Fighting FATE: pathophysiology, therapy, prevention and prognosis

Ivan Moses BVSc (Hons I) MANZCVS (ECC) DACVECC

Murdoch University School of Veterinary Medicine, Murdoch, WA, Australia

Feline Aortic Thromboembolism (FATE) is a serious cause of morbidity and mortality in cats. ATE has been most commonly associated with feline heart disease, particularly hypertrophic cardiomyopathy (HCM). HCM is the most commonly documented feline cardiomyopathy phenotype, affecting 14.7% of the feline population. ATE has a reported prevalence of 11.3% among cats with HCM. Up to 88% of cats presenting with FATE will not have previously diagnosed cardiomyopathy. Thromboemboli (TE) most commonly become lodged at the aortic trifurcation and affect one or both of the pelvic limbs. They have also been detected at the right subclavian artery, the mesenteric vasculature, the kidneys, brain or lungs. FATE results in ischaemia, severe pain, cold extremities and paresis of the affected limb(s).

Pathoaetiology

The vast majority of ATE appears to occur secondary to cardiomyopathy in the cat. Although it has been associated with other disease processes, particularly neoplasia, this is beyond the scope of this document. It is hypothesised that FATE originates within the left atrium and later becomes dislodged to embolize at distant sites. The formation of a TE is conventionally attributed to one or more components of Virchow's triad (Figure 1) being present. Abnormal or static blood flow and the presence of spontaneous echocontrast have been noted in feline patients and associated with increased risk of FATE. Endothelial injury has been previously documented histologically in the endocardium of cats with enlarged left atria. Several ex vivo studies have shown biomarkers of hypercoagulability in cats with HCM. Recently the concept of immunothrombosis and immune-mediated hypercoagulability has become a focus of research into thromboembolic disease processes. Neutrophils have been shown to be important, particularly through the release of neutrophil extracellular traps (NETs). These NETs consist primarily of antimicrobial granular proteins, citrullinated histones and cell-free DNA; they are designed to trap circulating pathogens, but also have potent procoagulant properties. Cats with HCM and FATE have been shown to have elevated circulating cell-free DNA and citrullinated histone levels, and NETs have been found to be dynamic structural components of the thrombi present within the ATE thrombus. Interested readers are encouraged to pursue further reading, particularly the 2023 review paper in Veterinary Clinics Small Animal by Shaverdian and Li.

Diagnosis

The presentation of FATE is often characterised by sudden onset severe pelvic limb pain and paresis/paralysis. The "5 P's" of thromboembolism – pain, paralysis/paresis, pulselessness, poikilothermy and pallor are all common findings. A blood glucose differential of >30mg/dL (1.7mmol/L) between systemic glucose and peripheral glucose has been found to be

diagnostic with a high degree of sensitivity and specificity. Similarly, a blood lactate differential of >2mmol/L is also consistent with thromboembolic complication. Use of infrared thermography has been shown to be highly accurate in diagnosing FATE, however it does require specialised equipment.

Treatment

Treatment of FATE in the acute phase generally consists of analgesia, supportive care and anti-platelet/anticoagulant therapy (Table 1). Approximately 50-70% of cats presenting with FATE have concurrent CHF at the time of diagnosis, however this is not associated with worsened prognosis. The use of thrombolytics has not yet been shown to improve outcomes in FATE, although research is ongoing. Administration of thrombolytics can be considered if the treatment is in the acute phase (<6 hours post thrombosis). Cost, availability, lack of strong evidence and clinician experience all limit the utilisation of thrombolytics in this population.

Prevention

The use of anticoagulant and/or antiplatelet therapy in all cats with significantly enlarged left atria is currently recommended by the CURATIVE guidelines. Aspirin has been shown to be less safe and less effective when compared to clopidogrel (75% vs 50% recurrence rate). More recently, the direct anti-Xa anticoagulant rivaroxaban has been shown to be similarly efficacious to clopidogrel at risk of relapse in FATE patients. One evaluation of combination therapy (rivaroxaban + clopidogrel) showed a markedly reduced risk of recurrence (16.7%) when compared to previously reported recurrence, and had minimal negative side effects.

Prognosis

The prognosis of FATE has long been considered poor to grave, given the likely underlying cardiac pathology, high risk of ischaemia reperfusion injury and AKI, high incidence of concurrent CHF and high level of acute care necessary to treat these patients. This has resulted in euthanasia rates of up to 95% in some studies. The recent BLASTT study reported an overall 37.5% survival rate, with previous retrospective studies showing survival rates 27-45% in cats with bilateral FATE. Some older literature did find that reduced number of limbs being affected had improved outcomes in some cases. More recently a 2022 abstract evaluating reteplase (a 3rd generation TPA) found a 75% survival to discharge rate – although this was in a small retrospective cohort. The reported mean survival times for cats discharged after ATE episodes is between 290-340 days (up to 502 days in cats on dual therapy) depending on the therapeutic protocol used.

Conclusions

In conclusion, FATE is a serious complication of feline heart disease, and prompt recognition and therapy is necessary to minimise patient suffering. Given the underlying pathology present and significant suffering associated with ischaemia, euthanasia is never contraindicated in these cases, however, if treated promptly and appropriately, approximately

30-40% of cases can survive to discharge and can have good intermediate to longer term prognoses.

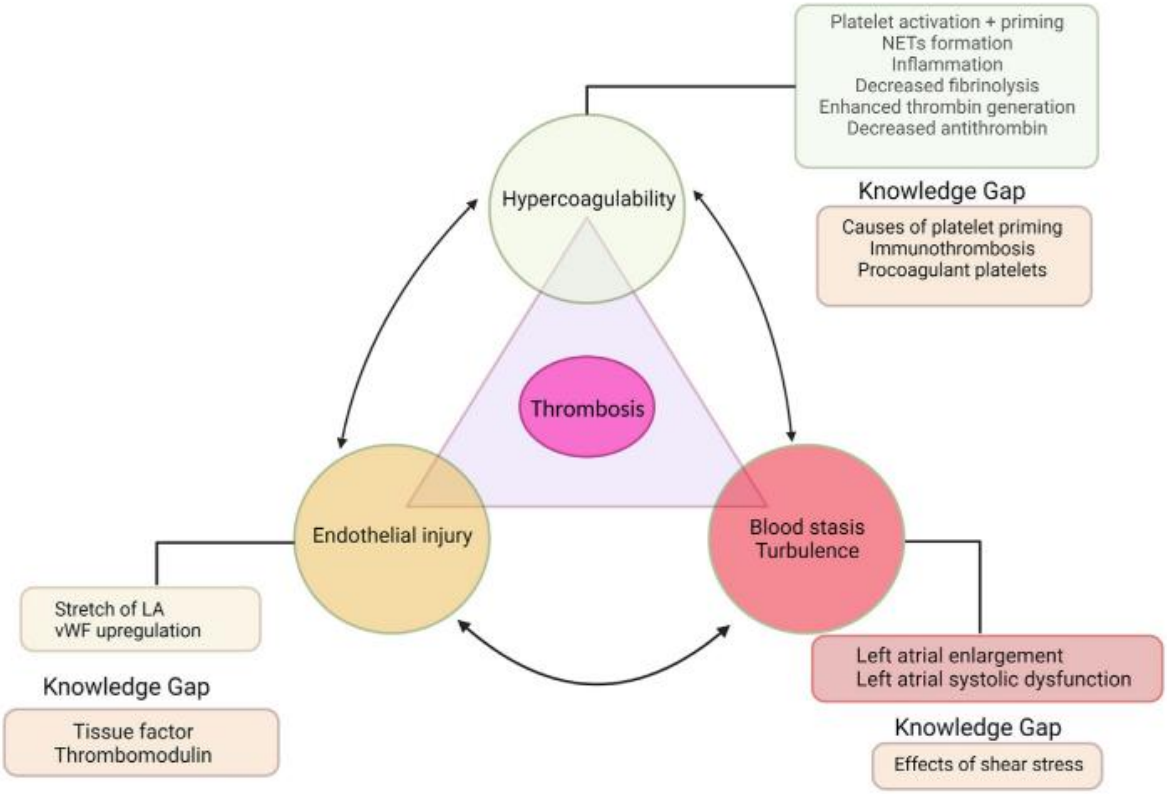

Fig. 1. Summary of Virchow's triad and potential underlying mechanisms in CATE. Blood stasis occurs due to left atrial enlargement and dysfunction resulting in intracardiac thrombosis and damage of the endocardium. Endothelial injury may initiate coagulation, by upregulating von Willebrand factor (vWF), tissue factor (TF), or downregulating thrombomodulin (TM), further exacerbating a hypercoagulable state, by facilitating platelet–neutrophil interactions and immunothrombosis.

Figure 1: Virchow's Triad of thrombosis risk – adapted from *Preventing Cardiogenic Thromboembolism in cats: Literature gaps, rational recommendations and future therapies*. VetClinSmallAnim, 2023

Table 1: Therapeutic options for ATE patients

Treatment	**Details, dose and route**
Analgesia	- Pure Mu opioid agonists recommended - Methadone 0.2-0.3mg/kg IV Q4 - Fentanyl CRI @ 3-5mcg/kg/hr - Gabapentin 50-100mg/cat PO Q12-24 (anxiolysis also, care with renally impaired patients)

Oxygen therapy	CHF is noted in 50-70% of cats with ATE – treat with O2 as required
Diuretic therapy	CHF is noted in 50-70% of cats with ATE – treat with furosemide as required - 2mg/kg IM initially if patient unstable - 2mg/kg IV Q4-6 initially then Q8 as RR/RE improve
Antiplatelet therapy - Clopidogrel (Aspirin no longer recommended)	- 18.7mg (1/4 of a 75mg tablet) PO Q24 – some sources give 37.5mg PO once as a "loading dose"
Anticoagulant therapy - Low molecular weight heparins (Dalteparin or Enoxaparin) have fewer side effects than unfractionated heparin - Rivaroxaban - Apixaban	- Dalteparin – 150-180IU/kg SC Q4-6 - Enoxaparin – 0.75-1mg/kg SC Q6 - Rivaroxaban – 1mg/kg PO Q24 – doses of up to 2.5mg/kg are reported - Combination therapy with clopidogrel appears to be more efficacious - Apixaban – <5kg 0.625mg PO Q12, >5kg 1.25mg PO Q12 - Limited evidence published
Thrombolytics - Alteplase & Reteplase recommended over urokinase/streptokinase due to side effects and efficacy	- Relatively high risk of bleeding, high cost, Ischaemia-reperfusion injury/AKI and degree of clinician expertise required. Has not been shown to improve outcomes vs traditional therapy - Ideally administered in <6 hours post thrombosis based on human guidelines - Alteplase – 1mg/kg IV over 1 hour with first 10% given over 1 minute. OR 0.1-0.5mg/kg/hr IV CRI - Reteplase 1IU/cat IV Q8
Adjunctive therapies - Pentoxifylline - Cyproheptadine	- Pentoxifylline – antioxidant, anti-inflammatory, vasodilator, improved rheology – 100mg PO Q12 - Cyproheptadine – potentially improves collateral circulation (when given prior to ATE) – 2mg/cat PO Q12

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