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.
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)
- Auscultation – Most practical screening for clinically relevant disease
- Does murmur intensity correlate to severity?
  To some degree – correlation to soft (1 to 2/6) murmurs ⇒ mild disease loud murmurs (5 or 6/6 = thrill) ⇒ remodeling
- Respiratory signs 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)

\[ \text{↑NT-pBNP = Dilation | ↑Wall tension = ↑Risk of CHF} \]

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

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 reverb *) ± PL Eff
- Echo ⇒ Heart disease, enlargement ↑ filling pressures

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)
- LVEDD = 2.5/5.2 = 1.54
- LVIs 1.6 cm (ESV = 7 ml; ESVi 22 ml/m²)
- 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)
- LVEDD = 3.4/5.2 = 2.10
- LVIs 1.8 cm (ESV = 9.72 ml; ESVi 32.4 ml/m²)
- 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/(24+D)
• 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:
  o Chronic Bronchitis
  o Lung diseases (many) – idiopathic pulmonary fibrosis, pneumonia, neoplasia, heartworm disease
• Noncardiac comorbidities: CKD, Endocrine, GI, HTN

6 – John Bonagura, DVM, DACVIM – Myxomatous Valve Disease (Vermont VMA)
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 **Thoracic radiography**

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 $11.7$ **likely 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 (now or at recheck)
- Spironolactone (now or at recheck)
- Recheck: Sleeping RR + QOL indicators (appetite, attitude, exercise, signs) + Renal panel ± Radiography
- Medications: Add/Adjust dosages accordingly to Stage/Signs/BUN

Managing Chronic CHF in Dogs – “Quad” Therapy
Diet – ACE-inhibitors – Furosemide – Spironolactone – Pimobendan

Therapeutic Evidence: Mechanistic vs. Clinical Trial

Summary: clinical trial evidence
In Preclinical MVD
- Pimobendan – effective in delaying CHF in B2
In CHF due to MVD in small-breed dogs (Stages C, D)
- 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; Symptomatic (Precapillary) Groups I, III or IV, V; Consider PDE-V inhibitor Sildenafil or Tadalafil