Feline Cardiology Mini Series

Session Two: Cats and Clots: Management of Feline Thromboembolic Disease & Feline Hypertension: Diagnosis and Management

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Cats and Clots: Feline Arterial Thromboembolism (FATE)

Introduction

- Feline arterial thromboembolism (FATE) is one of the most serious complications associated with cardiomyopathy in the cat.
- Thrombosis represents clot formation within a cardiac chamber or vascular lumen.
- Thromboembolization occurs when a clot or part of a clot lodges within a vessel.
- In cats, thrombi are found in the left atrial chamber, left ventricular chamber or both.
- Right-sided heart and deep vein thrombosis are rare in cats.
- Emboli most commonly lodge in distal aortic trifurcation (saddle thrombus), but can occlude a coronary, cerebral, renal, mesenteric or brachial artery.
- FATE can occur with any type of cardiomyopathy, but is most commonly associated with hypertrophic cardiomyopathy (HCM).
- Arterial thromboembolism is also sometimes seen in cats with no underlying heart disease, where the hypercoagulable state is due to systemic disease, E.g.
    - Protein losing disease (e.g. kidney disease)
    - Infection (e.g. endocarditis)
    - Neoplasia
    - Steroid administration.

Pathophysiology

- Thrombosis requires one or more of three essential conditions (Virchow's triad) to be present:
    1. Local vessel or tissue injury
        - Endothelial damage induces platelet adhesion and aggregation, and activates clotting cascade.
    2. Circulatory stasis
        - Enlarged left atrium/left atrial appendage due to diastolic/systolic impairment and poor atrial emptying.
        - Decreased clearance of activated clotting factors.
    3. Altered blood coagulability
        - Feline platelets are very reactive (platelet reactivity increased further in cardiomyopathic cats).
- Collateral circulation plays critical role in progression and resolution of clinical thromboembolic disease, and is modulated by vasoactive substances released by the clot (e.g. serotonin, prostaglandins, thromboxane A_2).
- Sudden complete arterial occlusion, coupled with decreased collateral circulation, causes substantial tissue injury and ischaemic neuromyopathy.

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Clinical Manifestations

- Clinical consequences of FATE are dependant on:
    - Site of arterial obstruction
    - Functional patency of collateral circulation
    - Duration and completeness of obstruction
    - Development of serious complications (e.g. self-mutilation, limb necrosis, hyperkalaemia etc).

History

- Often per acute onset of symptoms.
- Can be mmistaken for trauma/neurologic disease.
- Often no history of heart disease.

Physical examination

- Dependant on specific tissues/organs that are embolised.
    - Hind limb paresis/paralysis (unilateral or bilateral) from distal aortic thromboembolism ("saddle thrombus").
    - Forelimb paresis/paralysis from brachial artery thromboembolism (R forelimb affected >L forelimb).
    - Azotaemia from renal infarction.
    - Bloody diarrhoea from mesenteric infarction.
- Thromboemboli affecting extremities result in clinical signs that relate to the four "P"s:
    - Paralysis/Paresis
    - Pain
    - Pulselesness
    - Polar (cold distal limbs and pads).
- Painful/firm muscles
    - With saddle thrombus, cranial tibial and gastrocnemius muscles become firm from ischaemic myopathy by 10-12 hours post embolization; become softer 24 – 72 hours later.
- Vocalization due to pain.
- Dehydration and hypothermia (hypothermia is a poor prognostic indicator).
- Dyspnoea, tachypnoea, anorexia and syncope may also be present due to congestive heart failure (CHF).
- Sudden death is a possible initial clinical finding.

Cardiac evaluation

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

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    - Pulmonary crackles
    - Muffled heart and lung sounds.
- Thoracic radiography
    - Cardiomegaly usually evident
    - Evidence of CHF (pulmonary oedema, pleural effusion).
- Electrocardiography (ECG)
    - Abnormalities present in most cases, which include enlargement pattern, conduction system disturbance, supraventricular tachycardia, ventricular tachycardia, isolated premature atrial and ventricular complexes, and atrial standstill with sinoventricular rhythm (secondary to hyperkalaemia as a result of reperfusion injury).
- Clinical Pathology
    - Abnormalities present in most cases, which include azotaemia, increased lactate dehydrogenase and creatine phosphokinase (consistent with widespread muscle cell injury), hyperglycaemia, hyperkalaemia, hypokalaemia.
- Echocardiography
    - Provides rapid, non-invasive assessment of cardiac structure and function and detects intra-cardiac thrombi when present.
    - Left atrial enlargement usually present.
    - May see spontaneous echo contrast (“smoke”), associated with blood stasis and considered to be a marker for increased thromboembolic risk.
- Blood pressure measurement
    - Rule out systemic hypertension as a cause for underlying heart disease (increased cardiac afterload causing secondary left ventricular hypertrophy).
    - Ophthalmoscopy can also be performed to check for hypertensive retinal disease (retinal vessel tortuosity and retinal haemorrhage).

<u>Other diagnostic tests</u>

- Blood flow in affected limb can be assessed by:
    - Cutting nail to quick to check for bleeding
    - Doppler to detect blood flow in artery.
- Ultrasound to image thromboembolus in abdominal aorta.

<u>Differential Diagnoses</u>

- For acute posterior paresis:
    - Trauma
    - Intervertebral disc extrusion
    - Spinal lymphosarcoma or other neoplasia
    - Fibrocartilagenous embolus.

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- For acute forelimb monoparesis:
    - Trauma
    - Foreign body
    - Brachial plexus avulsion.
- Arterial thromboembolism is relatively easy to confirm from physical examination and cardiac evaluation.

Therapy

- Manage congestive heart failure or serious cardiac arrhythmias when present.

Reperfusion injury

- Hydrogen and potassium ions are released from damaged cells once reperfusion occurs to damaged muscle tissue.
- Can lead to severe metabolic acidosis and hyperkalemia.
- Often fatal (cardiac arrest).

Anticoagulant therapy

- These drugs have no effect on established thrombi, but help to prevent further thrombus formation from the activated blood-clotting pathways.
- E.g. Heparin, warfarin.
- Little published data on efficacy of anticoagulant therapy in cats.
- Must monitor clotting profiles closely.
- Bleeding is a major complication and can be fatal.

Unfractionated heparin:

- Binds to plasma ATIII to neutralise thrombin and activated factors XII, XI, X and IX
- Preventing activation of coagulation cascade
- Doses vary widely
    - Initial dose of 100-200 IU/kg IV
    - Then 50-100 IU/kg SQ q 6-8 hrs
- Adjust dose to prolong aPTT to 1.5 to 2.0 x pre-treatment values

- Bleeding is major complication
- Monitor coagulation profiles

Low molecular weight heparin

- Derived from de-polymerization of unfractionated heparin
- Only anti-factor Xa activity can be used to monitor LMWH
- The aPTT is not practical for monitoring patients receiving LMWH because LMWH does not significantly affect aPTT
- Prolongation of the aPTT is largely dependent on low thrombin activity
- The anti-thrombin activity of LMWH is much less than its anti-factor Xa activity

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- Cats have rapid absorption and elimination kinetics with LMWH and need frequent dosing
- Current dosage recommendations may not be adequate for all cats (need further studies):
    - Enoxaparin 1-2 mg/kg SQ only q12-24 hr
    - Dalteparin 100-200 IU/kg SQ only q12-24 hr
- Many cats will require at least q8 hr treatment
- Monitoring via anti-FXa is recommended when initiating therapy
- 'Target' anti-FXa levels in healthy cats or cats prone to ATE are unknown
- Bleeding seems less of a risk

Anti-Platelet therapy

- Prothrombotic factors are prevalent in feline cardiomyopathy, therefore pharmacologic measures that are directed at modifying platelet aggregation may prevent arterial thromboembolism.
- E.g. Aspirin, Clopidogrel
- GI side-effects are recognized side-effect

Aspirin

- Aspirin inhibition of Cyclooxygenase-1 (COX-1) decreases Thromboxane A2 (TXA2) production
- TxA2 needed for platelet recruitment and activation
- By modifying platelet aggregation, may prevent further thrombus formation
- Effectiveness??
    - retrospective studies show cats have high re-embolisation rates on aspirin
- Current recommended dose for cats is 18.75 mg per cat (1/4 of 75 mg tablet) PO q 48-72 hr

Clopidogrel

- Works by preventing a natural substance called adenosine diphosphate (ADP) from binding to its receptors on platelets
- ADP is one of the chemicals in the body that cause platelets to clump together and start the process of blood clotting
- Current recommended dose for cats is 18.75 mg per cat (1/4 of 75 mg tablet) PO q 24 hr

FATCAT study:

- The Feline Arterial Thromboembolism: Clopidogrel vs. Aspirin Trial (or FATCAT) study
- Enrolled 76 cats that had experienced thromboembolism as a result of heart disease and had survived for between 1 and 3 months
- Cats randomised to receive either clopidogrel or aspirin

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- Then followed for 12 months to determine how each group compared with respect to recurrence of thromboembolism and survival
- Results (released 2013) showed that cats receiving clopidogrel tolerated it well and survived longer, with a longer time to repeat thrombosis than did cats receiving aspirin
- This is the first demonstration of a clinical benefit to the use of clopidogrel to treat cats that have experienced thromboembolism secondary to heart disease

Is it better to use aspirin and clopidogrel together?

- The concurrent usage of aspirin & clopidogrel is recommended in human patients
- Platelet aggregation is prevented through 2 separate pathways
- No studies have been done on the efficacy of this combination in cats

Supportive measures

- Analgesia is very important as these cats are often extremely painful!!
- Most cats are hypothermic, dehydrated, anorectic and hypokalaemic, so it is important to maintain body temperature, hydration, nutritional support and electrolyte balance.
  - Care with IV fluid therapy if cat is in congestive heart failure.
- Bandage limbs to prevent self-mutilation of devitalized extremities.
  - Monitor limb viability closely.
  - Limb amputation or skin grafts may be necessary once stabilized.
- Monitor blood parameters closely (renal function, electrolyte status, coagulation profiles).
- N.B. Vasodilator therapy (E.g. ACP, hydralazine) has been suggested to encourage opening of collateral circulation – no proof of efficacy and may exacerbate systemic hypotension, so use with caution!

Prognosis

- Short-term prognosis will depend on nature of underlying cardiomyopathy and response of congestive heart failure to therapy.
- Can take up to 2 weeks for motor function to begin to return in limbs after saddle thrombus, and up to 6 weeks for motor function to be normal.
- Most cats experience further arterial thomboembolic episodes within days to months after initial episode, although some studies report survival for several years.

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Feline Systemic Hypertension: Diagnosis and Management

Background

- Average values for systolic/mean/diastolic systemic arterial blood pressure in calm, unsedated cats is 125/100/80 mmHg, respectively.
- Systemic hypertension is defined as a persistent, abnormal elevation of blood pressure.
- This can refer to an elevation in systolic pressure, diastolic pressure, or both.
- In cats, age has an effect on blood pressure, i.e. healthy cats greater than 11 years of age have been shown to have significantly higher blood pressure compared with healthy cats less than 11 years of age.

Indications for measuring blood pressure

- It is critical to measure blood pressure in animals with clinical signs that might be referable to systemic hypertension.
- Animals at risk should also be assessed to enable early identification of hypertension and appropriate intervention.
- Most cats with severe systemic hypertension are older.
- Systemic hypertension in cats is almost always secondary to another systemic disease process.
- Chronic renal failure and hyperthyroidism are most commonly implicated.
- This is in contrast with humans, in which most systemic hypertension is primary (essential).

Typical clinical signs of systemic hypertension

- Presenting signs associated with severe systemic hypertension include:
    - blindness and hyphaema
    - ataxia, seizure and sudden collapse (signs associated with cerebrovascular accident)
    - occasionally laboured breathing (signs related to congestive heart failure).
- Cats with acute severe hypertension may have a syndrome of progressive stupor, head pressing, seizures and death.
- If a diagnosis is established early, these clinical signs will usually resolve rapidly (within 24 hours) with effective anti-hypertensive treatment.

Organs at risk from systemic hypertension

- Systemic hypertension can damage a variety of tissues.
- The **eyes** are the organ most commonly reported to be affected by systemic hypertension in cats.
- The findings associated with hypertensive ocular injury include haemorrhage of the retina, vitreous or anterior chamber, retinal detachment and atrophy, retinal oedema, retinal vessel tortuosity and glaucoma.
- The **kidney** is susceptible to hypertensive damage.
- In a healthy kidney, the pre-glomerular arterioles constrict when blood pressure is elevated, to protect the renal glomerulus.

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- In cats with renal insufficiency, these preglomerular arterioles are dilated and poorly responsive to changes in blood pressure.
- This allows increased blood pressure to be transmitted directly to the glomerular capillary bed.
- This glomerular hypertension may cause glomerular damage and a progressive fall in renal function unless the hypertension is effectively treated.
- The **heart** is susceptible to hypertensive damage.
- As a result of it working against increased afterload, left ventricular hypertrophy may develop.
- This may regress with effective anti-hypertensive treatment.
- The **brain** is also susceptible to hypertensive damage.
- Signs associated with cerebrovascular haemorrhage (head tilt, depression, seizures) are seen clinically in cats with uncontrolled hypertension and are associated with a poor prognosis.

Blood pressure measurement techniques

- Blood pressure may be measured by either direct or indirect methods.
- Attention to the technique of blood pressure measurement is more important than which equipment is used.
- The procedure should be standardized within the clinic and carried out in the same way for each patient, by trained operators.
- **Direct** blood pressure measurement is the "gold standard".
- This involves placement of a 22-25-gauge needle or indwelling catheter into a peripheral artery (typically femoral or dorsal pedal artery).
- The needle or catheter is then attached to a calibrated pressure transducer, zeroed at the level of the sternum in the laterally recumbent patient, and the pressure is then displayed on a screen or recording chart.
- Advantages of this method are that it yields systolic, diastolic and mean pressures and it provides a "true" measurement.
- Disadvantages of this method are that it is technically difficult in unsedated animals, obese or small patients (and is therefore rarely performed in feline patients).
- It requires more physical restraint and induces more pain than non-invasive methods, thereby giving rise to sympathetic stimulation and raised blood pressure.
- Systemic hypertension is considered to be present when blood pressure measurements exceed 160/100 mmHg using direct arterial puncture in unacclimated animals.
- This method is best suited for anaesthetic or acute critical care blood pressure monitoring.
- **Indirect** blood pressure measurement is more applicable in a clinical setting as it is technically easier and requires less patient restraint.
- There are various methods of indirect blood pressure assessment (Doppler and Oscillometric).
- In cats the **Doppler ultrasound method** is preferred as it is the more accurate of the two indirect methods.
- All indirect techniques involve wrapping an inflatable cuff around an extremity to constrict a peripheral artery.

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- Choice of cuff size is very important.
- In cats, cuff width should measure 30-40% of the circumference of the limb.
- An oversized cuff may give falsely low recordings and an undersized cuff may give falsely high readings.
- If the ideal cuff size is midway between two available sizes, the larger cuff should be used, as it will theoretically produce the least error.
- If a limb is used, the limb should be kept at the level of the heart.
- The cuff size and the position of the cuff (limb or tail) should always be recorded in the animal's medical record for future reference, so that future results are comparable.
- The Doppler method utilizes a piezoelectric crystal to detect blood flow as a change in the frequency of reflected sound waves (Doppler shift) due to the motion of red blood cells in the underlying artery.
- For the Doppler technique, the cuff is usually placed over the median artery and the transducer is placed between the carpal and metacarpal pad.
- The transducer detects blood flow in the constricted artery once systolic blood pressure overcomes the pressure of the inflated cuff.
- The diastolic blood pressure may be estimated when the pitch of the Doppler flowmeter's sound changes.
- The Doppler signal is enhanced if the hair is clipped and acoustic gel is placed at the site of transducer placement.
- The technique is technically easy, does not cause the patient discomfort, and requires minimal restraint.
- This is the least expensive equipment.
- The major limitation of the Doppler method is imprecise discrimination of sounds designating the diastolic, and therefore the mean blood pressure.
- Therefore the Doppler method may be unreliable for the routine diagnosis of diastolic hypertension.
- Despite the relative ease of use, obtaining reliable values from an indirect device is not easy.
- Multiple blood pressure measurements should be obtained from each patient, rather than a single recording that is prone to inaccuracies.
- An average of all values should then be taken as an estimate of blood pressure.
- Ideally two different indirect devices should be used during each session and the results compared.
- If in doubt, the session can be repeated on another day and with cuff placement at another site.

Anxiety-induced artifact: The "White Coat Effect"

- The visit to the veterinary clinic, hospitalisation and other unusual environmental conditions in the veterinary hospital may induce anxiety in an animal.
- "White Coat Effect" refers to the false elevation in blood pressure that may be obtained secondary to catecholamine release associated with anxiety.
- The magnitude of this effect varies widely among animals and among visits in the same animal.

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- Blood pressure should be measured in a calm, motionless cat, before physical examination is performed, in a quiet room, away from other animals, humans and background noise to minimize the risk of anxiety-induced hypertension.
- The owner should be present if possible to calm the cat.
- The cat should be allowed a minimum of 10 minutes to acclimatize to its surroundings.
- Sedatives will affect blood pressure, so animals should not be sedated for blood pressure measurement.
- Multiple readings should be taken on an individual animal, preferably over several days, rather than relying on a single measurement for the basis of treatment.

Which animals to treat

- Systemic arterial blood pressure is a product of cardiac output and total peripheral resistance.
- Therefore antihypertensive therapy is generally aimed at reducing cardiac output, total peripheral resistance, or both.
- When treating a hypertensive animal, it is not usually possible to restore blood pressure to normal values with antihypertensive medications.
- The goal should be to restore blood pressure to within 30-50 mmHg of the normal range.
- Antihypertensive medications have a variety of side effects, so it is important that the clinician is confident of the diagnosis before embarking on therapy.
- The effectiveness of therapy should be judged on the basis of repeated blood pressure measurements.
- Due to the difficulties and uncertainty associated with blood pressure monitoring in cats, only those animals with marked elevations of indirectly measured blood pressure and /or clinical signs directly attributable to hypertensive injury, should be considered candidates for treatment.
- Although opinion between authors varies, as a general guideline, treatment is indicated in any animal with sustained systolic blood pressure greater than 200 mmHg or diastolic blood pressure greater than 120 mmHg, regardless of other clinical findings, due to the risk of ocular injuries with severe hypertension.
- Any cat with sustained elevations in systolic blood pressure greater than 170-180 mmHg or diastolic blood pressure greater than 100 mmHg, with clinical signs of retinal lesions, chronic renal disease or left ventricular hypertrophy, that could be caused or exacerbated by systemic hypertension, should also be treated.
- However, opinion still varies as to whether antihypertensive therapy is indicated in animals with moderate elevations of blood pressure (170-200/100-120 mmHg), but without clinical signs.
- Animals with mildly elevated blood pressure 120-170/80-100 mmHg should not be treated.
- Animals with normal blood pressure or in which blood pressure has not been measured should not be treated.
- Hypertension associated with chronic renal disease necessitates lifelong treatment with antihypertensive agents.

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- Hypertension associated with hyperthyroidism can usually be expected to resolve within 1-3 months following effective treatment of the underlying condition, unless chronic renal failure is also present.
- Periodic dosage adjustments based on blood pressure measurements are indicated.

Treatment options

- Non Pharmacologic therapy
    - Treatment of underlying medical conditions
        - E.g. hyperthroidism
    - Avoidance of drugs that can cause/exacerbate hypertension
        - Glucocorticoids
        - Phenylpropanalomine
        - Nephrotoxic agents (e.g. cyclosporine, aminoglycosides)
    - Dietary modification
        - N.B. Role of sodium restriction in feline hypertension is undetermined
    - Weight control
        - Controlling obesity may help
- Pharmacologic therapy
    - Calcium channel blockers
        - E.g. Amlodipine (second-generation calcium channel blocker has more effect on peripheral vasculature and less on cardiac contractility and heart rate).
        - Lower blood pressure by interfering with calcium-dependant contractions of vascular smooth muscle (decrease peripheral vascular resistance); may also decrease vascular responsiveness to Angiotensin II.
        - Potential side effects of amlodipine include anorexia, lethargy, hypotension, vomiting.
        - Amlodipine appears to be safe and effective as monotherapy for systemic hypertension in cats
        - Amlodipine is FIRST-LINE ANTIHYPERTENSIVE THERAPY IN CATS
    - Angiotensin-converting enzyme (ACE) inhibitors
        - E.g. Enalapril, benazepril, ramipril
        - Inhibit Angiotensin II production (potent vasoconstrictor), decrease aldosterone secretion (thus reducing renal sodium retention), increase vasodilatory prostaglandin synthesis, inhibit vascular hypertrophy.
        - Potential side effects include renal insufficiency, vomiting, diarrhoea, systemic hypotension.
        - May be particularly useful if proteinuria or heart failure present.
        - In cats, limited data but have been shown to be effective as monotherapy in cats with mild-moderate systemic hypertension associated with chronic renal failure; may be more efficacious if combined with a second anti-hypertensive drug.

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- Angiotensin II receptor blocker (ARB)
    - Telmisartan
        - New veterinary license for cats
        - To reduce the amount of protein lost in urine in cats suffering from chronic kidney disease
        - Used to treat some cases of systemic hypertension in humans
        - Not yet recommended for this use in cats
        - Insufficient clinical data on efficacy
- Beta-adrenergic receptor blockers
    - E.g. Propranolol (non-selective beta-1 and beta-2 blocker), atenolol (cardioselective beta-1 blocker).
    - Decrease heart rate, contractility, cardiac output, renal renin secretion and sympathetic outflow.
    - Potential side effects include bradycardia, bronchospasm, hypotension, glucose intolerance, CNS depression.
    - In cats, limited data but beta-blockers do not appear to be as effective as other anti-hypertensive drugs such as amlodipine.
- Diuretics
    - E.g. furosemide and spironolactone
    - Can be used to decrease blood volume and cardiac output.
    - Potential side effects include acid-base and electrolyte abnormalities, dehydration and hypovolaemia.
    - In cats, limited data but diuretics do not appear to be as effective as other anti-hypertensive drugs such as amlodipine.

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