Canine Myxomatous Valve Disease
Diagnosis, Staging & Medical Management
Lecture Notes

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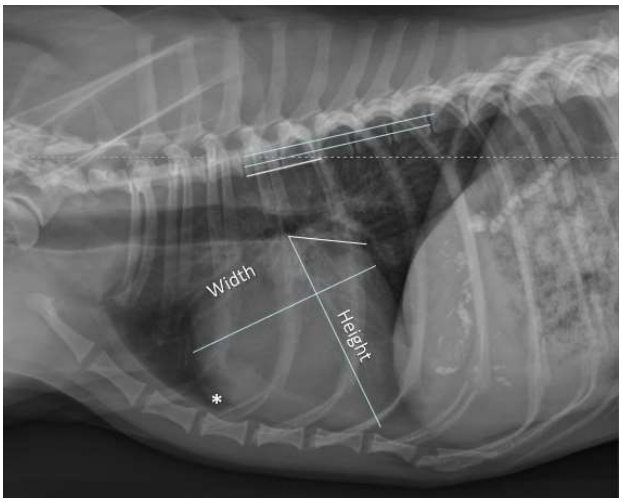
Topics: Canine Myxomatous Mitral Valve Disease –
Diagnosis, Staging, Outcomes & Management

Topic 1: Overview of myxomatous valve disease
- Lesions, Pathogenesis, Functional disturbances
- Recognition & Diagnosis → & Diagnostic Testing
- Clinical Outcomes → Therapeutic implications

Topic 2: Staging of myxomatous valve disease (A-B-C-D)
Topic 3: Drugs for treating the stages of MVD (overview)
Topic 4: Therapy of asymptomatic MVD (Stage B)
Topic 5: Therapy of CHF – Hospital and chronic (home)

Case Example: Oliver – 8-year-old MC Cavalier King Charles Spaniel

- Referred for evaluation of a **cardiac murmur**
- *Healthy* dog – great exercise capacity (miles each day) – good BCS
- *Respiratory* signs – none other than snoring when sleeping and rare cough
- RDVM: *systolic murmur* – suspects valvular heart disease
- Examination: **Grade 3 to 4/6 holosystolic murmur** (PMI: Left apex)
- Mild dental calculus; Physical Exam otherwise WNL
- Normal systolic **BP** (122 – 130 mmHg) | NT-proBNP – not performed
- Oliver – 8-year-old CKCS – No Clinical Signs
  Subjective Cardiomegaly – VHS ≈ 10.1 VB;
  vertebral left atrial score (VLAS) ≈ 2.1 VB



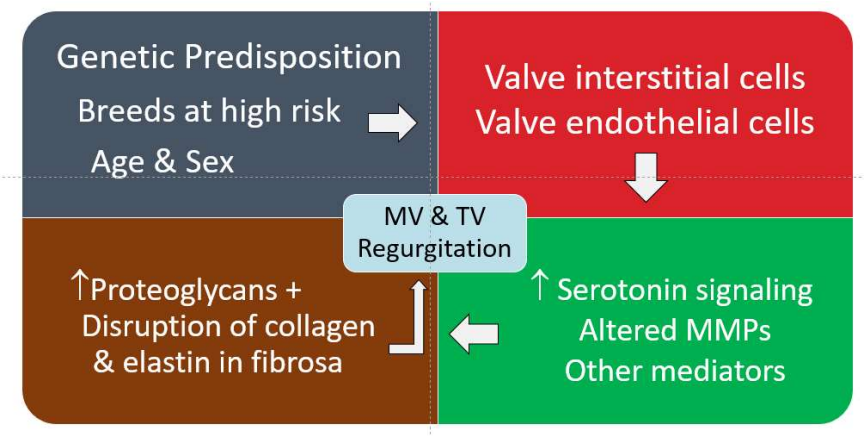
Echocardiogram – *Myxomatous disease* of mitral & tricuspid valves with left ventricular & atrial dilation – mild to moderate

Patient Management Decisions:
- How severe? – What stage of (asymptomatic) disease?
- What therapies (if any) should be initiated now? What criteria?
- Is echocardiography always needed?
- How should he be monitored at home?
- What about rechecks during asymptomatic phase?

Myxomatous Valvular Disease

- Degenerative disorder (Whitney classification)
- Nodular thickening of MV & TV
- Endocardium is smooth & glistening
  Endocardiosis – not an inflammation
- Valve leaflets appear expansive
  & often prolapse into the LA (+ RA)
- Ruptured chordae tendineae are common
- Histology: myxomatous change – deposition of glycosaminoglycans & proteoglycans
- Histopathology of Myxomatous Mitral Valve Disease
  Valve Thickening & Expansion/Disruption of Central Layers
- MMVD: Ruptured Chordae Tendineae are Common

Factors Involved in the Pathogenesis of MMVD



Functional (Pathophysiologic) Factors in MR

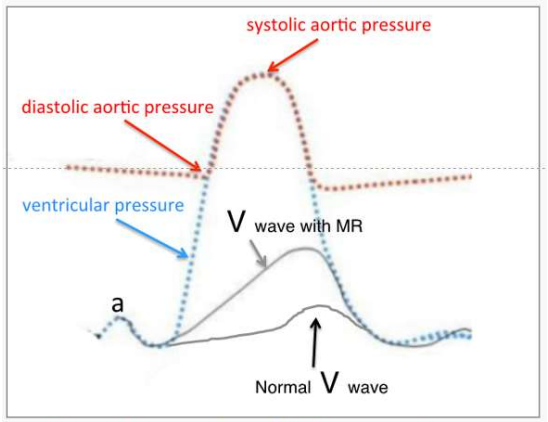
- Geometric Changes occur in LV – Septal Displacement to RV
- LV systolic function is normal to hyperdynamic

MR: V-waves – Impact on mean left atrial pressure & ventricular (diastolic) filling (Doppler E-wave)

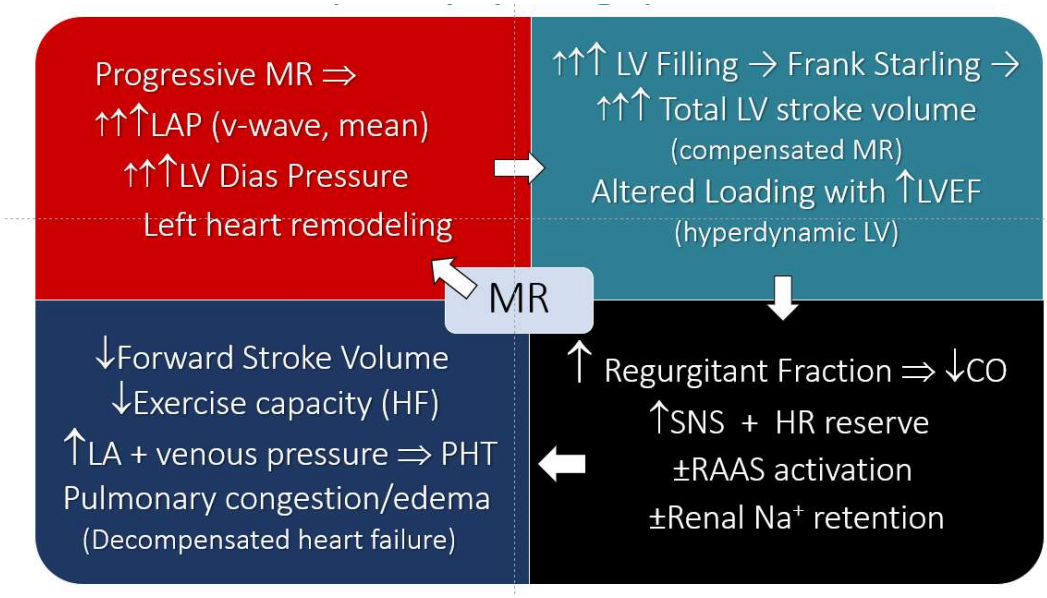
Increases in end-systolic left atrial and mean LA pressures.

Enhances early filling of ventricle to increase preload and support a larger total stroke volume.

Eventually high LA and pulmonary venous pressures can overcome lymphatic drainage of the lung leading to pulmonary edema.



Normal V-wave is from LA filling in systole
Pathologic V-wave from MR

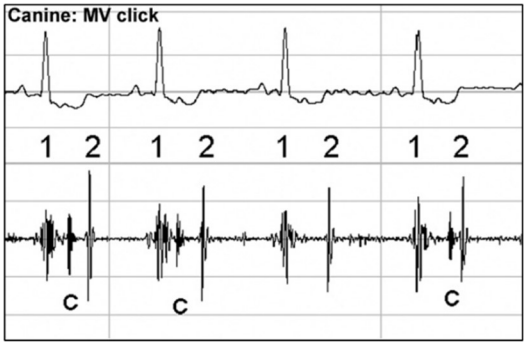


Diagnosis → Clinical Examination & Diagnostic Testing

- Accounts for great majority of cases of heart disease and CHF in general small animal practice
- Signalment: Most common in older dogs <15 kg
- Signs depend on Stage of Disease & Comorbidities

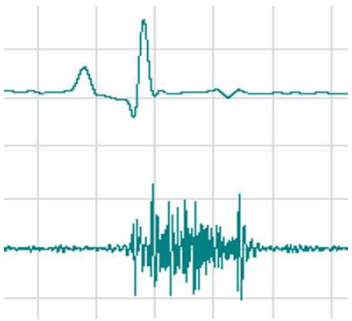
Clinical Signs of Myxomatous Valve Disease

- Nonspecific; Most have none caused by MMVD
- Exercise intolerance (overlooked); Syncope (infrequent)
- Coughing (variable, noncardiac)
- Tachypnea – Hyperpnea – Orthopnea – "Dyspnea" (distress)
- Abdominal swelling (ascites)
- Reduced appetite & weight loss (CHF)



Cardiac Auscultation in MMVD

- (Mid) - systolic clicks: Higher-pitched
  - Often confused as a gallop
  - Correlate to early MV or TV disease
- (Holo)systolic murmurs; PMI MV area & Apex
- Often TR as well (PH)
- <u>Auscultation</u> – Most practical screening for *clinically relevant* disease
- Does <u>murmur intensity</u> correlate to severity?
  To some degree – correlation to soft (1 to 2/6) murmurs ⇒ **mild** disease loud murmurs (5 or 6/6 = thrill) ⇒ **remodeling**
- <u>Respiratory signs</u> in a mature, small-breed dog but **(–) murmur**:
  Heart failure is an ***unlikely*** cause of the clinical signs



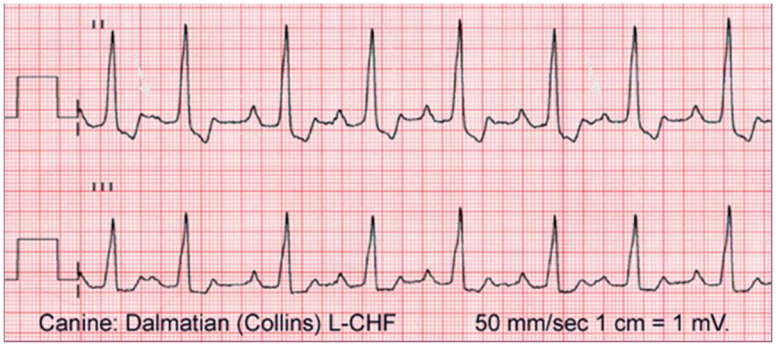
Non-invasive Blood Pressure

Higher BP increases MR fraction & Worsens left-sided CHF

- Comorbidities with risk for systemic HT include CKD and Cushing's disease
- Therapeutic implications:
  ACE inhibitors (or ARBs) (preclinical or chronic CHF)
  Amlodipine or Hydralazine (Decompensated-CHF)
  Nitroprusside or IV NTG (D-CHF) in ICUs

Electrocardiography

- **Minimal value** for sinus rhythm
- **AI** for future analysis?
- **Holter ECG** for prognosis (?)
  Not a routine procedure

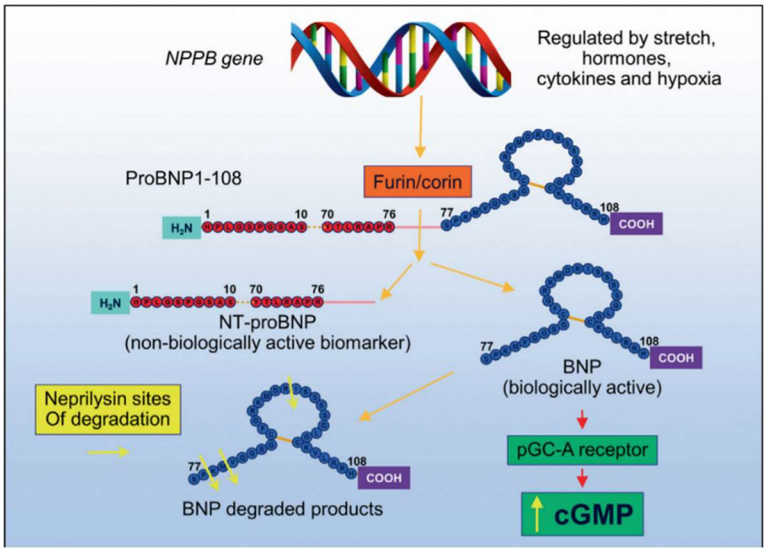


Natriuretic Peptides

(Heart: Endocrine organ)

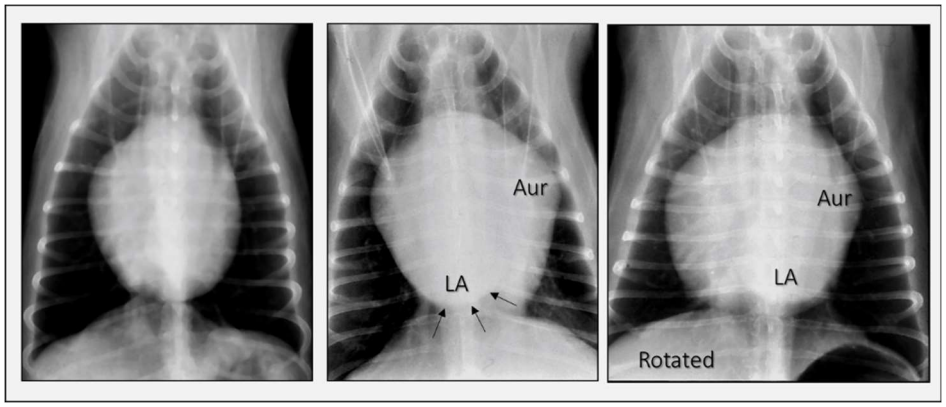
LA or LV stretch → ANP/BNP → natriuresis + vasodilation (~~RAAS~~)

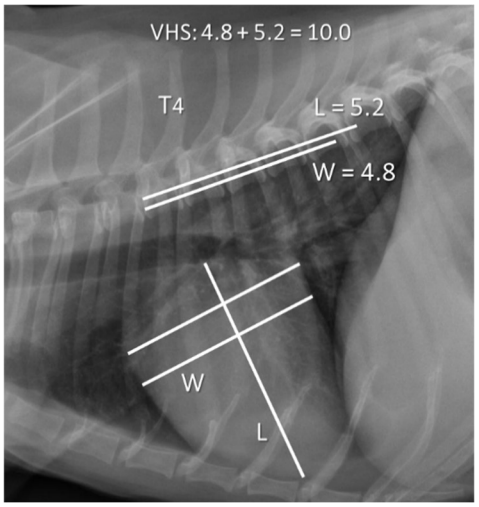
↑NT-pBNP = Dilation | ↑ Wall tension = ↑ Risk of CHF



Radiographic Findings in Myxomatous Mitral Valve Disease

- Slow progression from initial finding of a soft murmur; Often 4 → 5 years before "symptoms"
- Rapid increase in heart size ~6 mos before onset of CHF (Lord, EPIC)
- Quantifying Cardiomegaly – VHD
- Normal combined breed mean value 9.7 (variable); >10.5 to 10.8 often considered "significant" for enlargement, but it is normal for many breeds and this VHS does NOT predict stage B2 due to wide breed variations
- Serial evaluations predict risk of CHF + guide early therapy
- See Buchanan & other Websites for Breed-related VHS values
- VHS: Sources of Variability – Breed | Observer | Technique | Projection





Echocardiography can confirm the diagnosis

- Valve imaging & remodeling
- Doppler Echo Studies
- Used for Diagnosis of MR & Assessment of Severity
- Ventricular Systolic Function – Hyperdynamic (HFpEF)
- LV function more likely to deteriorate dogs > 20kg

Reference Slide for *Echocardiographers*→

Reference Slide for Echocardiographers:

M-mode *overestimates* volumes when there is LV Dilation & LVIDs/ESV (index) by M-mode *underestimate* systolic function

Example:

Prior to MR (5.2 kg)
LVIDd 2.5 cm (EDV ≈ 22 ml)
LVEDDN = $2.5/5.2^{0.294}$ = 1.54
LVIDs 1.6 cm (ESV ≈ 7 ml; ESVI 22 ml/m^2)
Fract Shortening = .36 (36%)
Calc. ESV/EDV = 7/22 ml*
Calculated EF = 68%*
Total/Forward Stroke Vol = 15.1 ml*
Regurgitant Fraction = 0%

Severe, chronic MR (5.2 kg)
LVIDd 3.4 (47.4 ml)
LVEDDN = $3.4/5.2^{0.294}$ = 2.10
LVIDs 1.8 cm (ESV ≈ 9.72 ml; ESVI 32.4 ml/m^2
FS = .47 (47%) – typical hyperdynamic LV
ESV/EDV = 9.72/47.4 ml*
EF = 80%*
Total SV = 37.7 ml, compensated, forward = 15.1 ml*
Est Regurg. Fract = (37.7-15.1 ml)/39 ml = 58%

*Using Teicholz method typically reported in literature: Vol = $7D^3/(2.4+D)$

Common Clinical Outcomes of Canine MMVD

Six-year cardiac mortality for preclinical disease was ~10%

1. **Cardiac Remodeling** (early signs of cardiac dysfunction ("heart failure") like exercise intolerance are often present but overlooked.
2. **Congestive heart failure** ⇒ left-sided > right-sided
3. **Pulmonary HTN** ⇒ exercise weakness collapse/syncope & ascites
4. **Arrhythmias** |**Bronchial compression** (?)| **Ruptured LA** (PE/ASD)

1. Remodeling (LA & LV dilation/eccentric hypertrophy) – "Sufficient" (Stage B2) remodeling is a trigger for more intensive monitoring of RR & initiation of pimobendan – specific criteria discussed below

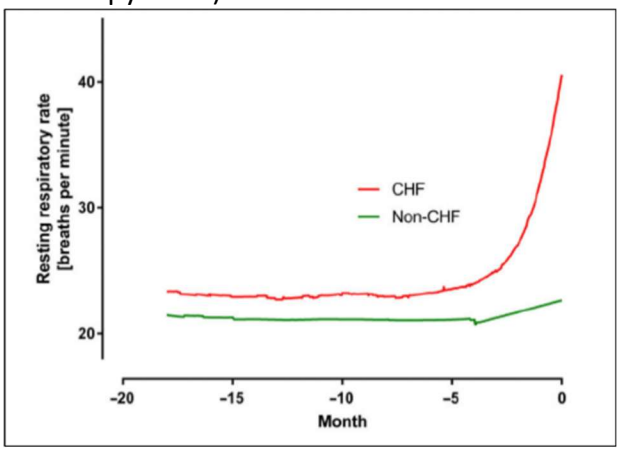
2. CHF – Transition from Asymptomatic Stage B2 → Stage C (CHF)
History: ⇑ RR, Effort ± Cough

- ♥Auscultation ↑HR + Murmur ±S3
- Lung auscultation - ↑bronchial sounds, crackles – But r/o lung disease
- ↑(NT-pro)BNP: Supportive of diagnosis (not diagnostic)
- Thoracic Radiography ⇒ Signs of L-CHF (upcoming)
- Thoracic POCUS ⇒ B-lines (nonattenuating reverbs ∗) ± Pl Eff
- Echo ⇒ Heart disease, enlargement ↑filling pressures

- Metabolic ⇒ Hypoxemia, ↑Lactate, ↑ BUN (+ effects of therapy K^+ Cl^-)

Recognizing CHF: Sleeping & Resting RR ± Cough

- Sleeping | resting RR <25/min ⇒ **stable**
- SRR or RRR >30 to 35/min or ⇒ r/o **CHF**



Documentation of Left-sided CHF

Radiographs: LA + LV dilation + pulm veins + perihilar to diffuse pulmonary interstitial to alveolar infiltrates that decrease with diuretic therapy.

3. Outcome: Pulmonary Hypertension – simplistically categorized as **precapillary** (pulmonary arterial/lung disease) and **post-capillary** (left-heart failure)

- Generally, sildenafil is prescribed when *symptomatic* precapillary pulmonary hypertension is diagnosed after treatment of L-CHF
- Any degree of left-sided CHF should be associated with an equivalent amount of post-capillary (Class 2) PH; in some cases, there is a precapillary component that is "reactive" (and reversible) or structural due to class 1, 3, 4, or 5 related disease(s).

PHT: General Causes & Veterinary Classification (Groups)

1. Pulmonary arterial hypertension
2. **Left-sided heart disease**
3. Respiratory disease | Hypoxia
4. Pulmonary embolic disease
5. Parasitic pulmonary disease
6. Multi-factorial or uncertain

- PHT is common in MMVD, but etiologies are poorly defined
- **Confirming PH:** Challenging without access to Doppler Echo
- **Symptomatic PH**: ↓↓ exercise tolerance, exertional collapse or syncope | possibly R-CHF - often a loud right-sided murmur of TR
- **Ascites** in myxomatous valve disease often due to a combination of tricuspid regurgitation + PH ± AF | Poor prognosis
- **PDE-V inhibitors** (sildenafil) prescribed if PH persists *after initiating therapy* for left-sided CHF (Class **II** vs. Classes **I- III- IV**-related PH)

4. Other Outcomes:

- **Arrhythmias** Complicating MVD – mainly atrial (APCs & AF)
- Outcomes: **LA Tear** – Consequences: Tamponade or ASD

Comorbidities common in Dogs with MMVD

- **Large airway diseases**: Laryngeal dysfunction, Tracheal collapse
- **Bronchomalacia** + **bronchial collapse**
- **Bronchopulmonary diseases**:
  - **Chronic Bronchitis**
  - **Lung diseases** (many) – idiopathic pulmonary **fibrosis**, pneumonia, neoplasia, heartworm disease
- **Noncardiac comorbidities**: CKD, Endocrine, GI, HTN

STAGING:

ACVIM – Four Stages of Myxomatous Mitral Valve Disease

Outlines Therapeutic Approaches by "Stage" of MMVD

Stage A – dogs at risk

Stage B – objective evidence of heart disease (murmur) but no signs of heart failure

B1 – Heart size is normal or there is **insufficient remodeling** to justify therapy based on clinical trial evidence

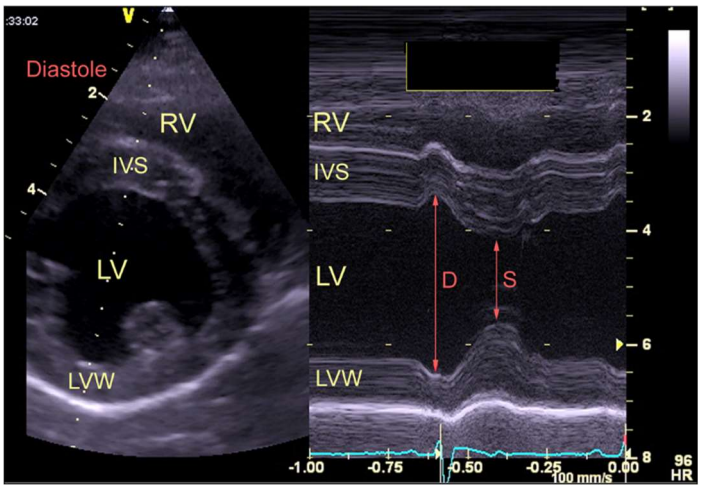
B2 – Evidence of remodeling (cardiomegaly) **sufficient to treat** based on clinical trial evidence – **pimobendan** ± others

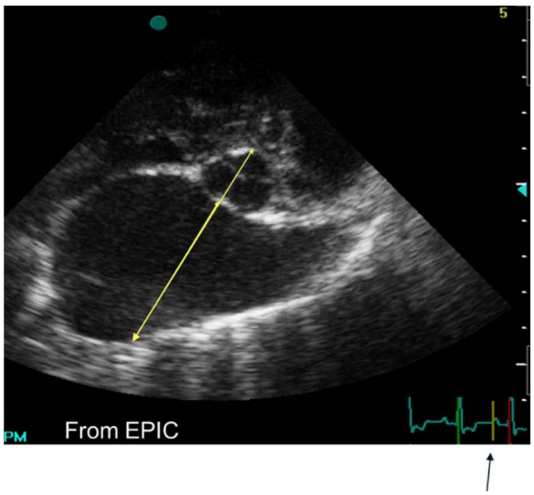
Stage C – Dog currently in or previously experienced **CHF** (on therapy)

Stage D – **Refractory CHF** – **unresponsive** to "standard" therapy & doses

Staging By Echo: LV & LA size increase with progressive MR

- **Current Staging of "B2" is based on the EPIC study criteria**:
- Therapy goal of that study: delay CHF / cardiac death
- Dogs ≥6 years of age; Weight: ≥ 4.1 & ≤ 15 kg
- Systolic murmur MR ≥ Grade **3/6**
- 2D Echo ⇒ characteristic valvular lesions of the mitral valve, LA/Ao (short-axis) **≥1.6**
- M-mode or 2D Echo ⇒ LV diastolic dimension (normalized) * **≥1.7 - LV** (not left atrial) size was the *strongest echo predictor of outcome in the EPIC and DeLAY studies*
- Color Doppler ⇒ MR (confirms auscultation)
- VHS ⇒ remodeling: VHS >10.5 - POOR CRITERION do not use this



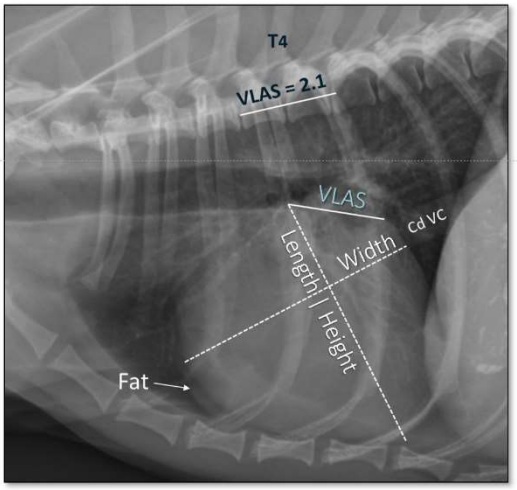


Therapeutic Impact of EPIC study: start **Pimobendan** (0.2-0.3 mg/kg PO bid)

DELAY study II (indicated Predictors of Cardiac Events); strongest predictors:
LV size (LVEDDN), NT-proBNP, LA size (LA/Ao)

Alternative Staging using <u>Thoracic radiography</u>

Vertebral Heart Sum (W+L) & Vertebral Left Atrial Score (VLAS)



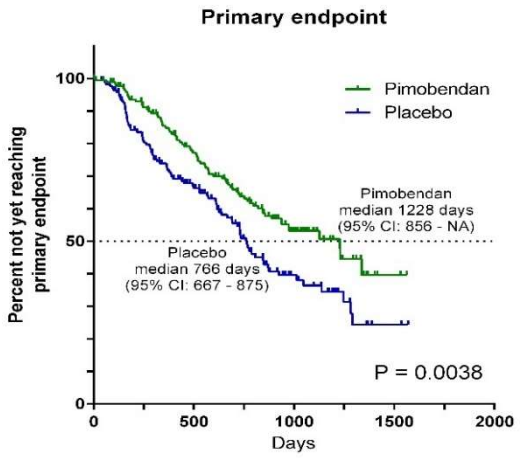
- **VHS** <10.8 VB is unlikely to fulfill stage B2 criteria (no therapy!)
- **VHS** >11.5 to 11.7 **<u>likely</u> fulfills B2** (EPIC-study) criteria for many breeds
- **VLAS** useful to identify **LA enlargement**
- **VLAS** >2.2 to 2.3 is likely enlarged; >2.8 to (3.0 VB) likely corresponding to at least moderate LA enlargement
- VHS & VHS "Velocity" (change/month) – **0.1 VB/month** (B2)

Cardiovascular Drugs for MMVD & Heart Failure Overview (see reference notes for more detail)

- Loop diuretics
- Inodilator (Pimobendan)
- RAAS inhibitors – ACE-inhibitors & spironolactone
- AF: Digoxin & Diltiazem to slow heart rate
- 'Direct' Vasodilators for Decompensated CHF & PH

Prospective Trials of Preclinical (B1 & B2) MMVD

- Enalapril: weak to no evidence for delaying CHF (*VETPROOF, SVEP*)
  - Not tested with pimobendan
  - ?? Suboptimal ACEi dosing; Genetic polymorphisms in ACE?
- *DELay Study* of Spironolactone & Benazepril (MMVD) – no benefit
  - Possibly less remodeling
- *EPIC Trial* of Pimobendan: **CHF or cardiac death**
  - Delayed onset of CHF/endpoint by ~15 months
  - When a dog with MR is Staged as "B2" prescribe → Pimobendan (Vetmedin®) 0.2 to 0.3 mg/kg b.i.d. PO (EPIC, not label dosage)



- Diet in B2 – watch "salt-shaker" & monitor appetite
- Consider RAAS inhibition if CKD or systemic hypertension are documented or in dogs with MR in large breed dogs (secondary DCM is more common)
- Start more frequent home monitoring including
- Sleeping RR (normal <25/min; <30 usually good)
- Follow Exercise tolerance
- Other signs to detect:
  - ↓ weight or BCS
  - Orthopnea
  - ↑↑↑ coughing (r/o primary airway or lung disease)

Hospital Therapy of Pulmonary Edema: "SO-FINE"

- Sedation (butorphanol) + Oxygen+ Furosemide (IV furosemide by bolus or possibly CRI) + Pimobendan (t.i.d. for acute CHF then b.i.d.)
- ± direct vasodilators for life-threatening pulmonary edema
- ± centesis for tense ascites (or large pleural eff, but CHF is less likely)

Transition from Hospital → Home Therapy (see textual notes for details)

- Sedation & Oxygen → Discontinued
- Injectable furosemide → Oral furosemide b.i.d.
- Pimobendan → Continued at b.i.d.
- (±Nitrate) → ACE inhibitor (<u>now or at recheck</u>)
- Spironolactone (<u>now or at recheck</u>)
- Recheck : Sleeping RR + QOL indicators (appetite, attitude, exercise, signs) + Renal panel ± Radiography
- Medications: Add/Adjust dosages accordingly to Stage/Signs/BUN

Managing <u>Chronic</u> CHF in Dogs – "Quad" Therapy
Diet – **A**CE-inhibitors – **F**urosemide – **S**pironolactone – **P**imobendan

Therapeutic Evidence: *Mechanistic* vs. *Clinical Trial*

Summary: clinical trial evidence
<u>In Preclinical MVD</u>

- Pimobendan – effective in delaying CHF in B2

<u>In CHF due to MVD in small-breed dogs (Stages C, D)</u>

- Furosemide & Torsemide – effective
- ACE-inhibitors – effective, but incremental value with pimobendan (on board) is uncertain
- Spironolactone – ditto + modest incremental benefit when added to benazepril & furosemide therapy
- Current approaches – "dual" vs. "triple" vs. "**Quad**"
- Diet - For Stages C & D – a cardiac diet with moderate sodium restriction + good quality protein + (?) heart metabolism support

Stage D CHF – ask why did CHF progress?
Compliance? AF? PHT? RCT? Stabilize & Modify Therapy

Stage D: Progressive disease despite "standard" therapy

- **Torsemide** (torasemide) – Potent loop diuretic – longer duration, better absorption, more potent ~1 mg torsemide ~10 mg furosemide
- Rx for refractory CHF (furosemide dosages >6 to 10 mg/kg/day)
- Longer duration of effect & better GI absorption (b.i.d. dosing)
- Beware: Renal function & Potassium
- Pulmonary (arterial) HTN in MMVD; <u>Symptomatic</u> (Precapillary) Groups I, III or IV, V; Consider PDE-V inhibitor **Sildenafil** or Tadalafil