

RECOMMENDATIONS

conversations with a cardiologist

November 2015

Feline Arterial Thromboembolism

ETIOLOGY AND CLINICAL PRESENTATION

Feline arterial thromboembolism (ATE) is a catastrophic disease associated with high morbidity and mortality. In this condition, a thrombus (nearly always cardiogenic in origin and related to blood stasis in the setting of a dilated left atrium) is dislodged to the systemic arterial system and lodges in the peripheral vasculature resulting in acute vascular occlusion of one or more arteries. In addition to the direct vascular obstruction, the acute thrombotic obstruction results in profound vasoconstriction of the collateral vasculature, exacerbating ischemia to the affected limb or organ. The prevalence of ATE is relatively high in feline medicine reported as 0.6% (1 in 175) of feline cases presented to a university teaching hospital¹ and 0.3% of all feline cases presented to first opinion veterinary practices.² Over 90% of feline ATE cases are presumed to be cardiogenic, occurring when left atrial (LA) enlargement results in variable degrees of blood stasis and endothelial damage within the left atrium or left auricular appendage, leading to intracardiac thrombus formation.^{1,3} However, a small percentage of cats with ATE will have a normal heart and lack any measurable LA enlargement. Pulmonary neoplasia and thyroid disease, even with an echoardiographically normal heart, are additional risk factors for this condition.³

The presenting signs are characterized by 5 "P"s – pain, paresis, pulseless, pallor, and polar meaning the affected limbs are painful, paretic, lacking a palpable pulse, discolored in the footpads (white, cyanotic, or grey), and cold (Figure 1). The hindlimbs are most commonly affected, with 77% of cases having both rear limbs affected.² Less commonly, a single hindlimb or single forelimb may be affected. Muscle enzyme activity is markedly elevated on serum biochemical analysis, with CK, AST, and ALT all increasing in the setting of acute skeletal muscle ischemia. Rarely, cats with ATE may be presented with clinical signs associated with acute neurologic, gastrointestinal, or renal infarction related to obstruction of those arterial beds.

THROMBOPROPHYLAXIS FOR CATS AT RISK

Left atrial enlargement is present in 93% of cats with ATE;³ it is reasonable to assume that an echocardiographic measure of LA size may be a useful measure of ATE risk. The maximal LA diameter is measured from a right-parasternal 4-chamber imaging plane optimized to be sagittal to the heart's long



axis (Figure 2). The measurement of LA diameter is then taken at the end of ventricular systole, 1-2 frames before the mitral valve opens, from the atrial septum to the posterior wall of the LA and parallel to the mitral annulus. In normal cats, this value is between 12 and 16 mm and a value greater than 16 mm is considered to indicate LA enlargement. As a general rule of thumb, 16 to 20 mm is considered mild dilation, 20 to 25 mm moderate dilation, and >25 mm severe dilation. The risk for ATE does not appear to relate in a directly linear relationship to LA size as some cats with mild LA enlargement have thrombi apparent on echocardiographic exam and cats with severe LA enlargement may present without thrombi. However, in a series of 260 cats with hypertrophic cardiomyopathy (HCM), the 43 cats with ATE had a larger LA size than cats in heart failure or those with preclinical disease.⁴ Given the above data and clinical experience, the CEG recommends thromboprophylaxis for all cats with moderate or severe LA dilation. Additionally, the presence of spontaneous echogenic contrast ("smoke") seen in the LA on an echocardiographic study suggests a prothrombotic state and would be an indication for thromboprophylaxis, even in the absence of LA enlargement.⁵

There are few studies proving efficacy of anti-thrombotic medications in cats at risk for ATE, but the threshold for starting preventative therapy is low given the devastating consequences of ATE. Anti-thrombotic options include platelet inhibitors or anticoagulants. The members of the CEG prefer platelet inhibitors because the safety profile for platelet inhibitors appears to be preferable to anticoagulants. Clopidogrel (Plavix[®]) is well-tolerated by cats, has proven

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anti-platelet effects in this species, and is dosed at 18.75 mg per cat orally once daily (¼ of a 75mg tablet). In the only blinded, prospective study evaluating thromboprophylaxis in clinical cats that had suffered a prior ATE event, clopidogrel was superior to aspirin with a difference in median survival time of 251 days in favor of clopidogrel.⁶ As generic forms of clopidogrel are now available, there is less of a cost difference compared to aspirin. However, aspirin can still be prescribed for thromboprophylaxis if clopidogrel is not feasible; the typical aspirin dose is ¼ of an 81 mg tablet per cat every 72hrs. Typically, the CEG members advise clients to choose 2 days per week to give the aspirin (e.g., Wednesday and Sunday) to improve compliance. An alternative dosing strategy for aspirin is 1-2 mg/kg every 24 hours. For those clients with severe cost concerns, aspirin is given as sole therapy. Some cardiologists choose sole therapy for those cats with moderate left atrial enlargement and advise dual-therapy using both aspirin and clopidogrel for cats with severe left atrial enlargement, prior ATE, or spontaneous echogenic contrast. Side effects of either drug appear to be primarily gastrointestinal, with roughly 10-15% of cats on aspirin developing inappetence, vomiting, diarrhea, melena, or hematochezia. If this develops, the aspirin should be discontinued and sole-therapy with clopidogrel continued.

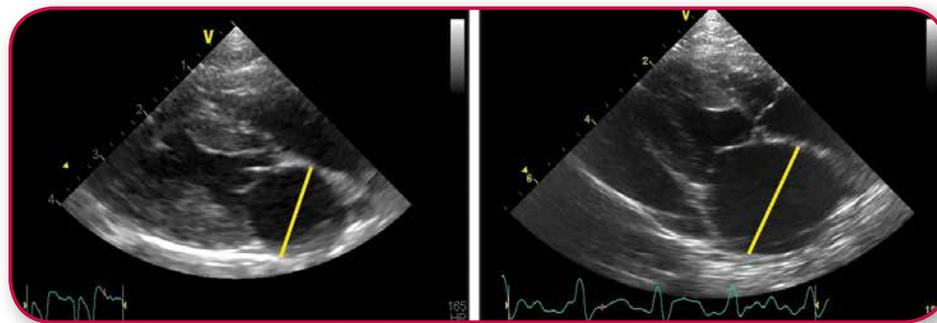


Figure 2 – Examples of left atrial size in two cats. On the left is a normal left atrium, measuring 15mm in width. On the right is a cat with severe HCM and heart failure, whose left atrium measured 29mm in width.

If echocardiography shows the presence of a thrombus in the left auricular appendage and the risk for ATE appears imminent, or the cat has previously suffered an ATE event, anticoagulant therapy in addition to anti-platelet therapy may be considered. Although efficacy data in cats is sparse, low-molecular-weight heparin may be given at 1-2 mg/kg SQ, q12-24h as enoxaparin (Lovenox[®]) or 100-200 U/kg SQ, q12-24h as deltaparin (Fragmin[®]) with a good safety profile. There are some studies that question the appropriateness of this dosing schedule in



Figure 1 – Rear limbs from a Sphynx cat affected several days previously by ATE. The right rear limb is devitalized distally, with catastrophic loss of perfusion and development of gangrenous necrosis.

the cat based upon Factor Xa inhibitory activity, but the issue remains unresolved. Resolution of thrombi in the left atrial appendage of cats has been observed on this dosing schedule, but this evidence is anecdotal. The downside to use of low-molecular-weight heparin is the requirement for subcutaneous injection and the cost of these medications, either of which

may be limiting for many clients. Home therapy with unfractionated heparin may be considered, but the dosing effects are more variable than the low-molecular-weight products and therefore there is a greater risk of under-dosing or causing bleeding tendencies with long-term therapy. The CEG does not recommend home therapy with unfractionated heparin. Another anticoagulant prescribed to cats at risk for ATE is warfarin, a vitamin-K antagonist. At this time, the CEG does not recommend home warfarin therapy for cats given the narrow therapeutic

index of this medication and the high degree of monitoring required. There are several new oral antithrombotics entering the human market, including direct thrombin inhibitors such as dabigatran and direct factor Xa inhibitors such as rivaroxaban and apixaban. These new medications have potential advantages over warfarin and low-molecular-weight heparin, but have not been sufficiently studied in cats and are likely to be cost-prohibitive for the foreseeable future. The CEG also recommends sending home 1 or 2 pre-filled syringes

containing an oral dose of buprenorphine (0.2 to 0.3 ml of a 0.3 mg/ml solution per cat) with clients of cats perceived at high risk for ATE to allow the client to provide analgesia promptly should an ATE event occur at home.

THErapy FOR ATE

Analgesia is the most important therapy for cats that present with signs consistent with acute ATE (cold, pulseless, cyanotic limbs with elevated muscle enzymes). The disease is painful and pure μ -agonist opioids should be given immediately, while further evaluations and therapy are being contemplated. The CEG recommends fentanyl as a constant rate infusion (2 to 4 mcg/kg bolus, followed by 2-5 mcg/kg/hr CRI), due to its potent analgesic properties, short half-life, and ease of dose adjustment pending the cat's response. In the absence of fentanyl or in a situation in which a CRI is not possible, methadone, hydromorphone, or oxymorphone may be considered with monitoring for an adverse hyperthermic or hypotensive reaction. If no pure μ -agonist opioid is available, mixed opioids such as buprenorphine or butorphanol may be considered, but are unlikely to be sufficient to provide complete analgesia.

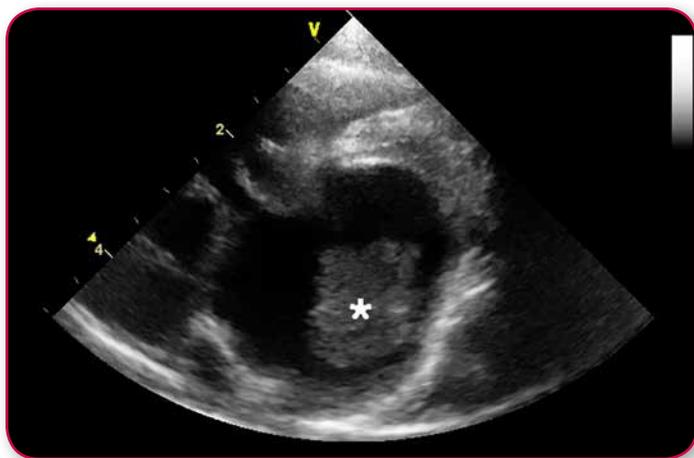


Figure 3 – Echocardiographic image from a cat showing a large thrombus (asterisk) free-floating in the left atrium.

Once the cat's pain is addressed, consideration should be given to whether further treatment is appropriate. Therapy for acute ATE is expensive and most cats will still have severe, life-threatening heart disease after surviving the acute event. Studies suggest roughly 1/3 of cats presented to a University referral hospital will be euthanized at the time of diagnosis, 1/3 of cats will succumb to the disease during treatment, and 1/3 will live through the event.¹ In the general practice setting, therapy is pursued less often, with 70% of cats euthanized at presentation. Of those pursuing treatment, 44% survived more than 7 days.²

If treatment is pursued, the patient can be further evaluated via laboratory testing and imaging. These tests may need to be delayed until the patient is stable if dyspnea is present. In these cases, provision of oxygen, thoracocentesis when

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appropriate, and administration of furosemide (2 mg/kg) if pulmonary edema is suspected may allow patient stabilization. Anti-thrombotic agents are often given to ATE patients in hopes of preventing progression of thrombus formation even after ATE has occurred. Heparin therapy is initiated, either as low-molecular-weight preparations at 1-2 mg/kg SQ, q12-24h for enoxaparin (Lovenox[®]) or 100-200 U/kg SQ, q12-24h for deltaparin (Fragmin[®]) or unfractionated heparin is given at 150 to 300 U/kg, SQ q8hrs for the first 24-48hrs. Platelet inhibitors, usually clopidogrel, can also be initiated at this time if the cat will take oral medications. Diagnostic testing includes full laboratory evaluation to confirm elevated muscle enzyme activities, screen for hyperthyroidism, monitor for evidence of end-organ damage secondary to thromboembolism, and assess for early evidence of reperfusion (hyperkalemia, acidemia). Thoracic radiographs are recommended to rule out congestive heart failure and for an initial assessment of cardiac size; echocardiography is advised when possible to stage the severity of heart disease and to confirm a cardiogenic origin for the ATE (Figure 3).

Fibrinolytic therapy with tissue plasminogen activator (tPA) has received variable attention in the past, with most studies showing no improvement compared to supportive care and antithrombotic therapy.⁷ However, some criticalists believe these studies lacked an adequate control group or failed to target cats within an optimal window of time for fibrinolytic therapy to have effect. Additionally, the cost of this therapy has declined in recent years making it more economically feasible. Currently, the CEG considers use of tPA in cats presenting with ATE if the event was witnessed and presentation is within 6 hours of the event. The medication is dosed at 1 mg/kg with 10% given as a slow bolus and the remaining infused over 1 hour, with close attention to the occurrence of side effects such as hemorrhage and development of hyperkalemia. Surgical thrombectomy is not advised for any ATE cases.

Beyond analgesia, anticoagulation and heart failure therapy, treatment largely involves provision of supportive care and monitoring for signs of reperfusion injury, with the intention of rapid therapy if reperfusion occurs. Close in-hospital monitoring is critical in the first few days after ATE;

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acute restoration of blood flow to ischemic muscle as a thromboembolus dissolves can result in rapidly fatal acute hyperkalemia, hypermagnesemia and acidemia. The cat's heart rhythm is monitored continuously for ECG changes in these cats to detect early signs of reperfusion (peaked T waves, widening of the QRS, absent P waves). Blood gases and electrolytes are monitored q8h to q12h to assess rising potassium levels and/or declining blood pH.

Gentle physical therapy of the affected limbs after the first 24 hours is recommended so long as the cat's pain is controlled. After ~36 hours, most cats do not appear painful and the analgesia can be gradually tapered. Once the cat has some use of the limb and a pulse is palpated, discharge may be considered. Of those cats that do not suffer life-threatening reperfusion injury, most will regain some limb function. Many cats have persistent neurologic deficits in the affected limb and some develop gangrenous changes to the distal limb related to absent perfusion. In these cases, distal amputation may be the only therapeutic option.

PROGNOSIS

The prognosis for this disease is generally poor. However, survival of more than a year after ATE has been observed. Rectal temperature at presentation was found to correlate with survival in retrospective studies; hypothermia was associated with higher mortality.^{1,2} Additionally, those cats with a single

limb affected have improved survival compared to those with two or more limbs affected.³ Median hospitalization time for those cats that survive is approximately 2 days.² The long-term survival of cats that leave the hospital is reported as 94 to 117 days (these cats were not given clopidogrel).^{2,3} The presence of congestive heart failure at the time of ATE did not affect survival to discharge, but did impact long term survival. Cats in heart failure survived a median of 77 days after discharge as compared to cats without heart failure living a median of 223 days.³ Moderate to severe azotemia or hematochezia are poor prognostic signs suggestive of systemic thromboembolism.

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