over a relatively short period of time.

We aimed at identifying the probable mode of inheritance of congenital cardiac disease in the local DdB population using pedigree analysis. Should such genes surface as promising candidates, a future genetic analysis can be performed using frozen whole blood samples, still being collected from both sick

and healthy DdB dogs. Pedigree analysis revealed that 13 patients with a valid pedigree documentation descended from at least one of 3 registered sires. The mode of inheritance could not be identified beyond doubt but the most likely was autosomal recessive.

A literature search revealed several genes postulated as contributing to normal cardio-morphogenesis. Some of these code transcription factors and/or replication regulators involved in numerous diverse processes in the mammalian cell, and are therefore unlikely to prove specific enough to be directly accountable for the clinically diagnosed disorders in these dogs. Therefore, none of these genes has emerged as a highly promising candidate for further study. In contrast, the NKX2-5 and GATA 4 genes do appear to be potentially important role players in the pathogenesis of SAS, TVD, or other congenital heart defects in DdB patients.

As evidence of gene involvement in congenital heart disease is rapidly accumulating, use of DNA samples collected from some of our cohort animals, as well as from current and future DdB patients with and without heart disease, will be performed to identify genetic differences between these two DdB populations.