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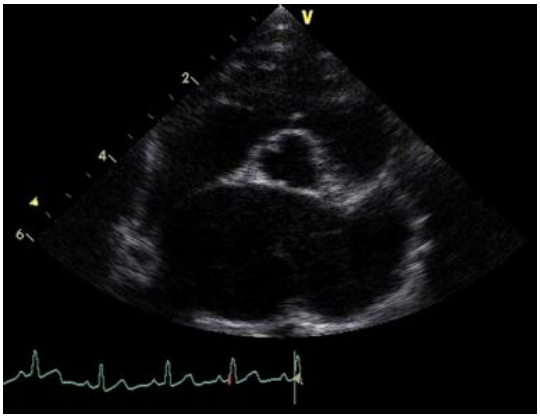
Feline Cardiology Mini Series

Session One: Feline Cardiomyopathies: Diagnosis and Treatment

Nuala Summerfield BSc BVM&S DipACVIM(Cardiology) DipECVIM-CA (Cardiology) MRCVS

European and RCVS Recognised Specialist in Veterinary Cardiology



Introduction

- Cardiomyopathies represent the most important type of feline cardiovascular disease seen in clinical practice.
    - Congenital heart disease is relatively rare in cats.
- Cardiomyopathies can be described as:
    - Primary
    - Secondary
        - E.g. secondary to systemic, metabolic or nutritional disorder.

- N.B. There is a generally accepted classification scheme for feline cardiomyopathies.
    - However, it is important to note that many cases may have overlapping features, so categories do not have sharply defined boundaries:
        - Hypertrophic cardiomyopathy (HCM).
            - Sub-classified into non-obstructive form (HCM) and obstructive form (HOCM).
        - Dilated cardiomyopathy (DCM).
        - Restrictive cardiomyopathy (RCM).
        - Unclassified cardiomyopathy (UCM).
        - Arrhythmogenic right ventricular cardiomyopathy (ARVC).

Hypertrophic Cardiomyopathy

- Most commonly encountered type of feline cardiomyopathy and therefore much more is known about HCM than other types of feline cardiomyopathy.
- Characterised by hypertrophied, non-dilated left ventricle, in the absence of other cardiac disease (e.g. aortic stenosis) or systemic disease (e.g. hyperthyroidism, systemic hypertension) capable of causing left ventricular hypertrophy.
- Left ventricular hypertrophy is defined as end-diastolic measurements of interventricular septum and / or left ventricular free wall > 6 mm in diameter.

- Some cats with HCM have a dynamic left ventricular outflow tract obstruction that causes a sub-aortic pressure gradient (obstructive form of HCM).
    - This is also termed hypertrophic obstructive cardiomyopathy (HOCM).
    - HOCM is typically caused by systolic anterior motion of mitral valve (SAM).
    - SAM results in a left sided systolic heart murmur caused by a combination of mitral regurgitation and dynamic sub-aortic stenosis.
- Cats with non-obstructive form of HCM may not have a heart murmur, as there is no turbulent flow within the cardiac chambers or great vessels.
- So it is important to remember that the absence of a heart murmur does NOT exclude the possibility of myocardial disease such as HCM!
- Non-obstructive form of HCM is more common than obstructive form of HCM.
- All age ranges are affected with HCM, but mean age is reported to be 4.8 – 7 years.
- Male predominance.
- Domestic shorthairs are most frequently affected.

- Inherited in some breeds:
    - Maine Coons, Ragdolls (each has a different mutation in the same gene MYBPC3)
    - Genetic test available, BUT:
        - Not all Maine Coons with HCM have this mutation so probably other genetic mutations involved.
        - Not all Maine Coons with this mutation appear to develop HCM.
- HCM is uncommon in Siamese, Burmese and Abyssinians.

Pathophysiology of HCM:

- Heart failure with HCM is due primarily to diastolic dysfunction.
- Left ventricular filling depends on:
    - Ventricular relaxation, which is an active, energy dependent process, i.e. the thicker the ventricular wall, the longer it will take to relax.
    - Chamber compliance, which is a passive process and is affected by amount of fibrosis within myocardium etc.
- Left ventricular filling pressure increases in cats with HCM, due to delayed ventricular relaxation and myocardial stiffness, which causes left atrial pressure to increase.
- As a result, pulmonary venous pressures increase and eventually pulmonary congestion develops.
- In cats, congestive heart failure may manifest as:
    - Pulmonary oedema (with left-sided CHF only).
        - Same as in dogs.
    - Pleural effusion (with both left and right-sided CHF).
        - Unlike dogs which only develop pleural effusion with right-sided CHF.
    - Pericardial effusion can also develop in some cats with advanced left-sided CHF as well as right-sided CHF.
        - Rarely see pericardial effusion in dogs with CHF.
    - It is the vascular anatomy that makes cats different to dogs!
        - In cats, visceral pleural veins drain into the pulmonary venous circulation, rather than into the systemic venous circulation (the parietal pleural veins drain into the systemic circulation).
        - The pericardium is lined with visceral pleura, so it is possible that the pericardial venous drainage also empties into the pulmonary venous circulation.
        - Therefore increases in pulmonary venous pressure are transmitted to the visceral pleural veins and probably, the pericardial veins.
        - CHF in cats can produce a serous, serosanguinous, pseudochylous or chylous effusion.
            - Not unusual for a serous effusion to progress to a pseudochylous or a chylous effusion (mechanism unknown).
- Other HCM sequelae include:
    - Myocardial ischaemia
    - Coronary arteriosclerosis
    - Ventricular and supraventricular arrhythmias
    - Left atrial thrombus formation.

Dilated Cardiomyopathy

- Rare since routine dietary supplementation with Taurine (essential amino acid in cats).
- Diagnosis is based on echocardiography.
    - Dilated, hypokinetic LV with relatively thin walls.

Restrictive Cardiomyopathy

- Normal to mildly hypertrophied LV walls.
- Mild ventricular dilation.
- Marked atrial dilation (often biatrial).
- Mitral +/- tricuspid insufficiency.
- Low-normal fractional shortening.
- Often have extensive endocardial, sub-endocardial or myocardial fibrosis causing severe diastolic dysfunction.

Unclassified Cardiomyopathy (UCM)

- Some feline myocardial diseases have features that do not fit into a discrete category of HCM, RCM or DCM etc.
- Or may display characteristics of more than one type of cardiomyopathy.
- Some cardiologists believe that UCM is not a true "type" of cardiomyopathy, but actually just represents an "end-stage" of the another form such as HCM.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

- Fibro-fatty infiltration of the right ventricular myocardium.
- Right ventricular chamber enlargement (+/- tricuspid regurgitation).
- Rule out congenital tricuspid valve dysplasia.
- Ventricular arrhythmias are common.
- Signs of right-sided congestive heart failure predominate.

Typical Cardiac History

- Asymptomatic cat with heart murmur, arrhythmia or gallop rhythm detected at routine evaluation.
    - Owner may report cat to be asymptomatic ("normal") at home.
      OR
- Tachypnoea, dyspnoea noticed by owner.
    - N.B. Coughing is rarely observed in cats with pulmonary oedema, unlike dogs (coughing is predominantly a feature of primary lower airway disease in cats e.g. feline asthma).
- Clinical signs associated with arterial thromboembolic episode.
- Syncope
    - Usually exertional syncope associated with left ventricular outflow tract obstruction (i.e. HOCM).
    - But tachy/bradyarrhythmias are also a possible cause of syncope in cats.
- Anorexia, vomiting (may precede overt signs of heart failure by a few days).

Physical Examination and Diagnostic Tests:

- Thoracic auscultation
    - Tachycardia
    - Cardiac arrhythmias
    - Heart murmur
    - Gallop (S_4) sounds
    - Pulmonary crackles

- Muffled heart and lung sounds.

- Careful cardiac auscultation while palpating femoral pulses.
  - Murmurs in cats are often sternal or parasternal.
  - Murmur intensity may be variable.
  - Gallop rhythms and arrhythmias in cats may be intermittent.
- Pay close attention to the pulmonary auscultation, breathing pattern and rate.
- The majority of murmurs in cats arise from the left ventricular outflow tract (LVOT) and right ventricular outflow tract (RVOT).
  - In the dog LVOT and RVOT are up on the side of the chest, at the "heart base".
  - In the cat, they are down on the sternum.
- Higher incidence of physiologic or iatrogenic murmurs in cats vs. dogs
  - i.e. Heart murmurs in the absence of structural heart disease.
  - Cats have very compliant thoracic cages.
  - It is possible to induce a soft murmur in a cat by pressing too hard with a stethoscope while auscultating, effectively "squashing" the heart, most likely the compliant right ventricle, producing dynamic right ventricular obstruction.
  - Important to auscultate cats in a standing or sitting position and to only gently apply the stethoscope to the chest

- Thoracic radiography
  - Cardiomegaly usually evident (unless cat only has mild or early cardiomyopathy without significant left atrial enlargement – more likely in asymptomatic patient).
  - Evidence of congestive heart failure (pulmonary oedema +/- pleural effusion).

- Electrocardiography (ECG)
  - ECG abnormalities are highly variable.
    - If present, these can include enlargement pattern, conduction system disturbance (left anterior fascicular block), supraventricular tachycardia, ventricular tachycardia, isolated premature atrial and ventricular complexes.

- Echocardiography
  - Provides rapid, non-invasive assessment of cardiac structure and function.
  - Required for definitive diagnosis of type of cardiomyopathy:
    - Allows assessment of severity of left ventricular hypertrophy in HCM.
    - Allows detection of left ventricular outflow tract obstruction in HOCM.
    - Allows diagnosis of other causes of turbulent blood flow giving rise to cardiac murmur (e.g. mitral regurgitation).
    - Allows evaluation of myocardial function (diastolic and systolic).
    - Allows detection of intra-cardiac thrombi.
    - Allows detection of other concurrent cardiac conditions (e.g. aortic stenosis, which could be a possible cause of left ventricular hypertrophy).

- Blood tests
    - Haematology.
        - Typically normal.
    - Biochemistry
        - May see pre-renal azotaemia in CHF.
        - Otherwise non-specific, but important as baseline for medication monitoring.
        - Renal parameters and electrolytes should be monitored with ACE inhibitors, diuretics and antiarrhythmic therapy.
    - Thyroid (T4)
        - Rule out hyperthyroidism as potential cause of left ventricular hypertrophy in older cats (check for goiter).
    - NT-proBNP
        - BNP is neurohormone secreted by the ventricle in response to increased wall stress (pressure +/- volume).
        - It counteracts the effects of RAAS stimulation, resulting in natriuresis and vasodilation.
        - Commercially available assay utilises ELISA technology (feline specific).
        - Assay detects inactive NT-proBNP, as more stable than active compound.
        - Potential roles of NT pro-BNP
            - Distinguishing cardiac from non-cardiac dyspnea:
                - NT-pro BNP is increased in cats with clinically relevant structural heart disease.
                - Highest increase is seen in symptomatic cats with CHF.
                - Therefore may be useful additional diagnostic test for distinguishing cardiac from non-cardiac dyspnoea in the cat, particularly when symptoms are ambiguous.
                - Do not use as sole test for CHF!
                - NOT a substitute for good physical exam, history, Xrays.
                - Recent study *(Singletary et al JVIM 2012)* showed that NT-pro BNP, when used together with standard diagnostic tests, significantly improved diagnostic accuracy and confidence in a general practice setting.
            - As a screening test for occult cardiomyopathy:
                - Conflicting data on utility of NT-pro BNP to detect cats with asymptomatic (occult) cardiomyopathy.
                - Study by *Fox et al JVIM 2011* showed that NT-pro BNP could reliably discriminate normal cats from cats with occult cardiomyopathy in a selected study population of > 200 cats.
                - Was most reliable for identifying moderate to severe occult cardiomyopathy.
                - Further studies needed to assess NT-pro BNP test performance in unselected general feline population (i.e. true screening test).
            - Limitations:
                - Not 100% reliable!
                - If NT-proBNP is normal in a cat suspected of having heart disease (e.g. cat with heart murmur), an echo is still needed to rule out cardiomyopathy.

- Renal dysfunction, systemic and pulmonary hypertension can affect the levels of circulating NT-proBNP in cats and produce false positive results.
- Indiscriminate testing of patients with little likelihood of CHF will lead to high incidence of false positive results and frustration for clinician and owner.

Therapy:

- The clinical course and outcome of cats with cardiomyopathy is hard to predict, which complicates therapy decisions.
- Diuretics are certainly NOT indicated in asymptomatic cats that have never had congestive heart failure and may in fact be detrimental in these patients by stimulating the renin-angiotensin-aldosterone system (RAAS) prematurely.
- However, it is unclear whether beta-blockers, calcium channel blockers and ACE-inhibitors delay disease progression, protect against sudden cardiac death, or improve prognosis in asymptomatic cats with cardiomyopathy.

- <u>Treatment considerations for asymptomatic but potentially high-risk patients</u>

  - Several important features may increase the risks of morbidity and mortality in asymptomatic cats, and therefore may warrant prophylactic treatment.

  i. Cats with occult HCM and marked left ventricular hypertrophy.
     - "Marked hypertrophy" refers to interventricular septum and/or free wall thicknesses in diastole > 8 mm.
     - The following drugs may be beneficial:
       - Beta-blockers
         - To slow heart rate, decrease dynamic left ventricular outflow tract gradients and decrease myocardial oxygen demand.
       - Calcium channel blockers
         - To improve ventricular diastolic relaxation and filling.
       - ACE Inhibitors
         - To blunt neuroendocrine (RAAS) activation and prevent cardiovascular remodelling.

  ii. Spontaneous echo contrast ("Smoke")
     - Indicative of left atrial blood stasis and considered to be associated with increased thromboembolic risk.
     - Anti-coagulant or anti-platelet therapy could be considered (please refer to notes on feline arterial thromboembolic disease for further detail).

  iii. Tachyarrhythmias
     - Rapid heart rates will decrease diastolic filling time, which can:
       - Increase dynamic left ventricular outflow tract gradients in cats with HOCM.
       - Decrease cardiac output.
       - Increase myocardial oxygen demand.
       - Decrease coronary artery perfusion.
     - Beta-blockers are useful for controlling supraventricular AND ventricular tachyarrhythmias in cats.

iv. Syncope
- Recurrent syncope is a risk factor for sudden death in humans with HCM.
- In cats with HCM, this is usually exertional syncope associated with left ventricular outflow tract obstruction (i.e. HOCM).
- Beta-blocker therapy may help to decrease or abolish dynamic left ventricular outflow tract obstruction, and therefore control syncope.
- NB. Arrhythmias (tachycardias & bradycardias) can also cause syncope.

v. "High risk" family history
- Maine Coon, Ragdoll, Sphynx, British Shorthair, Persian, Norwegian Forest Cat are all predisposed breeds for HCM.
- N.B. Maine Coons, Ragdolls, Sphynx often develop HCM at a young age.
- Recommend serial echocardiographic monitoring of any at-risk cat.
- In the case of familial HCM early intervention with Ca-channel blocker or Beta-blocker may be helpful?? (mixed opinions).

- <u>Treatment of symptomatic cats</u>

  - **Initial emergency treatment (first 24-48 hrs):**
    - Therapy should be aimed at:
      - Eliminating life-threatening pulmonary oedema and pleural effusions.
      - Controlling haemodynamically significant tachyarrhythmias – to improve ventricular filling and relaxation, and to decrease dynamic left ventricular outflow tract obstruction.
      - Managing arterial thromboembolism and its consequences (please refer to accompanying notes on feline arterial thromboembolic disease (FATE) for more detail).
      - N.B. Avoid stressing dyspnoeic cats – these are VERY unstable patients!
      - Hospitalisation for cage rest and close monitoring.
      - Oxygen therapy.
      - Thoracocentesis as required
        - Significant volume pleural effusions must be drained initially – will not resolve with furosemide therapy.
      - Blood pressure if possible.
      - Furosemide IV or IM (1-2 mg/kg boluses).
        - Usually need to give IV every 2-6 hours as peak IV effect at 30 mins.
        - Cats are more sensitive to furosemide side effects (e.g. dehydration, hypokalaemia, azotaemia) than dogs - monitor closely!
      - Pimobendan for systolic support?
        - Off licence use.
        - Suggested dose: 1.25 mg per cat PO q 12 hr.
      - ACE I
        - Continue if already on ACE I.
        - If not, stabilise any hypotension before starting ACE I in acute phase.
      - Nitroglycerine ointment (2%)?
        - Venodilation to decrease venous congestion.
        - WEAR GLOVES!
        - Pea sized bleb applied to hairless area inside pinna q 6-8 hr.

        - Address heart rate and rhythm if necessary to stabilise patient
            - Calcium channel blockers
            - Beta-blockers
                - CARE in cats with low FS% as may decrease systolic function further and worsen CHF.
            - Digoxin not used for acute situation.

        - Consider any concurrent systemic disease when deciding on best treatment options.
            - Systemic hypertension, Hyper T4, CRF.

- **Chronic maintenance therapy**
    - Therapy should be aimed at:
        - Maintaining cardiac compensation.
        - Preventing arterial thromboembolism.
        - Preventing further myocardial remodelling.
        - Improving quality of life.
        - Prolonging survival.
        - Identifying and treating underlying systemic conditions and risk factors.
            - E.g. systemic hypertension, hyperthroidism, taurine-deficient diets etc.
    - Diuretics
        - Goal of diuretic therapy is to control signs of congestive heart failure.
        - As soon as breathing normalises (< 30 breaths / min), furosemide is changed from IV IM to PO administration and the dose is gradually decreased to lowest possible effective dose.
        - **Furosemide**
            - Typically start off by giving 5 mg per cat PO q 12-24 hrs.
            - May need higher maintenance dose in some cats
            - It may be possible to gradually decrease this dose further, as long as owners are instructed to monitor respiratory rate and effort closely at home.

        - As heart failure progresses, cats will require increasing doses of furosemide and may benefit from the addition of a second diuretic, such as a potassium sparing diuretic (e.g. spironolactone).
        - **Spironolactone**
            - Weak diuretic. NOT first line diuretic (not a substitute for furosemide).
            - Aldosterone antagonist, independent of diuretic action.
                - May be more important role?
            - 2 mg/kg PO q 24 hr effectively inhibits aldosterone and has diuretic effect in dogs.
            - Suggested starting dose: 3.125 - 6.25 mg per cat PO q 24 hr.
            - Increased absorption if given with food.
            - Usually well tolerated (but can cause facial pruritus, lethargy, vomiting, diarrhoea, hyperkalaemia).
        - N.B. BUN, creatinine and electrolytes should be monitored in all cats on chronic diuretic therapy.

- Additional pharmacologic options can be considered for the following theoretical reasons:
  - Beta-blockers
    - To decrease dynamic left ventricular outflow tract gradients.
    - To control tachyarrhythmias.
    - To decrease dynamic LVOT gradients (HOCM).
    - To control tachyarrhythmias.
    - SVTs and VTs in cats.
    - Start dosing low and increase to effect.
    - **Atenolol**: 6.25 mg per cat PO q 12-24 hr.
    - Also available as liquid - Tenormin syrup (Atenolol 5mg/ml).
    - Enables a lower dose to be given (e.g. small or geriatric cat).
    - May improve compliance (easier than giving pill?).
    - Absorption of liquid seems to be better than tablet form so start cautiously.
    - Can cause lethargy and bradycardia.

  - Calcium channel blockers
    - To improve ventricular diastolic relaxation and filling.
    - Improve diastolic relaxation and LV filling.
    - Decrease dynamic LVOT gradients in cats with HOCM (less effective than beta-blockers?).
    - Control tachyarrhythmias (SVTs only).
    - Start low and increase dose to effect.
    - Can cause lethargy, vomiting, bradycardia.
    - **Diltiazem** (Hypercard 10mg)
    - May need to give PO q 8 hr, which often makes compliance a problem.

  - ACE inhibitors
    - To blunt neuroendocrine (RAAS) activation and prevent cardiovascular remodelling.
    - N.B. theoretical concern that decreasing blood pressure with ACE inhibitors could be deleterious in cats with severe dynamic left ventricular outflow tract obstruction or syncope.

  - Inodilators
    - Positive inotrope.
    - Vasodilation.
    - Anti-cytokine effects (clinical relevance?).
    - Anti-platelets effects (clinical relevance?).
    - **Pimobendan** licensed for CHF in dogs.
    - Not licenced for cats.
    - Myocardial failure can occur in the latter stages of HCM and in cats with UCM or RCM.
    - BUT, many cats with HCM and heart failure often have left ventricular outflow tract obstruction (LVOT), and as a positive inotropic agent pimobendan could potentially worsen this obstruction.
    - Therapy with pimobendan should only be considered if there is evidence of systolic dysfunction and absence of significant LVOT obstruction.

        - A prospective, randomized, controlled clinical trial is required to more accurately assess efficacy, safety and dosage of pimobendan therapy in cats.
        - Suggested dose (from personal experience): 0.625 – 1.25 mg per cat PO q 12 hr (depending on size of cat and degree of systolic dysfunction).

HCM prognosis

- Minimal survival data for other types of cardiomyopathy, as most studies have focused on HCM.
- Asymptomatic HCM / HOCM cats:
    - Variable prognosis reported.
    - Most progress very slowly over 3-5 years.
    - Predisposed breeds that develop HCM at young age can have more rapid progression (e.g. Maine Coon, Ragdoll, Sphynx) with earlier onset of clinical signs.
- Cats with HCM and CHF:
    - Variable prognosis reported.
    - Study in 1992 showed a 3 month survival rate.
    - Study in 2002 showed a 1.5 year survival rate.
        - Is this because we are becoming better at diagnosing and treating CHF?
- Cats with HCM and systemic thromboembolism:
    - Also variable prognosis reported!
    - But in general considered poor.
    - 2 months to 11 months depending on study.