Summer 2012

The Murmur

CVCA News and Updates

- Drs. Schmitt and Hickey, our third year residents, passed their ACVIM qualifying examinations this year and will take the Cardiology Certifying Examinations next June.

- CVCA is participating in multiple studies including:
  - Boxer ARVC Genome project: investigating amplifiers in genetic mutations responsible for ARVC in boxers
  - CP2/Mitral Valve Insufficiency project: determining causative genes associated with DMVD dogs
  - Idexx BNP project: developing assay to assess NT-proBNP in serum
  - Serial Cardiac Troponin I and NT-proBNP in dogs with pericardial effusion: determining the effect of the timing of sample collection in interpreting CTnI as an indicator of the presence or absence of hemangiosarcoma in dogs with pericardial effusion

Dear Colleagues,

We sincerely appreciate your patience during the ACVIM Forum this year. We were fortunate to be able to send 10 of our doctors to the conference this year and wanted to pass along some pearls of wisdom we thought would be useful in your practice.

CVCA

CHESAPEAKE VETERINARY CARDIOLOGY ASSOCIATES

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PREDICTING FIRST ONSET OF CHF IN DOGS WITH DEGENERATIVE MITRAL VALVE DISEASE

Degenerative mitral valve disease (DMVD) is the most common acquired cardiovascular disease affecting greater than 33% of all dogs over the age of ten. Although the preclinical stage of disease is typically several years in duration, it is not uniformly benign. Due to the highly variable course of disease and outcome, studies are constantly underway to identify risk factors associated with disease progression. The following paragraphs are brief summaries of two of these studies.

The first was a retrospective study evaluating survival characteristics and prognostic variables of 256 dogs with mild to moderate DMVD. 27% of dogs died or were euthanized during the observation period with a median survival time for the whole population being 588 days. Twelve percent of deaths were classified as cardiac-related with 3% being the result of refractory CHF. For cardiac-related deaths, a negative effect on survival was associated with left atrial and ventricular enlargement and E:A ratio on transmitral inflow Doppler evaluation. When cardiac deaths and progression of heart failure class were combined as a single end point, the presence of a murmur, syncope, left atrial enlargement, increased E wave velocity, and cough were associated with a worse prognosis.

The second set of data we are summarizing tried to determine if NT Pro BNp could be used to predict the first episode of CHF in dogs with DMVD. CVCA participated in many of these and other studies over the past several years. The PREDICT cohort identified four factors that placed asymptomatic dogs at significant risk for CHF before their next scheduled visit (avg 4 – 6months). These factors included left atrial to aortic root ratio, NT-proBNP concentration > 1500, left ventricular diastolic internal dimension to aortic root ratio, and vertebral heart score > 12.

Conclusions

Based on these and other studies, CVCA feels serial echocardiographic evaluation is the most sensitive method of determining a dog's risk for development of CHF. With serial monitoring, we identify patients with progressive cardiac enlargement and evidence of elevated left atrial pressure. For these patients, the risk of CHF is increased so early intervention with medical therapy may delay the onset of clinical signs of CHF and/or control the severity of clinical signs once present. We realize that serial echocardiographic examinations may not be possible for all families. In these situations, we feel that serial NT-proBNP evaluations and chest radiographs to evaluate VHS can be very useful in identifying at risk patients. If you have any questions about how to perform a VHS measurement or how to interpret an NT-proBNP concentration in a patient, please do not hesitate to contact one of our offices. In addition to answering questions via phone, we are also willing to come to your hospital to provide a lunch and learn on these topics or others.

PIMOBENDAN IMPROVES SURVIVAL IN DOBERMANS WITH PRECLINICAL DILATED CARDIOMYOPATHY

The PROTECT study evaluated Doberman Pinschers 4-9 years of age with pre-clinical DCM over a period of five and one half years. Seventy-six dogs were randomized into placebo and Pimobendan-treated groups. In the Pimobendan group, 49% of dogs developed CHF or had a sudden cardiac death (SCD) event compared to 68% of dogs in the placebo group. The median time to develop CHF or sudden cardiac death (SCD) was statistically different between the groups (718 days for the Pimobendan group vs. 441 days in the placebo group). In humans, the PICO trial showed a non-significant tendency toward a higher mortality rate in Pimobendan-treated patients. The mechanism of increased mortality was not proven, but there was suspicion toward a pro-arrhythmic effect of Pimobendan related to increased cytosolic calcium levels. Potentially lethal ventricular tachycardia develops in at least 50% of Dobermans with SCD being the first clinical sign in 30-50% of affected dogs typically between 6-8 years of

age. In the PROTECT study, there was no difference in arrhythmia frequency between groups, however, dogs were allowed to be treated with anti-arrhythmic medications as clinically indicated. Overall, the study found that Pimobendan led to a 9 month delay in time to onset of CHF or SCD.

Recommendations

CVCA recommends screening Dobermans for dilated cardiomyopathy with a holter monitor and echocardiogram starting around 3 years of age. It is now known that a Doberman's echocardiogram will become equivocally abnormal within one year of arrhythmia development and unequivocally abnormal by two years post arrhythmia diagnosis. Previously, CVCA has reserved the use of Pimobendan for dogs with clinical signs consistent with forward failure and/or congestive heart failure. In light of the PROTECT study information, we will be considering its use in Dobermans with echocardiographic evidence of occult dilated cardiomyopathy.

UPDATES ON HYPERTROPHIC CARDIMYOPATHY FROM THE ACVIM FORUM 2012

Background and Comparisons to the Disease in People

Hypertrophic cardiomyopathy (HCM) is the most common heart disease diagnosed in cats, with a reported prevalence up 5-30% in populations of asymptomatic cats. The age at onset is variable, with some breeds such as the Sphynx and Maine Coon more frequently developing echocardiographic signs as young adults. Sadly, many cases are diagnosed late in the disease - only after the onset of symptoms of congestive heart failure(CHF) or thromboembolism. Pre-CHF diagnosis is only possible if the cat develops an auscultable arrhythmia, murmur, or high NT Pro BNP. level to trigger a cardiac evaluation.

HCM in humans is quite similar to the disease in cats. Some patients develop asymptomatic concentric hypertrophy later in life while the most aggressive cases develop severe hypertrophy and suffer sudden cardiac death as juveniles or young adults. Both cats and people develop HCM as a result of genetic mutations . - with over 600 mutations in 14 genes found so far in people. Treatment in people is focused on prevention of sudden cardiac death through implantable cardioverter-defibrillators, medical treatment of congestive heart failure, and occasionally surgery to address outflow obstruction.

Screening Tests

Screening for cats with early hypertrophic cardiomyopathy is difficult because many cats lack significant findings on physical examination that would raise the suspicion for heart disease. NT-proBNP concentrations may be useful with alues of < 100pmol/L unlikely to be associated with significant cardiomyopathy, while values > 270pmol/L are often identified in cats with significant disease. Intermediate values may or may not be indicative of cardiomyopathy. An early echocardiogram allows for specific diagnosis of the disease, is beneficial for planning anesthesia or fluid therapy, raisies the owner's awareness in monitoring for clinical signs at home, and establishes a baseline for future comparison. CVCA is currently undertaking a study to evaluate changes in NT-proBNP with treatment of the obstructive form of HCM.

Genetic testing for HCM is in its infancy in veterinary medicine. To date, only 2 mutations have been identified: A31P, which is specific to Maine Coon cats, and R820W, which is specific to Ragdoll cats. Each involves a single base pair substitution in the myosin binding protein C gene, and both are autosomal dominant. These mutations exhibit incomplete penetrance, such that cats positive for the mutation do not always develop phenotypic disease. Other, as of yet unidentified, mutations also contribute to the development of HCM, therefore a negative genetic test does not guarantee a cat will not develop HCM. Genetic screening is of more practical value for breeding colonies as opposed to individual owners.

Treatment

While treatment of cats with HCM following the onset of congestive heart failure with diuretics, antithrombotics, and angiotensin-converting enzymes inhibitors is relatively noncontroversial, there are varying opinions regarding the role of therapy prior to the onset of heart failure.

The decision to treat a patient with preclinical HCM is based upon echocardiographic findings such as the presence of chamber enlargement, reclot material (spontaneous echocontrast or "smoke"), outflow obstruction, inflow velocities, pulmonary pressures and severity of concentric hypertrophy. Medications started prior to heart failure may include antithrombotics (low dose aspirin or Plavix [clopidogrel]), beta-blockers (atenolol), calcium channel blockers (diltiazem), and angiotensin-converting enzymes inhibitors. The rationale for therapy is to decrease risk of thromboembolism, potentially improve diastolic function, slow progression of myocardial fibrosis, and to control heart rate in cats with outflow obstructions.

The Future

Research in experimental animal models of HCM (rabbits) is showing the potential for medications in the treatment of preclinical HCM, including spironolactone and statins. Gene therapy, by which genetic code to promote the production of a normal protein that is defective, deficient, or absent in disease, is also demonstrating early promise in the laboratory as a therapeutic modality for numerous cardiovascular diseases.