Why could thrombolysis be an option for cats with acute aortic thromboembolism?

Feline aortic thromboembolism, or 'saddle thrombus', is a common syndrome initiated by the sudden migration of a left atrial thrombus into the systemic arteries. It is usually caused by cardiomyopathy of varying types and severity. It is easily diagnosed clinically using the '5P rule' (pulselessness, pallor, polar, pain and paralysis). Although the prognosis for feline aortic thromboembolism has historically been considered poor, this is not validated by retrospective or prospective studies. Indeed, a prospective study on cats with aortic thromboembolism and bilateral pelvic limb paralysis showed a 37.5% discharge rate, with a calculated 95% confidence interval of 22.5% to 52.5%, and with some cats surviving for more than a year. Treatment includes supportive care, treatment of cardiac disease if applicable and nursing care. Thrombolysis is recommended in many thromboembolic diseases in humans, including pulmonary thromboembolism, acute myocardial infarction and acute ischemic stroke, and has been recently suggested in cats suffering from acute (within 6 hours) aortic thromboembolism. Most clinicians will use the tissue plasminogen activator alteplase. Complications of treatment of feline aortic thromboembolism, with or without thrombolysis, include acute kidney injury (20%) as well as reperfusion injuries (25%). Thromboprophylaxis with clopidogrel or clopidogrel and rivaroxaban is recommended for long-term management of cats with aortic thromboembolism.

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Julien Guillaumin, Docteur Vétérinaire, Dip ACVECC, Dip ECVECC; College of Veterinary Medicine & Biomedical Sciences; Colorado State University; 300 West Drake Rd; Fort Collins. Email: Julien.guillaumin@colostate.edu

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Feline aortic thromboembolism, also known as 'saddle thrombus' is one of the most common clinical causes of thromboembolism in veterinary medicine (Smith et al, 2003; Guillaumin et al, 2020). It is initiated by the sudden migration of a left atrial thrombus into the systemic arteries and its prevalence rate has been reported as 1 in 379 cases in UK general practice (Smith et al, 2003; Borgeat et al, 2014). It is a devastating syndrome with short-term consequences, characterised by acute pain, paralysis and rhabdomyolysis in the affected limb(s) (Guillaumin et al, 2020). Feline aortic thromboembolism also has long-term implications, including management and prognosis of concomitant cardiac disease, as many feline aortic thromboembolism patients also suffer from severe cardiac disease (Smith et al, 2003; Borgeat et al, 2014; Guillaumin et al, 2020). Although the prognosis for feline aortic thromboembolism is considered poor, with treatment, the survival rate from retrospective studies is between 27% and 45% (Laste and Harpster, 1993; Schoeman, 1999; Smith et al, 2003; Welch et al, 2010; Borgeat et al, 2014).

Clinical presentation

The age distribution is middle-aged to older cats, with the mean or median age at admission between 7 and 12 years old (Smith et al, 2003; Borgeat et al, 2014; Guillaumin et al, 2020). Male cats are predisposed, with approximately two-thirds of cases being male, and both pelvic limbs are affected in 75% of cats (Smith et al, 2003; Borgeat et al, 2014; Cambournac et al, 2022). Although the vast majority (90%) of cats have underlying cardiomyopathy of varying types and severity, approximately 20% were previously diagnosed with cardiac disease (Smith et al, 2003; Borgeat et al, 2014). This complicates things from an owner education standpoint: clinicians need to address both short-term concerns, such as treatment of acute paralysis and pain secondary to the embolism, as well as long-term concerns, particularly with management of congestive heart failure and advanced heart disease.

Physical examination findings and emergency workup

The road to successful thrombolysis, as in humans, starts with rapid recognition of the clinical process. The diagnosis of feline aortic thromboembolism is usually clinical, using the '5P rule' (pulselessness, pallor, polar, pain and paralysis). Other tools can help with recognition, including a lack of Doppler signal in the affected limb(s), visualisation of thrombus in the distal aorta using ultrasound, measurement of glucose or lactate (low and high respectively, compared to an unaffected limb or jugular vein), as well as infrared thermography can be used (Pouzot-Nevoret et al, 2018; Guillaumin et al, 2019; Eberlé et al, 2022).

If the aortic thromboembolism is cardiogenic, signs of congestive heart failure may also be present, such as dyspnea, pulmonary crackles and cyanosis. Congestive heart failure is present in around 50–70% of cats with aortic thromboembolism, but it is unclear if it is associated with a worse prognosis. Bedside echocardiography can confirm the presence of cardiomyopathy, the severity of it, the size of the atria and the evidence of spontanous echo contrast ('smoke'). It allows better education of the owner and a more informed discussion about moving forward with treatment. Baseline bloodwork (chemistry panel) is important for baseline renal value and assessment of renal dysfunction and/or early reperfusion. Azotaemia, elevation in creatine kinase, hyperkalemia and metabolic acidosis can be found.

Prognosis and prognosis factors

The prognosis for feline aortic thromboembolism has historically been considered 'poor', which does not seem to be validated by retrospective or prospective studies. However, cats with aortic thromboembolism have been plagued with euthanasia rates as high as 90%, which seems to be clinician- or clinic-related (Smith et al, 2003; Borgeat et al, 2014; Cambournac et al, 2022). Recently, a prospective study on cats with aortic thromboembolism and bilateral pelvic limb paralysis showed a 37.5% discharge rate, with a calculated 95% confidence interval of 22.5–52.5%, and with some cats surviving for more than a year (Guillaumin et al, 2020). This aligns with the retrospective studies, showing survival rates between 27% and 45% (Pion et al, 1987; Laste and Harpster, 1993; Schoeman 1999; Moore et al, 2000; Smith et al, 2003; Welch et al, 2010; Borgeat et al, 2014). Overall, available retrospective studies differ vastly regarding information available for inclusion criteria (for example, one limb affected versus bilateral syndrome), in-hospital treatment, medications dispensed at discharge and outcome data (Rush et al, 2002; Smith et al, 2003; Menon et al, 2004; Mutch and Booth, 2012; Borgeat et al, 2014; Kearon et al, 2016; Guillaumin et al, 2019; Guillaumin et al, 2020; Cambournac et al, 2022).

Some studies identified outcome factors such as number of limbs affected, motor function or presence of heart failure. Cats with motor function at admission or one limb affected have a better prognosis (70% survival to discharge) than cats with bilateral pelvic limb paralysis (35–50% survival to discharge) (Smith et al, 2003; Borgeat et al, 2014). Smith et al (2003) showed that other non-survivor baseline characteristics included lower rectal temperature, lower heart rate, higher phosphorous levels and an absence of motor function. Presence of congestive heart failure, elevated blood urea nitrogen, glucose and sodium levels were not more common in non-survivors at baseline, although *P* values were 0.08 and 0.09 for presence of congestive heart failure and elevated blood urea nitrogen respectively, so it is possible that more cases reported would have reached statistical significance. In the same study, the presence of congestive heart failure was correlated with a shorter long-term survival. Interestingly, the outcome may vary with the clinical experience of the veterinarian in treating those cats (Smith et al, 2003; Guillaumin et al, 2020).

In a recent study, non-survivors baseline characteristics included lower rectal temperature, congestive heart failure, and being presented after hours or to a specific study clinic (Guillaumin et al, 2020). Interestingly, after multivariable analysis, only lower rectal temperature and being presented to the clinic #2 retained statistical significance (Borgeat et al, 2014). This illustrates the euthanasia bias discussed earlier. The prospective bilateral lysis of aortic saddle thrombus with early tissue plasminogen activator study showed higher rectal temperature and lower affected limb lactate were associated with higher survival. Specifically, a receiver operating characteristic curve yielded an optimal cut-off was 35.7°C (sensitivity 75%, specificity 74%) and 11.5 mmol/L (sensitivity 64%, specificity 92%) (Guillaumin et al, 2020).

Therefore, it is probable that recruitment bias exists in feline aortic thromboembolism, with the possibility that euthanasia can be driven by clinician's perception of the disease process. Each owner should be presented with a fair understanding of causes for feline aortic thromboembolism, long-term prognosis (especially with cardiac diseases) and treatment options including natural course of the disease with thrombolysis, thromboprophylaxis or euthanasia. In retrospective studies, survival time after discharge was between 117 and 345 days (Moore et al, 2000; Rush et al, 2002; Smith et al, 2003).

Thrombolysis and evidence in humans

Plasmin is the central enzyme responsible for thrombus degradation (Mutch and Booth, 2013). The two major plasminogen activators found in circulating blood are tissue-type plasminogen activator and urokinase. Several fibrinolytic agents have been described in clinical practice, including the first generation thrombolytics streptokinase and urokinase, the second generation tissue-type plasminogen activator analogue alteplase, and more recently, the third generation thrombolytic recombinant tissue-type plasminogen activator reteplase.

In humans, the American College of Chest Physicians published guidelines (Kearon et al, 2012; Lansburg et al, 2012) for the use of thrombolytic therapy in patients with various diseases including pulmonary thromboembolism, acute myocardial infarction and acute ischemic stroke. The consensus guidelines suggest the use of thrombolytic therapy for patients with acute pulmonary thromboembolism associated with hypotension who do not have a high bleeding risk (Kearon et al, 2016). In the case of patients with acute ischemic stroke, the guidelines recommend intravenous tissue-type plasminogen activator in patients for whom treatment can be initiated within 3 hours of symptom onset, and downgrade their recommendations to a suggestion between 3 and 4.5 hours after symptom onset (Menon et al, 2004). Distal aortic throm-

bosis or thromboembolism is uncommon in people and there is no consensus on treatment. In adults, the current recommended treatment includes surgical thrombectomy, local tissue-type plasminogen activator infusion and vascular stenting. In infants and children, where the syndrome is more prevalent and their size limits options, cases are usually treated with a systemic tissue-type plasminogen activator constant rate intravenous infusion (Mulcaire-Jones et al, 2020).

Thrombolysis in feline aortic thromboembolism – the past

The first reported study on feline thrombolysis is a French aortic thrombosis model from 1969 (Abastado, 1969), which used an intravenous streptokinase continuous rate infusion. Using angiography, they showed that the thrombus disappeared in 84% of cats. In the 1980s, a tissue-type plasminogen activator (specifically alteplase) was used in several cats at UC Davis (Pion et al, 1987; Pion, 1988a; Pion, 1998b). Information available showed a shortened time to perfusion and ambulation as all cats discharged were walking within 48 hours of presentation. In a 1987 abstract on 6 cats, the mean length of clinical signs was 17 hours (a range of 5–29 hours) and tissue plasminogen activator was used at 0.25–1 mg/kg/hr intravenous continuous rate infusion for a total of 1–10 mg/kg. Discharge from hospital was reportedly 43%, but seems to include 3 out of 6 cats (50%).

Many reports from this study focused on the risk of severe reperfusion injuries, which created a gap in the literature. In 2010, an uncontrolled prospective study investigated alteplase in 11 cats with aortic thromboembolism (Welch et al, 2010). Cats were enrolled within 12 hours of onset of clinical signs, and an additional dose of tissue plasminogen activator was administered to 36% of the cases. Return of pulses and improved limb function occurred in 67% of the cats, although only 27% of the cats were discharged from the hospital.

In 2019, a retrospective study shed some light on the complications seen with treatment of feline aortic thromboembolism, comparing a thrombolysis group with the tissue-type plasminogen activator alteplase (n=16) to a robust control group treated without thrombolysis. It showed a 44% survival to discharge in the tissue plasminogen activator group, and more importantly, showed no worsening in survival rate in the tissue plasminogen activator group to the control group (44% versus 29%, respectively), as well as no differences in complications rates, including rates of reperfusion injury (42% versus 50%, respectively) or acute kidney injury (25% versus 25%, respectively) (Guillaumin et al, 2019).

Therefore, it appears that thrombolysis in feline aortic thromboembolism does not carry a substantial increased risk compared to standard treatment. A recent expert consensus suggested that thrombolytic agents can be considered for treatment of acute (<6 hours) arterial thromboembolism following an assessment of the risk and benefit in individual cats (Sharp et al, 2022).

Thrombolysis in feline aortic thromboembolism – the present and future

Since the consensus statement was published, significant literature has been added regarding thrombolysis in feline aortic thromboembolism. A prospective, randomised, placebo-controlled study using alteplase in feline aortic thromboembolism, the bilateral lysis of aortic saddle thrombus with early tissue plasminogen activator study confirmed retrospective study findings that tissue plasminogen activator does not worsen the prognosis in feline aortic thromboembolism (Guillaumin et al, 2020). Survival to discharge was 45% for the tissue plasminogen activator group and 30% for the placebo group, but the study lacked statistical power to detect a difference (Guillaumin et al, 2020). In that study, complications for the tissue plasminogen activator and placebo groups included acute kidney injury (22% and 19%, respectively, P=1.00) and reperfusion injuries (33% and 19%, respectively, P=0.45). Therefore, prospective data shows that approximately 40% of cats with bilateral aortic thromboembolism will survive to discharge, and some studies suggest a median survival time after discharge of 117–345 days (Moore et al, 2000; Rush et al, 2002; Smith et al, 2003).

In an abstract, a multicentric aortic thromboembolism retrospective study looked at over 100 cats and is the first study showing a positive impact of thrombolysis (Cambournac et al, 2022). Specifically, the arterial recanalisation proportion was higher in tissue-type plasminogen activator-treated cats than in those who were not treated with tissue-type plasminogen activator (54.5% versus 20.9%, P<0.001) and functional recovery was higher in tissue plasminogen activator-treated than in those without (26.1% versus 13.8%, P=0.007). However, tissue-type plasminogen activator did not provide a survival benefit, although the reported survival (approximately 35%) is lower when compared to previous reports (Cambournac et al, 2022). Finally, another abstract published in September 2022 and using reteplase (a third generation tissue plasminogen activator) showed a 90% survival to discharge in bilateral feline aortic thromboembolism (Hassdenteufel et al, 2022).

Those studies, coupled with advances in prevention of reoccurrence of aortic thromboembolism with clopidogrel or clopidogrel and rivaroxaban, show possible short-term and long-term treatment options for cats with aortic thromboembolism (Hogan et al, 2015; Lo et al, 2022).

Tissue plasminogen activator treatment options

Most current literature in cats with aortic thromboembolism uses a treatment used for acute ischemic stroke – for a total dose of 1 mg/kg, 10% of the dose is given as a slow bolus, and the rest over a 1 hour period (Guillaumin et al, 2019; Guillaumin et al, 2020; Cambournac et al, 2022). However, as mentioned earlier, the current recommendation for saddle thrombus in the human paediatric population, as well as historical feline aortic thromboembolism cases, is to use a continuous rate infusion (Abastado et al, 1969; Pion et al, 1987; Mulcaire-Jones et al, 2020). Specifically, the dose of alteplase used in people is a continuous rate infusion at a dose of 0.1–0.5 mg/kg/hr with careful monitoring of reperfusion and complications. A continuous rate infusion can be complicated, as it may require multiple catheters or a central catheter.

Ancillary treatments when using a tissue plasminogen

The ancillary treatments for feline aortic thromboembolism are targeted towards treatments of the primary disease process (in-

cluding the processes of congestive heart failure), pain management and nursing care, as well as thromboprophylaxis and development of collateral circulation.

Treatment of cardiac disease and congestive heart failure

Oxygen supplementation, judicious use of furosemide and oxygen and other cardiac treatments may be warranted. Pain control can be achieved using opioids such as methadone or fentanyl, and nursing care is important. Hospital stays are usually 2–5 days, but early reports on clinical reports of feline aortic thromboembolism show an interval of 2–6 weeks before seeing neuromuscular function and ambulatory abilities in cats exhibiting spontaneous resolution. Moreover, distal extremity necrosis, dry gangrene, muscle retraction and amputation may be necessary in some cats (around 5% of cases) with spontaneous resolution. The use of an anticoagulant is recommended in order to decrease worsening of thrombus. The Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care guidelines recommends treatment with thromboprophylaxis for feline aortic thromboembolism patients, with the benefits outweighing the risks (Sharp et al, 2019). The guidelines do not differentiate between in-hospital treatment, prevention for feline aortic thromboembolism survivors and prevention for high-risk aortic thromboembolism patients. The guidelines recommend the use of clopidogrel, unfractionated heparin or low-molecular weight heparin. The recommended dose for clopidogrel for prevention of feline aortic thromboembolism is 18.75 mg orally once a day (Pion et al, 1988a). If heparin is used, the guidelines suggest an initial subcutaneous dosage of unfractionated heparin of 250 units/kg every 6 hours or dalteparin at 75 units/kg subcutaneously every 6 hours. Finally, rivaroxaban appears safe and well-tolerated in cats and a dose of 0.5–1 mg/kg/day is recommended in this species (Pion et al, 1988). A recent study showed excellent tolerance when using clopidogrel and rivaroxaban as a dual therapy. Specifically, cats had an aortic thromboembolism event and the presence of an intracardiac thrombi or presence of 'smoke'. Median survival time from the onset of therapy was 257 days for all cats, and 502 days for cats with aortic thromboembolism. Recurrence rate of aortic thromboembolism while on dual therapy was 16.7%; no cat developed a new aortic thromboembolism while on dual therapy (Lo et al, 2022).

Conclusions

In conclusion, although there is no strong evidence that thrombolysis improves outcome in saddle thrombus cats, it is clear it does not worsen their prognosis. Further research is needed to optimise current thrombolysis protocols, mitigate complications and advance long-term thromboprophylaxis options. CA

Conflict of interest

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KEY POINTS

- With treatment, survival of feline aortic thromboembolism cases is approximately 30–40%.
- Thrombolysis, especially with tissue plasminogen activator, can be attempted, although strong evidence for a survival benefit is lacking.
- The main complications of treatment for feline aortic thromboembolism, with or without thrombolysis, are acute kidney injuries and reperfusion injuries.
- Around 30–40% of the treated cats with aortic thromboembolism will develop complications.
- Long-term survival (more than a year) is possible after treatment for aortic thromboembolism.

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