Chronic Degenerative Valve Disease:

natural history and management of the most common cardiac disease in dogs

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- CDVD is a chronic disease due to myxomatous degeneration of valve leaflets, and chordae tendineae
    - Most commonly affects the mitral valve, although in approximately 30% of cases both mitral and tricuspid valve are involved. The aortic valve is occasionally affected, more rarely the pulmonic valve.
    - CDVD is the most common cause of mitral valve insufficiency in dogs
- CDVD is the most common acquired cardiovascular disease in the dog representing 75-80% of all cardiovascular diseases in this species
- Older, small breeds dogs (< 20 kg) are more commonly affected, but the disease can also be present in large breed dogs.
    - CDVD in large breed dogs is characterized by a more rapid progression and a more severe systolic dysfunction (*Borgarelli et al. Comparison of mitral valve disease in German Shepherd dogs and in small breeds JVC 2004, 6: 27-34*)
- Males present the disease 1.5 times more commonly than females although there is no evidence that CDVD progresses differently between sexes

Etiology

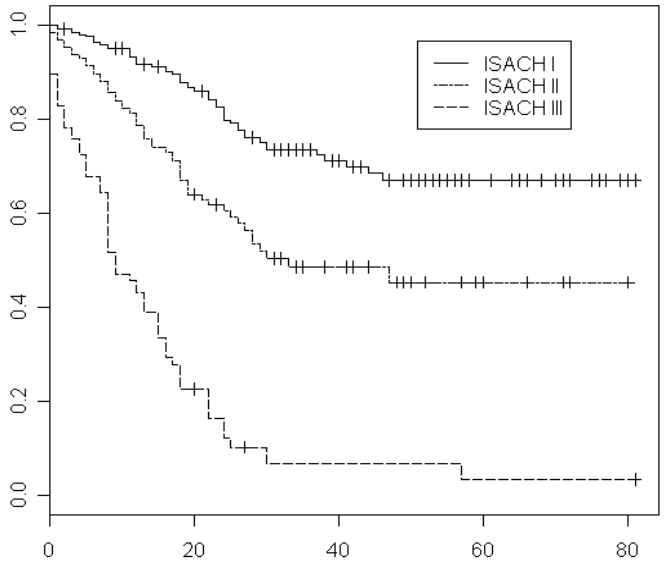
The cause of CDVD is unknown

- Possible inherited component is some breeds
    - Parental cardiac status had a marked influence on the prevalence and severity of murmurs typical of CDVD in 5 yrs. old offspring (*Swenson L et al. Relationship between parental cardiac status in CKCS and prevalence and severity of chronic valvular disease in offspring JAVMA 1996, 208; 2009-2012*)

    - A polygenic mode of inheritance has been suggested in 190 Dachshunds (*Olsen et al. Epidemiology and Inheritance of mitral valve prolapse in Dachshunds, JVIM 1999, 13; 448-456*)

- Mitral valve prolapse, defined as systolic displacement of the mitral valve leaflets into the left atrium, has been suggested as being associated with CDVD in dogs
    - Displacement would be associated with increased shear stress imposed on the mitral valve leaflets and endothelial damage (myxomatous degeneration would be a consequence of a continuous damage-repair cycle)
- Genome expression patterns of tissue from dogs with CDVD showed that 229 transcripts were differentially expressed (159 was upregulated and 70 was downregulated). Genes involving cell signaling, inflammation, extracellular matrix, immune function, cell defense , and metabolism were generally upregulated. Inflammatory cytokines and the serotonin-transforming growth factor-β pathway were identified as contributory to the pathophysiologic aspects of CDVD (*Oyama MA and Chittur SV Genomic expression patterns of mitral valve tissues from dogs with degenerative mitral valve disease AJVR 2006, 67; 1307-1318*)

- **Natural history**
    - CDVD is characterized by a long pre-clinical period, and many affected dogs do not progress to congestive heart failure (CHF) and therefore die of other diseases
    - In one study including 558 dogs affected by CDVD at different stages of CHF, more than 70% of the asymptomatic dogs were alive at the end of the follow-up period of 6.6 year (*Borgarelli et al. Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease JVIM 2008, 22, 120-128*)



- In another study, 82% of 72 asymptomatic dogs were still asymptomatic at 12 months from inclusion in the study (*Chetboul V et al. Association of plasma N-terminal pro-B-type natriuretic peptide concentration with mitral regurgitation severity and outcome in dogs with asymptomatic degenerative mitral valve disease. JVIM 2009, 23; 984-994*)

- The Vet-Proof study, that aimed at evaluating the efficacy of treatment with the angiotensin converting enzyme inhibitor (ACE-I) enalapril at delaying the onset of CHF in asymptomatic dogs, showed a median time free of CHF of 851 days for the treated group and of 778 for the placebo group (*Atkins et al. Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency JAVMA 2007, 231; 1061-1069*)

- The SVEP study had the same aim but included only CKCS, and reached similar results also when the analysis included only dogs with cardiomegaly at the time of inclusion (*Kvart et al. Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation JVIM 2002, 22; 120-128*)

- These data provide evidence that asymptomatic CDVD represents a relatively benign condition similarly to what has been reported in people

Once a dog progresses to CHF, survival time can be related to several factors. These include owner compliance in providing adequate care, treatment, cardiovascular complication such as pulmonary hypertension or rupture of chordae tendinae and other concomitant diseases such as renal or endocrine

- In one study, dogs with moderate and severe CHF (class 2 and 3 according to the ISACHC classification) showed a median survival time of 33 and 9 months, respectively (*Borgarelli et al. JVIM 2008, 22, 120-128)*
- In the QUEST trial, the median survival time for all dogs to reach the primary endpoint represented by sudden cardiac death, euthanasia as a consequence of the cardiac disease or treatment failure, was about 6 months (*Haggstrom J et al Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study JVIM 2008, 22; 1124-1135*)
- Similar survival time has been found in the LIVE study, in the group of dogs treated with enalapril (*Ettinger et al. Effects of enalapril maleate on survival of dogs with naturally acquired heart failure. The Long-Term Investigation of Veterinary Enalapril (LIVE) Study Group JAVMA 1998, 213; 1573-1577*)
- In the BENCH study the mean survival time for dogs receiving benazepril was about 14 months (*The-BENCH-group. The effect of benazepril on survival times and clinical signs of dogs with congestive heart failure: results of a multicenter, prospective, randomized, double-blinded, placebo-controlled, long-term clinical trial JVC 1999, 1; 7-18*)

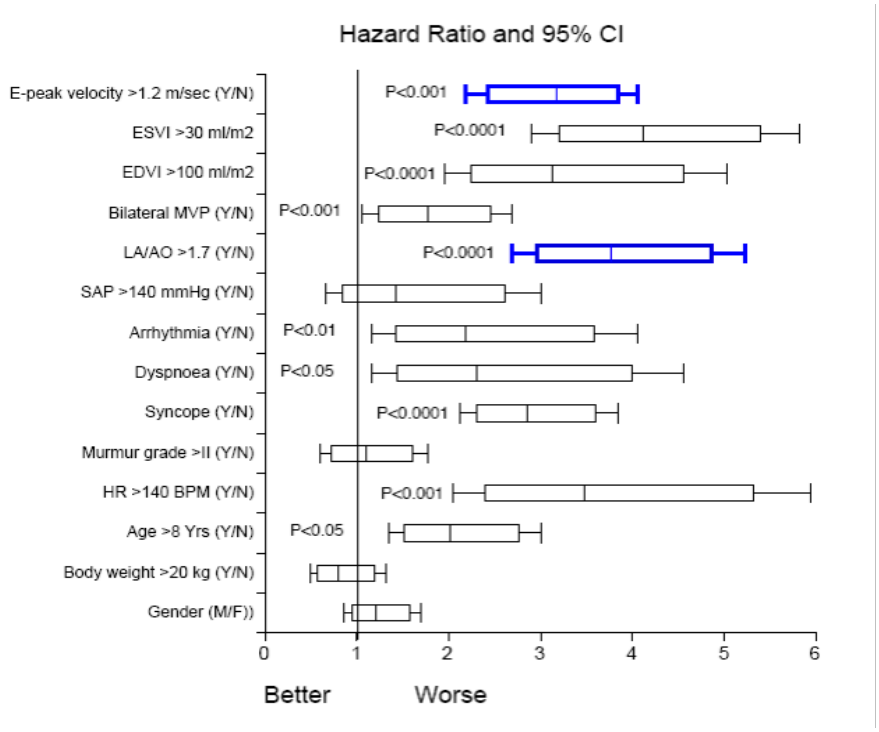
These studies suggest that dogs with moderate to severe CHF due to MMVD can still have a relative long survival with appropriate medical management.

Prognostic indicators

Risk factors associated with rapid progression of mild CDVD include: age, degree of MR (as indicated by murmur intensity and/or jet size by colour Doppler echocardiography), and severity of valvular changes.

Although one study reported a comparably favourable long-term prognosis in dogs with ruptured chordae tendineae, presumably most of the dogs in that study had rupture of minor chords because rupture of major chords has been associated with an increase in regurgitant volume and a poor prognosis (*Serres et al Chordae tendineae rupture in dogs with degenerative mitral valve disease: prevalence, survival, and prognostic factors (114 cases, 2001-2006) JVIM 2007, 21; 258-264*)

In one study several variables have been associated with an increased risk for cardiac death in the univariate analysis. However only the left atrium to aortic root ratio calculated using 2D echocardiography remained significant in the multivariate model (*Borgarelli et al JVIM 2008*)



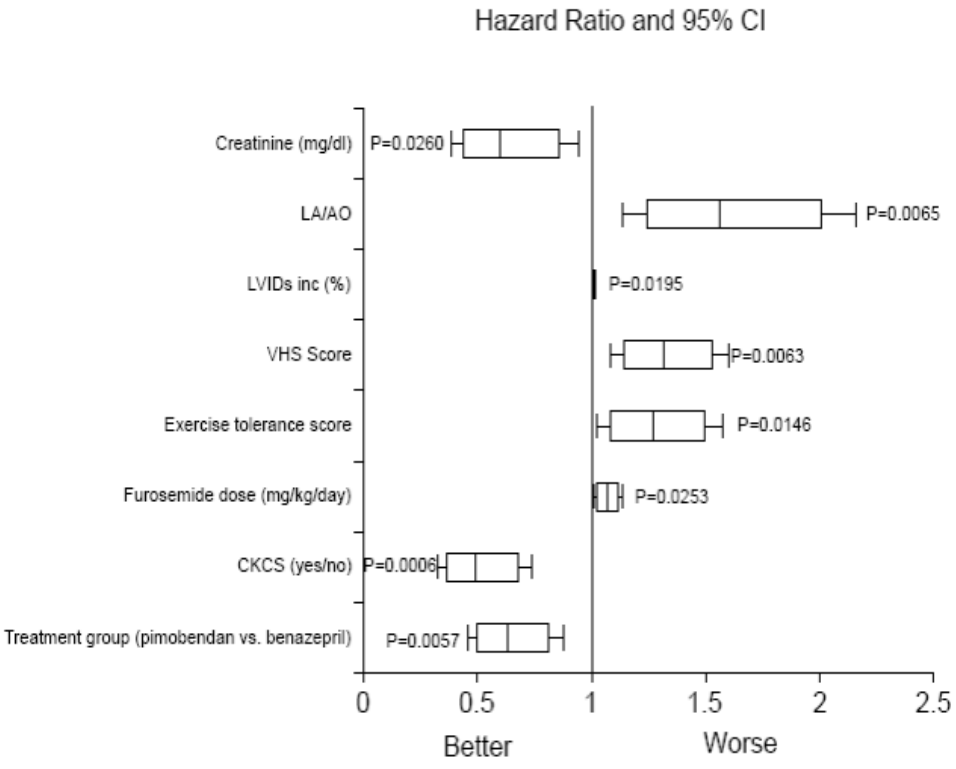
Some clinical variables have been shown to have prognostic value after the onset of CHF in dogs with CDVD.

- The type of adjunct therapy influences survival.
    - Increased survival has been reported in dogs treated with pimobendan as well as the ACE-inhibitors enalapril and benazepril

(*Ettinger and others 1998, The BENCH Study Group 1999, Häggström and others 2008*)

- Expected survival time decreases with increasing maintenance dose of furosemide

- Expected survival time decreases with exercise intolerance, increasing cardiac size and severity of MR (VHS score), lower serum creatinine concentration (possibly indicating cardiac cachexia), and decreasing systolic function (increased end-systolic dimension) *(Häggström and others 2008*)



- La/Ao over 1.7 was associated with a 2.1 higher risk of death due to cardiac disease (*Borgarelli et al JVIM 2008*). An La/Ao ratio represented one of the independent predictors of outcome in the QUEST study

- Breed could affect the outcome after onset of CHF. The breed CKCS has been associated with a better prognosis when compared to a group consisting of other breeds
- The development of complications, such as atrial fibrillation, rupture of major chordae tendineae, pulmonary hypertension, and myocardial infarction have been suggested to confer a worse clinical outcome, although clinical evidence is lacking.

The ACVIM consensus statement for the Diagnosis and Treatment of Canine Chronic Valvular Heart Disease (Atkins et al. JVIM 2009, 23: 1142-1150)

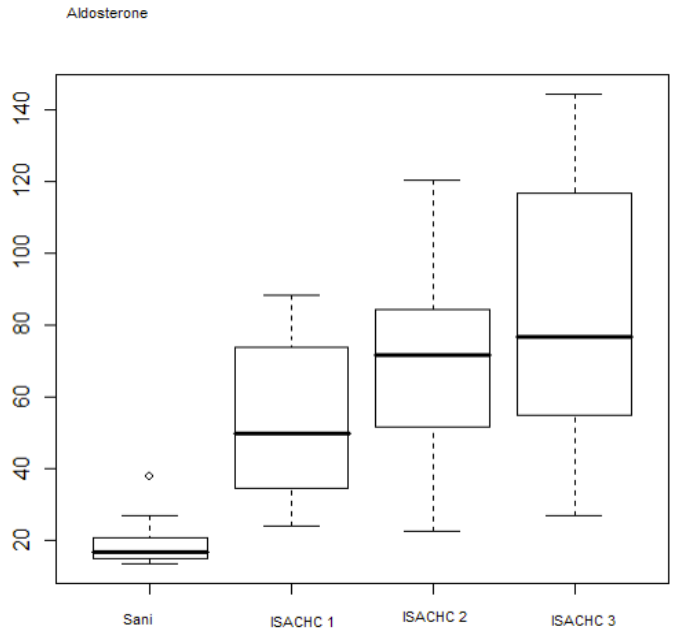
The goal of these guidelines was to link severity of clinical signs to appropriate treatment for each stage of illness. The consensus panel adapted the 2001 American College of Cardiology/American Heart Association classification system for the treatment of chronic heart failure to the management of canine CVDV.

	Definition
Stage A	Dogs at risk for CDVD but that have no identifiable cardiac structural disorder (i.e. Cavalier King Charles Spaniel, Dachshunds)
Stage B1	Dogs with CDVD, that have never developed clinical signs and do not have radiographic or echocardiographic evidence of cardiac remodeling
Stage B2	Dogs with CDVD, that have never developed clinical signs and have radiographic or echocardiographic evidence of cardiac remodeling (i.e. left-sided heart enlargement)
Stage C	Dogs with CDVD and past or current clinical signs of heart failure associated with structural heart remodeling. • Dogs presenting heart failure for the first time may present severe clinical signs and may require hospitalization • These dogs needs treatment to stay free from symptoms of heart failure
Stage D	Dogs with end-stage CDVD and heart failure that is refractory to standard therapy (i.e. furosemide, ACE-I, pimobendan +/- spironolactone).

- This classification introduces for the first time the concept of patients at risk for developing heart disease but that currently do not have a heart disease (Stage A). These patients are dogs of breeds at risk, such as the Cavalier King Charles Spaniel or the Dachshund
    - The recognition of this stage should encourage the veterinary community to develop appropriate screening programs and adopt measures able to reduce the risk for an animal of developing the disease
    - As early onset disease is associated with a worse prognosis, proposed screening programs aim at breeding only dogs whose parents show the disease at an older age (> or = 5yr).
- The ACVIM classification implies that dogs with CDVD can move vertically from stage A to D but cannot go back.
- Stage B dogs represents the majority of dogs presenting CDVD. The sub-classification proposed for these patients underlines the fact that asymptomatic dogs are a non homogeneous group, including patients with very mild disease and others, that although have never developed CHF, present a more advanced disease and are more likely to develop clinical signs of CHF. <u>The heterogeneity in this group may be an important reason for the conflicting data concerning neuro-hormonal activation in the veterinary literature</u>
- Identification of biomarkers able to identify with high sensitivity and specificity patients at higher risk for developing CHF represents a major challenge in veterinary cardiology
        - A recent study conducted on 72 asymptomatic dogs with CDVD showed that the N-terminal fragment of proBNP (NT-proBNP) is correlated with the severity of mitral regurgitation. In this study a cut off of 466 pmol/L had 80% sensitivity and 76% specificity with an area under the curve of 0.81 in predicting 12-month progression (cardiac death or CHF)
    - Treatment of Stage B dogs has been object of some controversies in the past years. The ACVIM consensus group recommend unanimously of not treating dogs with CDVD in stage B1 of the disease. The same group however does no reach a consensus for

dogs with cardiac enlargement. Two multicenter double blinded studies evaluating the efficacy of enalapril on delaying the onset of CHF in dogs with CDVD without clinical signs have shown no significant effect of ACE-I therapy on the primary outcome variable, which was time from inclusion in the study to the onset of CHF (*Kvart et al. Efficacy of enalapril for prevention of congestive heart failure in dogs with myxomatous valve disease and asymptomatic mitral regurgitation JVIM 2002, 22; 120-128*; *Atkins et al. Results of the veterinary enalapril trial to prove reduction in onset of heart failure in dogs chronically treated with enalapril alone for compensated, naturally occurring mitral valve insufficiency JAVMA 2007, 231; 1061-1069)*

- Another study reported of a possible benefit of an early treatment with benazepril. However, this is a retrospective case series, which invariably is associated with systematic errors and its results, should be interpreted with caution. A prospective randomized multicenter double-blinded study involving a larger number of dogs would be necessary in order to confirm the results of this study (*Pouchelon et al Effect of benazepril on survival and cardiac events in dogs with asymptomatic mitral valve disease: a retrospective study of 141 case JVIM 2008, 22; 905-914*)
- Data from a pilot study in dogs with naturally occurred CDVD (*Chiavegato D. PhD thesis University of Torino, Italy*) showed that asymptomatic dogs have higher aldosterone levels compared to normal dogs.



- Stage C includes animals with documented cardiac structural abnormalities and current or previous clinical signs of CHF.
    - The ACVIM consensus group unanimously recommends treating these patients with a combination of furosemide, ACE-I and pimobendan.
        - ACE-I and pimobendan are the only drugs that have a *level of evidence A* for treatment of heart failure in dogs.
    - The ACVIM consensus also underlines that the presence of cough and a murmur in a dog with CDVD is not enough to establish the diagnosis of CHF.
    - If it is possible to discontinue the furosemide administration in a patient with a history of CHF, without reoccurrence of clinical signs of CHF, the diagnosis of CHF should be revised.
    - A consensus was not reached for the use of spironolactone, digoxin or Beta blockers.
    - Maintaining adequate caloric intake (60 kcal/kg body weight) to minimize weight loss is an unanimous recommendation of the ACVIM consensus group
    - STAGE C is a dynamic stage. Affected dogs can be stable for some time and present sudden onset of pulmonary edema. These patients need hospitalization and more aggressive therapy (see treatment for acute heart failure stage D)
- Stage D includes dogs refractory to the treatment for stage C. These dogs can present acute or chronic heart failure.
    - The ACVIM consensus doesn’t really define what refractoriness to standard treatment is. In human beings this is usually defined as occurrence of CHF despite the use of the maximum tolerated doses of drugs. In the QUEST study refractoriness to treatment was defined as the presence of persistent dyspnea, progressive ascites, severe cardiac cachexia or severe exercise intolerance despite receiving or failing to tolerate a daily dose of furosemide of 12 mg/kg PO and of spironolactone of 6 mg/kg PO, in addition to other medications.

- Refractory CHF requires the use of higher doses of diuretics and this increases the risk of inducing renal failure or electrolyte imbalances.
- The ACVIM consensus recommends the following treatment for acute refractory CHF:
    - Furosemide as an IV bolus followed by additional IV boluses or CRI at a dosage of 1 mg/kg/h
    - Centeses, as needed
    - Oxygen supplementation
    - More vigorous afterload reduction (sodium nitroprusside, hydralazine or amlodipine)
    - Careful monitoring of renal function and blood pressure
- The ACVIM consensus group recommends the following treatment for chronic refractory CHF:
    - Higher dose of furosemide. It can be necessary to change the route of administration in these patients (i.e. 1 dose SQ and 2 doses PO)
    - Spironolactone (if it was not started in stage C)
    - Avoid the use of Beta blockers (however if a dog was previously on a beta blocker some ACVIM panelists would suggest to not discontinue it).
    - No consensus was reached on:
        - Adding a third diuretic (hydrochorthiazide)
        - Increasing the dose of pimobendan (3rd 0.3 mg/kg daily dose)
        - Digoxin
        - Sildenafil (for dogs with pulmonary hypertension)
        - Cough suppressants or bronchodilators

... ACVIM Consensus Group ... the presence of cough and a murmur ... is not enough to establish the diagnosis of CHF. (Atkins et al. JVIM 2009) .....

Congestive Heart Failure Is Not a Primary Cause of Coughing in Dogs with Chronic Degenerative Mitral Valve Disease (MMVD).

Abstract presented at the 2011 ECVIM Congress, Sevilla, Spain.

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Introduction

Coughing is an important physiological mechanism that maintains healthy respiratory function by removing potentially harmful substances from the airways. Stimulation of the cough reflex does not occur in deeper airways or respiratory parenchyma (smaller bronchi, bronchioles, alveoli). According to this observation, cardiogenic pulmonary oedema (congestive heart failure; CHF) should not be an expected cause of cough. The aim of our study was to investigate the association between presence of coughing and potential causes of cough, such as CHF, airway disease and cardiomegaly in dogs affected by naturally acquired MMVD.

Methods

Clinical records of 204 dogs affected by MMVD that underwent full cardiac evaluation were retrospectively reviewed. Exclusion criteria included incomplete records, equivocal diagnosis, concomitant presence of other cardiac disease, administration of antitussives and/or furosemide in the 24h prior to cardiology consultation. Echocardiographic and radiographic interpretations were reviewed in a blind fashion by 2 boarded cardiologists and 2 boarded radiologists respectively. Univariate and multivariate logistic models were utilized to assess the patient's likelihood of exhibiting coughing. Interaction models were also generated to address the interaction of increased left atrial (LA) size and presence of airway disease.

Results

Univariate analyses showed that CHF is not a predictor of coughing (OR = 1.27; 0.66, 2.45), while airway disease (OR = 3.85; 2.15, 6.88) and increased

LA size (OR = 3.48; 2.15, 6.88) enhance the risk of coughing in dogs with MMVD. The same risk factors were significant in multivariate analyses. While compelling to suggest that a divergent interaction effect is present, the interaction terms were non-significant for the enlarged LA by airway disease (p = 0.3992) suggesting that both of these main effects are acting statistically independently.

Conclusion

This study supports our hypothesis that CHF is not a primary cause of coughing in dogs with MMVD. Instead, airway disease and cardiomegaly represent important risk factors for the development of cough in these patients. This important finding should be taken into account when considering diagnosis and clinical management of CHF in dogs with MMVD.

Conclusions

- CDVD is a very common disease
- Most dogs do not progress to CHF
- CDVD occurs in dogs commonly affected by upper and/or lower airways dz
- Tachypnoea/dyspnoea appear to be more reliable signs of CHF than coughing, thereby RRR/SRR should
- Thoracic radiographs are absolutely necessary to diagnose L-CHF and to optimize treatment
- Treatment in the early stages of dz is not recommended

Thank You For Your Attention.