



FELINE AORTIC THROMBOEMBOLISM

Recent advances and future prospects

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Introduction

Feline aortic thromboembolism (FATE), also known as 'saddle thrombus', is probably the most common form of thromboembolism seen in clinical veterinary medicine.^{1,2} It is initiated by the sudden migration of a left atrial thrombus into the systemic arteries, and its prevalence has been reported as 1/175 cases in a tertiary US veterinary center,¹ and 1/379 cases in UK general practice.³ FATE is a devastating syndrome, with short-term consequences characterized by acute pain, paralysis and rhabdomyolysis in the affected limb(s).² FATE also has long-term implications, as many patients are suffering from severe cardiac disease, and recurrence of the syndrome is common.^{1–3} After several decades that have seen a lack of scientific progress, more data have been published on FATE in recent years, informing on progression, prognosis and treatment options for cats with this clinical syndrome.

The major cause of FATE is cardiomyopathy, accounting for 90% of cases. Neoplasia represents the second most common cause, with pulmonary neoplasia dominating that category.

Overview of causes of arterial thromboembolic disease

The major cause of FATE is cardiomyopathy, accounting for 90% of cases.^{1–3} However, and despite a median age of 8–12 years at diagnosis of FATE, only 20% of cats have a known cardiomyopathy at the time.¹ In other words, in 80% of cases, FATE is the first clinical manifestation of cardiomyopathy. It has been shown that around 25% of cats with hypertrophic cardiomyopathy (HCM) will develop FATE.⁴ As male cats are predisposed to cardiomyopathy, it is common for FATE cats to be male (75% of cases).^{1–3}

In approximately 10% of cats with FATE, the cause of the thromboembolism is non-cardiogenic. Neoplasia represents the second most common cause of FATE, with pulmonary neoplasia dominating that category. Other, less common causes of feline thromboembolism include infection, inflammatory disease, hyperthyroidism and administration of corticosteroids or progesterone agonists.⁵

Practical relevance: Feline aortic thromboembolism (FATE) is commonly encountered in clinical medicine, especially in emergency situations. This often devastating syndrome usually develops secondarily to severe heart disease, and has short- and long-term consequences.

Clinical features: The clinical presentation of FATE is consistent with peripheral ischemic neuropathy, usually in both pelvic limbs. Diagnosis is relatively straightforward, but can be assisted with Doppler ultrasound, point-of-care ultrasound or infrared thermal imaging.

Recent advances and future prospects: Interpretation of survival rates in cats with FATE has been hampered by historically high admission euthanasia, but recent studies suggest a survival rate with supportive care of 30–40%. Moreover, with advances in post-FATE thromboprophylaxis, median survival times of over 1 year are being achieved. Future directions include use of thrombolytic agents and treatment of common FATE sequelae such as acute kidney injury and reperfusion injury.

Outline: This article, aimed at small animal veterinarians, including emergency practitioners, reviews key aspects of the clinical presentation, diagnosis and treatment options for FATE, with a view to guiding client and veterinarian decision-making. Three case studies are included to illustrate the practical application of information presented in the review.

Evidence base: There are limited prospective studies on FATE, although the recent literature reflects a resurgence in clinical research interest in the past few years. Advances in FATE treatment will benefit many cats and it is important that research efforts continue to identify appropriate treatment modalities.

Keywords: Thromboembolism; thrombolysis; cardiomyopathy; TPA; thromboprophylaxis; CURATIVE





Figure 1 Paralysis in an 11-year-old male castrated domestic shorthair cat with feline aortic thromboembolism (FATE). Note the position of the pelvic limbs. A fentanyl constant rate infusion is being used to manage pain in this patient

Clinical presentation

The clinical diagnosis of FATE is relatively straightforward, with signs mostly consistent with peripheral neuropathy (Figure 1). In approximately 70–75% of cases, both pelvic limbs are involved, whereas 10–15% of affected cats have only one pelvic limb involved; the remaining cases have either right or left forelimb involvement.^{1–3}

Most clinicians diagnose FATE on physical examination using the ‘5P rule’, which characterizes the presenting signs of pallor (ie, purple, cyanotic or pale toes; Figure 2), polar/poikilothermy (ie, cold extremities), pulselessness, paralysis/paresis and pain. Findings using diagnostic tools include: absence of Doppler flow; direct visualization of a thrombus on ultrasound, infrared thermal imaging or angiography; and a low glucose or high lactate measurement in the affected limb(s) compared with normal limbs.^{2,6,7} Infrared thermography can also be used to assess reperfusion in affected limbs.

As mentioned, 80% of cats with FATE have a hitherto unrecognized cardiomyopathy as a cause of the thromboembolism,^{1–3} and so it is



Figure 2 Close-up view of one of the paws of the cat pictured in Figure 1. Note the purple/pale discoloration of the paw pads



Most clinicians diagnose FATE on physical examination using the ‘5Ps’: pallor, polar (poikilothermy), pulselessness, paralysis/paresis and pain.

important to assess for signs of cardiac disease and congestive heart failure (CHF), such as dyspnea, pulmonary crackles and cyanosis. CHF is present in around 50–70% of cats with FATE,^{1–3} but is not associated with a worse prognosis. Cardiac auscultation abnormalities such as a murmur or gallop rhythm are identified in two-thirds of cases. It is not uncommon (ie, 10–20% prevalence) for vomiting to occur in cats prior to presentation with FATE.^{1,3}

Diagnostic testing

Once a diagnosis of FATE has been established, it is important for the clinician to thoroughly assess the cat for comorbidities. Bedside echocardiography, or cardiac point-of-care ultrasound (C-POCUS; see box), can confirm the presence of a cardiogenic origin of FATE (ie, CHF), and can suggest the presence of a cardiomyopathy. C-POCUS is a screening test and is not a replacement for a complete echocardiographic examination performed by a trained cardiologist.⁸ It lacks detailed information on heart morphology and function, and may fail to detect all cardiac abnormalities. It can nevertheless provide emergency clinicians with information that is useful both for treating the cat and for client education.

The author recommends using C-POCUS and thoracic POCUS (T-POCUS) for rapid assessment of cardiac and thoracic structures. Chest radiography can be performed upon stabilization to assess for the presence of CHF or pulmonary neoplasia.

Baseline blood work (chemistry panel or venous blood gas analysis) is important to establish renal values and assess for renal dysfunction and/or early reperfusion. Findings may include azotemia, elevated creatine kinase, hyperkalemia and metabolic acidosis. Testing can be performed relatively quickly and without sophisticated equipment, and parameters should be serially monitored every 6–12 h during hospitalization.

Prognosis

The prognosis for cats with FATE has traditionally been considered poor, but ‘poor’ is rarely defined. FATE also has been associated with euthanasia rates as high as 90%, which seem to be clinician- or clinic-related.^{1,3,9} A recent prospective multicenter investigation of cats with bilateral pelvic limb paralysis (the BLASTT study) reported an overall 37.5% discharge rate, with a 95% confidence interval of 22.5% to 52.5%, with some cats experiencing >1 year survival.² This aligns with findings from retrospective studies, which have shown a survival rate of between 27% and 45%

Cardiac point-of-care ultrasound⁸

- ❖ C-POCUS requires an ultrasound machine with 2D (B-mode) capabilities, and a phased-array or curvilinear probe, ideally with a small footprint. High-frequency sector probes of 7–12 MHz are preferred. Isopropyl alcohol 70% (on the cat) and/or water-soluble acoustic coupling gel (on the probe) should be used. Parting or shaving the hair is crucial.
- ❖ Light sedation can be used; for example, butorphanol (0.2 mg/kg IV or IM) in combination with midazolam (0.2 mg/kg IV or IM) or alfaxalone (0.5 mg/kg IV or IM).
- ❖ The author recommends selecting the cardiac setting, which provides a high-contrast image and is ideal for evaluating the heart chambers. The depth of field can be adjusted to 4–6 cm in cats, so that the entire heart can fit on the screen.
- ❖ A full C-POCUS examination consists of right parasternal short- and long-axis views, with the left atrial-to-aortic ratio (LA:Ao) providing the most valuable information. C-POCUS can be performed in sternal, right lateral or left lateral recumbency, but the best pericardial window is the right pericardial window.
- ❖ The author prefers to start with the right parasternal short-axis ventricular ('mushroom') view (Figure 3; see also Video 1 in the supplementary material). In this view, the probe is positioned parasternally on the right side of the thorax, with the probe marker directed cranially toward the cat's elbow, creating a 25–35° angle that allows the scan plane to be perpendicular to the axis of the heart. Moving the probe in small circles, while maintaining the same axis, can help to optimize the mushroom view. The scan plane is directed through the right ventricle in the near field and

the left ventricle in the far field, with symmetrical papillary muscles. The main purpose of the mushroom view is to evaluate the size, contractility and wall thickness of the left ventricular chamber. The most common cardiomyopathy phenotype in cats with FATE is HCM, which is characterized by left ventricular concentric hypertrophy.

- ❖ The second view is the right parasternal short-axis view at the level of the heart base (ie, left atrium to aorta [LA:Ao] view) (Figure 4; see also Video 2 in the supplementary material). This view is obtained by fanning toward the base of the heart, making sure that the scan plane stays perpendicular to the axis of the heart. The scan plane goes through the right side of the heart in the near field, the aorta in the center and the left atrium in the far field. The aorta should be round and, ideally, the three cusps of the aortic valve should form a Y shape. The main purpose of this view is to evaluate the size of the left atrium. An increased LA:Ao ratio (ie, >1.7) is typically diagnostic of cardiogenic FATE.

- ❖ The final C-POCUS views are the right parasternal long-axis four- and five-chamber views. From the positioning for a mushroom view, the probe is rotated 90° to change from a short-axis to long-axis view, with the probe marker pointing toward the cat's spine or shoulder. The scan plane is directed through the right ventricle and right atrium in the near field, and the left atrium and left ventricle in the far field (four-chamber view; see Video 3 in the supplementary material), with the aorta between the left and right atrium in the five-chamber view. The main purpose of these views is to look for left ventricular hypertrophy in cats with HCM.

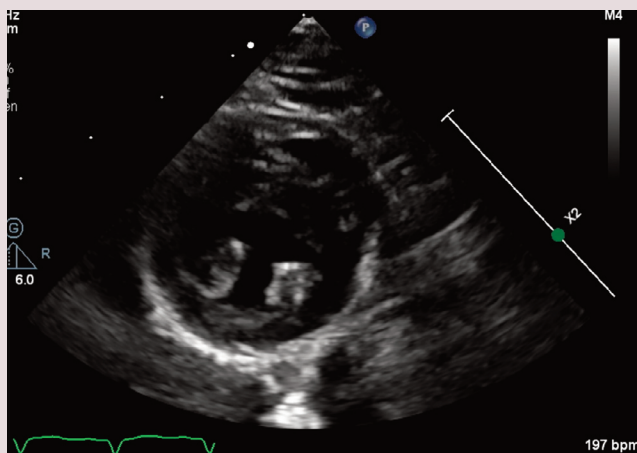


Figure 3 Right parasternal short-axis ventricular ('mushroom') view in a cat with HCM. Courtesy of Kaitlin Abbott-Johnson

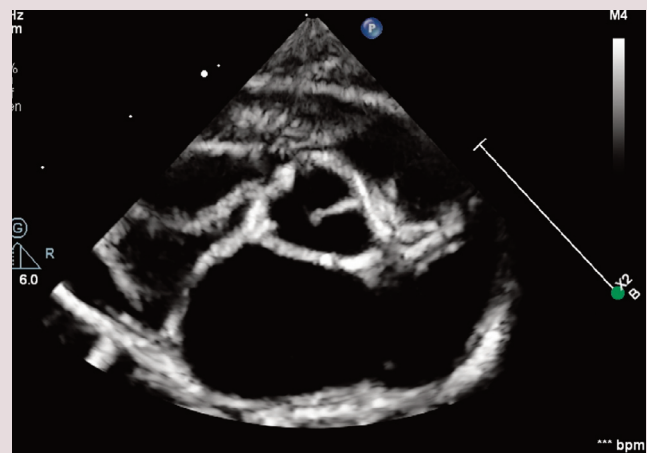


Figure 4 Right parasternal short-axis view at the level of the heart base, showing an increased LA:Ao ratio in a cat with HCM. Courtesy of Kaitlin Abbott-Johnson

for cats suffering from bilateral FATE,^{1,3,10–13} however, interpretation of findings is hampered by vastly different inclusion criteria (ie, one limb affected vs bilateral syndrome), in-hospital treatment, medications dispensed at discharge and outcome data between different retrospective studies.^{1–3,11,12,14–16} It should be noted that, despite most studies having been conducted in university settings or referral hospitals, mortality of cats hospitalized or treated for FATE remains high.^{2,9,15}



When considering the prospects for patients (see 'Prognostic factors' box), it is again important to note that, until recently, studies have mostly been retrospective in nature; and, while some have identified outcome factors, many reported non-survivor admission characteristics, which differ from actual prognostic factors.

Moreover, while euthanasia rates had been increasing over the past few decades – the rationale being that treatment options were limited, and both the short- and long-term

Prognostic factors

❖ **Motor function, and one limb vs bilateral FATE** Cats with motor function at admission or only one limb affected have a better prognosis (70% survival to discharge rate) than cats with bilateral pelvic limb paralysis (25% survival to discharge rate).^{1,3} Note that the 25% survival to discharge rate for bilateral FATE, gleaned from selected retrospective studies,^{1,3} needs to be contrasted with the 35–40% rate determined in the principal prospective study that is currently available.²

❖ **Rectal temperature at admission** Two studies have shown that a lower rectal temperature is predictive of non-survival. A retrospective study showed an optimal cut-off for rectal temperature of 37.2°C (98.9°F),¹ whereas a prospective study showed an optimal rectal temperature of 35.7°C (96.2°F).²

❖ **Limb lactate levels** A recent study showed that FATE with a higher lactate level in the affected limb(s) (11.5 mmol/l cut-off) was predictive of a poorer prognosis, although the median affected limb lactate in the population studied was 11.2 mmol/l, so the clinical relevance of this finding is unknown.²

❖ **Time from FATE event to treatment** A study of 15 clinical cases of FATE in Egypt showed that the time from the thromboembolic event to treatment was prognostic, emphasizing the importance of prompt diagnosis and treatment.¹⁴

❖ **Effect of treatment** Overall, a treatment effect has been challenging to identify, particularly given the often small sample size and high euthanasia rates in both retrospective and prospective studies on FATE. Not receiving treatment with aspirin and/or clopidogrel has been shown in one large retrospective study to be associated with a poor prognosis.³ Another large retrospective study was able to show that cats receiving early thrombolysis with tissue plasminogen activator (TPA) had an increased chance of recanalization and functional recovery, although this did not translate into a survival benefit.⁹ Interestingly, the outcome in cats with FATE may also vary dependent on the level of available clinical expertise, with clinicians or clinics with more experience of FATE achieving higher survival rates.^{1,2}

prognosis was very poor – more recent research investigating thrombolysis and long-term treatment options has challenged this notion.^{2,9,15,16} If the cat survives the FATE episode and can be discharged with appropriate oral medications,¹⁵ long-term survival may be much higher than previously thought. Indeed, retrospective studies have shown that survival times after discharge could be up to 350–500 days, with the use of rivaroxaban and clopidogrel producing the highest survival times and lowest re-embolization rates.^{1,4,11,15} Thus, in facilitating decision-making, veterinarians must ensure each client has a fair understanding of the causes of FATE, long-term prognosis (especially with cardiac disease) and treatment options, including the impact of thrombolysis, thromboprophylaxis and euthanasia on the natural course of disease.

Emergency treatment

Emergency treatment of FATE revolves around analgesia, treatment of the primary disease (eg, HCM), nursing care and thromboprophylaxis, and may also include thrombolysis and promotion of the collateral circulation (see Table 1 and ‘Management of FATE’ algorithm).

Analgesia

Pain control is important for FATE patients. Analgesia with a pure μ -agonist is recommended, and the author’s preference is initial treatment with methadone, followed by a constant rate infusion (CRI) of fentanyl (1–5 $\mu\text{g}/\text{kg}/\text{h}$ IV), titrated to effect (Table 1). Other opioids, such as oxymorphone, hydromorphone or buprenorphine, can be used if the

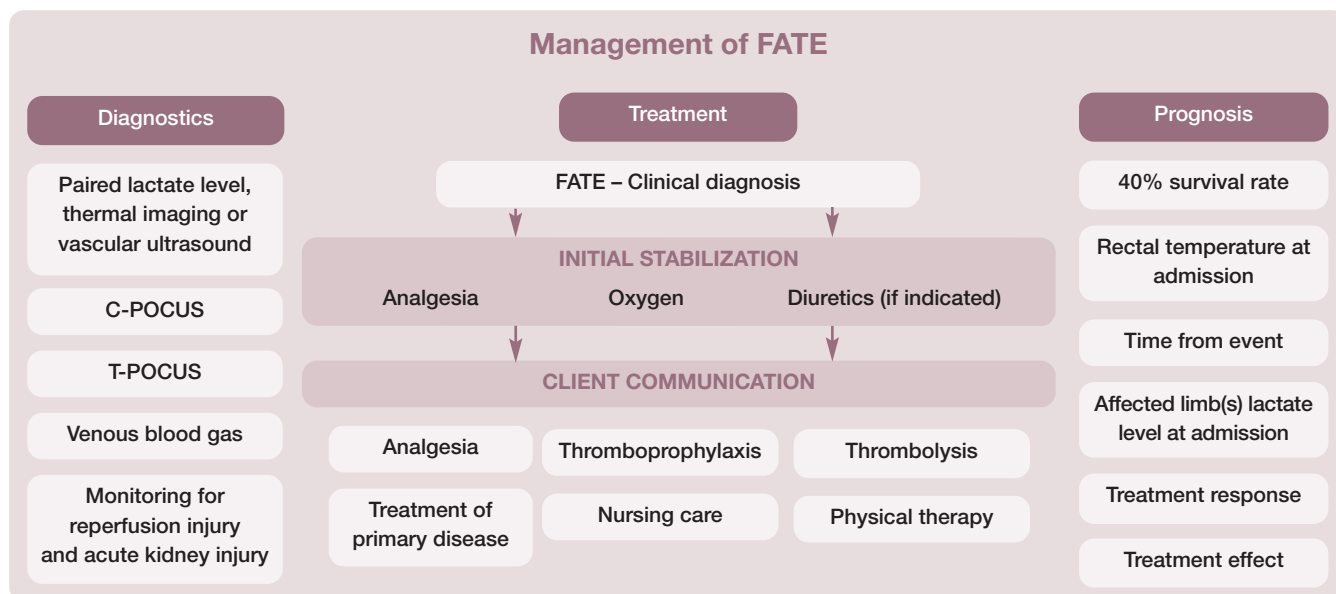


Table 1 Medical treatments for FATE

Category	Dose	Advantages	Disadvantages	Side effects	Monitoring*
Analgesics					
Methadone	0.1–0.4 mg/kg IV or IM	Powerful analgesic Reversed by naloxone	Availability Cost	Can cause hyperthermia Sedation also possible	Body temperature Ventilation
Fentanyl	1–5 µg/kg/h IV CRI	Potent analgesic Can be titrated Reversed by naloxone	Availability Cost	Can cause hyperthermia	Body temperature Ventilation
Gabapentin	50–100 mg/cat PO q12–24h	Analgesic/anxiolytic	Oral medication Needs to be dosed 2–3 times daily	Sedation	Non-specific
Buprenorphine	0.01–0.02 mg/kg IM, IV or SC q4–8h (except for the long-acting formulation) 1.2–3 mg/kg transdermal once	Long duration of action Single-dose transdermal formulation is available	Cannot be reversed	Can cause hyperthermia	Body temperature Ventilation
Antiplatelet therapies					
Aspirin	5–81 mg/cat PO q72h	Inexpensive	Oral medication Therapeutic effect at non-toxic dose unclear <i>No longer recommended</i>	Vomiting Diarrhea Azotemia Bleeding	Renal values Bleeding
Clopidogrel	18.75 mg PO q24h 37.5 mg PO once can be used as a loading dose	Shown to be superior to aspirin alone ¹⁷ Currently recommended for prevention/treatment of FATE, based on expert consensus ¹⁸	Oral medication	Bleeding	Bleeding
Anticoagulant therapies					
Unfractionated heparin	350–375 IU/kg IV, then 150–250 IU/kg SC q6–8h	Inexpensive Potent anticoagulant	Dose-dependent bleeding risk Considerable intra- and interindividual variation in pharmacokinetics	Bleeding	Monitoring of aPTT, with a target of 1.5–2 x baseline, is recommended
Dalteparin (LMWH)	150–180 IU/kg SC q4–6h	Fewer side effects and more predictable pharmacokinetics compared with unfractionated heparin	Cost Inability to use aPTT for monitoring	Bleeding	Monitoring of antifactor Xa possible, but availability and cost limit its use in practice
Enoxaparin (LMWH)	0.75–1 mg/kg SC q6h	Fewer side effects and more predictable pharmacokinetics compared with unfractionated heparin	Cost Inability to use aPTT for monitoring	Bleeding	Monitoring of antifactor Xa possible, but availability and cost limit its use in practice
Rivaroxaban ¹⁵	0.5–1 mg/kg PO q24h Doses up to 2.5 mg PO q24h have been published	When combined with clopidogrel, efficacy may be superior	Cost Oral medication	Bleeding	Viscoelastic tests can be used
Apixaban ¹⁹	0.2 mg/kg PO Alternative dose regimen: <5 kg – 0.625 mg PO q12h >5 kg – 1.25 mg PO q12h	Oral anticoagulant	Cost Less information available compared with rivaroxaban Oral medication	Bleeding	Viscoelastic tests can be used
Thrombolytic agents					
Alteplase	1 mg/kg IV over 1 h with 10% as a slow bolus (eg, over 1 min) 0.1–0.5 mg/kg/h IV CRI	Recently, has been suggested to improve recanalization in cats with FATE ⁹	Cost Availability Outcome – improvement still unknown at this time	Bleeding Seizures reported	Non-specific
Reteplase	1 IU/cat IV q8h	Promising therapy	Cost Availability Limited research to date	Bleeding	Non-specific
Adjunct therapies					
Pentoxifylline	100 mg/cat PO q12h	Minimal side effects	Unknown efficacy for promotion of collateral circulation	Minimal	Non-specific
Cyproheptadine	2 mg/cat PO q12h	Minimal side effects Appetite stimulant	Unknown efficacy for promotion of collateral circulation	Minimal	Non-specific

*Monitoring for azotemia and reperfusion injuries is recommended for all cats with FATE, whether or not thrombolysis is used
aPTT = activated partial thromboplastin time; CRI = constant rate infusion; FATE = feline aortic thromboembolism; LMWH = low molecular weight heparin

preferred options are not available. Many cats arriving very distressed and in obvious pain can readily be managed with short-acting opioids, which allows for further investigation and stabilization, and client communication. After initial stabilization, and ideally in the light of objective measures (eg, Feline Grimace Scale),^{20–22} additional sedation, analgesia and anxiolytics may be needed.

Treatment of primary disease

Assessment of the cat for cardiac disease and the presence of CHF is important for emergency stabilization. The majority (ie, 90–95%) of FATE patients are suffering from cardiac disease, including HCM and hypertrophic obstructive cardiomyopathy (HOCM), with 50–70% of patients having concurrent CHF.^{1,3} Therefore, treatment of cardiomyopathy and CHF should be instituted, where appropriate.²³

Treatment of cardiac disease and CHF involves oxygen supplementation, judicious use of furosemide, and oxygen therapy; other cardiac treatments may be warranted. Readers are referred to consensus guidelines on cardiomyopathies from the American College of Veterinary Internal Medicine for further information.²³ The recommendation that furosemide be used judiciously relates to the fact that many cats with FATE are dehydrated on presentation; overly aggressive use of diuretics can worsen a pre-renal component of acute kidney injury (AKI).

The author recommends assessing renal function with venous blood gas analysis or a biochemistry panel at admission and closely monitoring renal values. The need for diuretics and control of CHF should be carefully balanced in cats with pre-existing azotemia or even borderline high creatinine values.



The CURATIVE guidelines recommend treatment with thromboprophylaxis for FATE patients, with benefits outweighing the risks.

Thromboprophylaxis

Anticoagulant therapy is recommended to decrease the risk of the thrombus worsening. Options include unfractionated heparin (UFH), low molecular weight heparin (LMWH), aspirin, clopidogrel or a novel oral anticoagulant such as rivaroxaban or apixaban (Table 1).

The Consensus on The Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE) guidelines, published in 2019, provide current recommendations for a cat with cardiac disease and acute FATE.¹⁸ Although comprising mainly expert opinion rather than evidence-based recommendations, the CURATIVE guidelines suggest that administration of clopidogrel in combination with LMWH can be considered in cats at risk of FATE. The recommendation would be clopidogrel (18.75 mg PO q24h) and one of the LMWHs, dalteparin or enoxaparin (Table 1). Enoxaparin in cats can be used at a dose of 0.75–1 mg/kg SC q6h to reduce inter-individual variation in peak anti-Xa activity.¹⁸ Recently, based on results from the FAT CAT¹⁷ and SUPER-CAT studies (B Brainard, personal communication, 2023) and a retrospective investigation from Lo et al,¹⁵ a combination treatment with clopidogrel and rivaroxaban/apixaban appears to be the preferred long-term treatment option.^{15,24}

See the box 'Thromboprophylaxis: summary of guidance' and the later section 'Prevention of future episodes of FATE' for further information and discussion.

Thrombolysis

Recent expert consensus has suggested that thrombolytic agents can be considered for treatment of acute (<6 h duration) FATE

Thromboprophylaxis: summary of guidance

- ✦ The CURATIVE guidelines recommend treatment with thromboprophylaxis for FATE patients, with benefits outweighing the risks.¹⁸ The guidelines do not differentiate in-hospital treatment, prevention for FATE survivors and prevention for cats at high risk of FATE. The guidelines recommend the use of clopidogrel, UFH or LMWH.

- The recommended dose for clopidogrel for prevention of FATE is 18.75 mg PO q24h.¹⁸ A loading dose of 37.5 mg total is suggested, as it may be useful for obtaining therapeutic plasma concentrations more rapidly.²⁵

- If using heparin, the guidelines suggest 350–375 IU/kg IV, then 150–250 IU/kg SC q6–8h for UFH, or dalteparin at 75 IU/kg SC q6h. They suggest enoxaparin at 0.75–1 mg/kg SC q6h for cats at risk of venous thromboembolism, although no specific recommendations regarding LMWH are made for FATE.

- ✦ Enoxaparin is recommended q6h to reduce inter-individual variation in peak anti-Xa activity.¹⁸ Recently, the use of enoxaparin

IV as a CRI for FATE has been described, with excellent success, though the authors noted that the true benefit of the protocol remains to be evaluated in future prospective studies.²⁶

- ✦ Rivaroxaban appears safe and well tolerated in cats and a dose of 0.5–1 mg/kg PO q24h is recommended.¹⁸

- ✦ A recent study demonstrated excellent tolerance to use of clopidogrel (18.75 mg PO q24h)/rivaroxaban (2.5 mg PO q24h) dual therapy: median survival time from onset of therapy was 257 days for all cats in the study population deemed at high risk of cardiogenic FATE, and 502 days for cats with FATE. The recurrence rate for FATE while on dual therapy was 16.7%, and no cat newly developed a FATE episode while on dual therapy.¹⁵

- ✦ Although the CURATIVE guidelines do not specifically mention apixaban, the recommendation would be expected to be similar to that for rivaroxaban. Apixaban has been used in cats at 0.2 mg/kg PO, showing a half-life of 8.3 h, and was an effective factor Xa inhibitor in cats (Table 1).¹⁹

following an assessment of the risks and benefits in individual cats.²⁷ Evidence available for inclusion in the systematic review leading to this consensus guidance included:

❖ A 1987 abstract involving six cats from the University of California, Davis, where TPA was used at 0.25–1 mg/kg/h IV as a CRI, providing a total of 1–10 mg/kg. The discharge rate from the hospital was reported as 43%, but included 3/6 cats (ie, 50%).¹³

❖ A 2010 uncontrolled prospective study investigating the TPA alteplase in 11 cats with FATE.²⁸ Cats were enrolled within 12 h of the onset of clinical signs, and an additional TPA dose was administered to 36% of cases (4/11 cats). In 6/9 (67%) cats, there was return of pulses and improved limb function, although only three (27%) of the 11 cats were discharged from the hospital.

❖ A 2019 retrospective study comparing a thrombolysis group receiving the TPA alteplase (n = 16) with a robust control group treated without thrombolysis. It showed no worsening in survival rate, as well as similar complication rates (ie, AKI and reperfusion injury), between the groups.²⁹

Since the consensus guidance was published, the earlier mentioned BLASTT study, a prospective, randomized, placebo-controlled investigation using alteplase for FATE, showed a survival to discharge rate of 45% for the TPA group and 30% for the placebo group, though the study lacked power to detect a statistical difference.² In 2022, a relatively large retrospective study comparing TPA-treated cats with non-TPA-treated cats, published as an abstract, showed a positive impact of thrombolysis on functional recovery and arterial recanalization.⁹ However, TPA did not provide a survival benefit in that study, and the reported overall survival was approximately 35%.⁹ Finally, another abstract published in 2022 reported a 90% survival to discharge rate for cats with bilateral FATE receiving reteplase (a third-generation TPA).¹⁶

Most studies use a treatment regimen for thrombolytic agents similar to the one for acute ischemic stroke: a total dose of 1 mg/kg, with 10% of the dose administered as a slow bolus, and the rest over 1 h.^{2,9,29} In pediatrics, a CRI at a dosage of 0.1–0.5 mg/kg/h is used, with careful monitoring of reperfusion and complications.³⁰

Nursing care

Nursing care is extremely important for cats with FATE. Physical therapy involving passive range of motion and leg warming can be attempted if tolerated by the patient. Hospital stays are usually 2–5 days but, based on early reports of clinical FATE,³¹ an interval of 2–6 weeks is to be expected before seeing

Figure 5 Self-mutilation 3 months after recovery from FATE. The cat, who suffered from severe cardiomyopathy, underwent pelvic limb amputation and recovered well



Recent expert consensus suggests that thrombolytic agents can be considered for treatment of acute (<6 h duration) FATE following an assessment of the risks and benefits.



The focus of the next step in research on FATE is to investigate drugs to promote the development of collateral circulation.

improvement in neuromuscular function and ambulatory ability in cats exhibiting spontaneous resolution. Moreover, distal extremity necrosis, dry gangrene and muscle retraction may develop in some cats (around 5% of cases³¹) showing initial spontaneous resolution (Figure 5), necessitating amputation. Attention to nutrition, elimination and stress reduction is vital for optimal recovery.

Ancillary treatments

Complications, especially AKI and reperfusion injury, develop frequently (see 'Ongoing care'), regardless of whether thrombolysis is attempted. In terms of AKI, it is now believed that bilateral renal thrombosis is uncommon, and we know that the clinical syndrome of FATE can be induced with vasoconstricting agents without a physical clot.^{2,32} Therefore, the focus of the next step in research on FATE is to investigate drugs to promote the development of collateral circulation, such as vasodilators and/or antioxidants.

There are several candidates. Pentoxifylline is an antioxidant, anti-inflammatory drug and vasodilator with red blood cell deformability (ie, rheology) properties.^{33,34} Cyproheptadine, when administered before thrombus formation, preserves collateral circulation and prevents paralysis; this drug is a serotonin antagonist and antihistamine, and is commonly used as an appetite stimulant.^{35,36} Other potentially useful agents include cilostazol, an antiplatelet drug and vasodilator, and flunarizine, a calcium channel blocker.

Ongoing care

Ongoing care for a cat following a FATE episode may be best suited to a 24/7 veterinary facility with solid expertise in nursing care and a multispecialty medical team. Indeed, studies on cats with bilateral FATE have shown that they commonly suffer from complications such

as reperfusion injury (20–50% prevalence) and AKI (30%), regardless of whether thrombolysis is attempted.^{2,29} Sudden death is relatively uncommon (10–15%) and usually occurs during the first 12 h.²

Approximately 40% of cats with FATE who develop complications will survive if appropriate treatment is instituted.² The author

Case notes 1

Quilate, a 6-year-old male castrated Bengal cat, was presented to the emergency service with acute immobility in his hindlimbs. The signs were noticed by his owner at 5:30 am on day 1. He had a known restrictive cardiomyopathy, but was not on thromboprophylaxis treatment.

Presentation Quilate was bright, alert and reactive, but non-ambulatory on his hindlimbs. He had no motor function in his left hindlimb and mild motor function in his right hindlimb. Both limbs were cool to the touch, with the left being colder; thermal imaging confirmed a temperature gradient $>2.4^{\circ}\text{C}$. He had a heart rate of 180 bpm, respiratory rate of 40 breaths per min and was hypothermic with a rectal temperature of 36.7°C (98.5°F). On thoracic auscultation, crackles could be heard in all lung fields and his previously noted heart murmur was difficult to appreciate over the lung sounds.

Triage and initial assessment Supplemental oxygen was immediately given and an intravenous catheter placed. A 2 mg/kg furosemide bolus was administered in addition to 0.2 mg/kg methadone. The lactate level in Quilate's left hindlimb was 7.6 mmol/l. FATE was diagnosed and, after discussion, the owner confirmed they were interested in moving forward with treatment, including thrombolysis.

Diagnostics performed at admission showed a mild hemoconcentration (PCV 47%, total protein 8.1 g/dl), mild thrombocytopenia (91,000/ μl), hyperglycemia and mild azotemia (creatinine 2.06 mg/dl, potassium 3.5 mmol/l). Chest radiography and T-POCUS revealed CHF. An echocardiogram performed under mild sedation with fentanyl revealed a bridging lesion across the left ventricle with progressive left atrial and left auricular enlargement. There was 'smoke' in the left atrium with a suspected organized thrombus in the left auricle.

Initial treatment Given the recent acute onset (<6 h) of clinical signs, TPA (alteplase) was administered at a dose of 1 mg/kg and as a CRI; as recommended for pediatric cases, 0.1 mg/kg was given over 1 min initially, and then a 0.1 mg/kg/h CRI was commenced. Quilate was hospitalized on supplemental oxygen, furosemide (1–2 mg/kg IV q6–8h), fentanyl CRI (2–5 $\mu\text{g}/\text{kg}/\text{h}$), LMWH (enoxaparin, 1 mg/kg SC q8h) and clopidogrel (18.75 mg PO q24h). In an effort to help with the development of collateral circulation, pentoxifylline (100 mg PO q12h) and cyproheptadine (2 mg PO q12h) were

started during the TPA infusion. Quilate's pain seemed adequately controlled with the fentanyl CRI, and his breathing improved in response to the oxygen/furosemide therapy. Overnight, his creatinine was noted to have risen to 2.89 mg/dl but his potassium was stable at 3.5 mmol/l.

Hospitalization On day 2, Quilate was brighter and more interactive. His lung sounds and breathing pattern were markedly improved. The right hindlimb seemed to have regained some motor function, but his left hindlimb was still relatively immobile and cold to the touch. Given the continued increase in creatinine levels and improvement in lung sounds, and following recheck thoracic radiographs, his furosemide was reduced to 1 mg/kg q8h and he was weaned off the oxygen. During passive range-of-motion exercises, Quilate was noted to be painful, so gabapentin (50 mg PO q8h) was added.

Venous blood gas analysis that afternoon showed a continued increase in creatinine (up to 3.89 mg/dl), with potassium stable at 3.0 mmol/l. Therefore, intravenous fluid therapy (lactated Ringer's solution) was initiated at half maintenance rate (1 ml/kg/h). Six hours later, venous blood gas analysis showed stable creatinine, but lactate and total proteins were increased. Fluids were increased to full maintenance (2 ml/kg/h). Quilate continued to breathe comfortably, so his furosemide dosage was decreased to 1 mg/kg q12h. His motor function continued to show mild improvements and he was able to get himself safely to the litter box and back. His appetite had also improved.

On day 3, Quilate continued to improve clinically, with improved motor function in his left hindlimb, and return-to-normal motor function in his right hindlimb. His creatinine continued to improve, and his potassium had stabilized. He was weaned off fluids and discharged with the following treatment and recommendations: clopidogrel 18.75 mg PO q24h, apixaban 1.25 mg PO q12h, furosemide 6.25 mg PO q12h, gabapentin 50 mg PO q8h and referral to a local rehabilitation service.

❖ **What this case demonstrates:** Quilate was a younger cat with a known cardiomyopathy, so client communication was easier as the client was aware of the potential for complications and also the treatment options. He came in with a rectal temperature that was between the two published cut-off values for poor prognosis, and he already had mild azotemia, as well as CHF. However, his lactate level in the affected limb was below the published cut-off for poor prognosis. He was treated with a new thrombolysis protocol inspired from recommendations in pediatric patients, as well as with medications aimed at improving collateral circulation. He did develop some AKI and was treated with intravenous fluids after his CHF resolved. Quilate quickly regained the use of his hindlimbs and was discharged on day 3, with only mild complications encountered. Overall, the case was considered a great success!

recommends monitoring kidney function and potassium values early and serially in order to identify possible complications and treat accordingly, possibly by adjusting the diuretic dose. Intravenous fluids may be needed to manage AKI if it develops during treatment, and can be challenging to balance with cardiomyopathy. It should be noted that, although AKI in FATE cases has traditionally been thought to be due to thrombosis of one or both renal arteries, chronic renal infarction was the most common renal abnormality observed at necropsy in the BLASTT study.² This information, coupled with the relatively high packed cell volume (PCV) and total protein levels seen at admission in cats with FATE, raises the question of whether pre-renal azotemia or

exacerbation of chronic renal disease is the main cause of AKI in FATE cases.

Therapeutic measures such as judicious fluid therapy, careful use of diuretics or venodilator (eg, cilostazol) treatment may warrant consideration. It is possible that such complications may be mitigated with drugs targeted at vasodilation, antioxidation and development of collateral circulation such as pentoxifylline or cyproheptadine.^{33,35} As mentioned, further studies are needed to investigate the potential benefits of these medications.

If FATE is treated, cats usually improve within 24–48 h in terms of their ambulation status and/or the presence of pulses. However, some studies have shown that only

Case notes 2

Americano, an 11-year-old male castrated domestic shorthair cat, was presented to the emergency service with acute-onset hindlimb paralysis.

Relevant history Americano was last seen as normal approximately 2 h prior to presentation. His owners thought he had suffered a cat bite, as he was an indoor cat living with three other cats. He was a known diabetic and had received his regular insulin dose on the morning of day 1.

Triage and initial assessment On presentation, Americano was mildly obtunded and crying, but responsive; he was not able to use his hindlimbs bilaterally (see Video 4 in the supplementary material). His rectal temperature was 37.9°C (100.2°F), his heart rate was 150 bpm and his respiratory rate was 32 breaths per minute. Both hindlimbs were cold to the touch and he showed flaccid paralysis. No murmur or gallop rhythm was detected, and Americano was eupneic without pulmonary crackles.

Initial treatment Americano was immediately triaged in the treatment area. An intravenous catheter was placed and he was given supplemental oxygen. Fentanyl was started at 2 µg/kg/h after an initial 2 µg/kg bolus. Initial diagnostics with C-POCUS, T-POCUS and venous blood gas analysis indicated a probable cardiogenic origin of FATE without signs of CHF and an overall stable cat (creatinine 0.6 mg/dl, systemic lactate 2.6 mmol/l, potassium 3.7 mmol/l).

The owners were informed of the FATE diagnosis and prognosis, and were offered the option of enrollment in a randomized clinical trial using TPA or placebo. After talking to

their primary clinician, they elected to move forward with TPA without enrollment in the trial. Americano was started on TPA within 30 mins of presentation, with a 1 mg/kg IV dose over 1 h, with 10% of the dose given as a bolus over 1 min.

Full echocardiographic examination confirmed the presence of severe HCM with spontaneous echo contrast and two organized thrombi in the left atrium (see Video 5 in the supplementary material). Americano started to regain motor function during this examination, while receiving TPA.

Hospitalization Americano was hospitalized on fentanyl (2–5 µg/kg/h IV CRI), enoxaparin (1.5 mg/kg SC q8h), clopidogrel (18.75 mg PO q24h) and furosemide therapy (1–2 mg/kg IV, as required). He was weakly ambulatory on all four limbs 6 h after instigation of TPA treatment (see Video 6 in the supplementary material). Recheck venous blood gas analysis the first night of hospitalization showed an increase in creatinine to 1.0 mg/dl, but potassium was stable at 4.0 mmol/l. As Americano was not in CHF, he did not receive any furosemide and was not on supplemental oxygen therapy. It was elected to maintain renal function monitoring. His motor function continued to improve during his stay, and he started to eat on day 2.

Echocardiographic examination on day 3 revealed resolution of both left atrial thrombi. Creatinine was down to 0.8 mg/dl, with normokalemia. Americano was discharged to his owners on day 3, being able to walk normally (see Video 7 in the supplementary material). He was followed up for just over 18 months after his FATE event. He was latterly hospitalized for a hypoglycemic episode, which he survived, before being lost to follow-up.

✚ **What this case demonstrates:** This is an excellent example of things going well with a case of FATE. Americano was presented within the right time frame and was normothermic, which is a positive prognostic factor. He received a first-time diagnosis of HCM. His owners elected to pursue treatment with thrombolysis, and he responded extremely well to this therapy, along with supportive care, never developing any complications. Americano was followed up for 555 days after the initial event, despite being an older cat with diabetes mellitus and severe HCM. Note that this case dates back a few years prior to the publication of this review. Had Americano been treated more recently, he would have been discharged on clopidogrel and rivaroxaban/apixaban therapy.

50% of cats with FATE will survive 48 h, so a survival bias is probable, whereby cats who improved survived, whereas cats who did not improve or developed complications may have been euthanized.² If an improvement is not noted within 24–48 h, the long-term prognosis and options such as amputation and/or devices for ambulation assistance should be discussed.³⁷

Prevention of future episodes of FATE

The ideal long-term management for cats with FATE is unclear at this point. The CURATIVE guidelines, which as mentioned do not differentiate between hospitalized patients, FATE survivors or cats at high risk, recommend long-term use of clopidogrel, UFH or LMWH. The recommended dose for clopidogrel for prevention of FATE is 18.75 mg PO q24h.¹⁸ If using heparin, the guidelines suggest an initial SC dosage for UFH of 250 IU/kg q6h or dalteparin at 75 IU/kg SC q6h. Finally, rivaroxaban appears safe and well tolerated for long-term use in cats, with a recommended dosage of 0.5–1 mg/kg PO q24h.¹⁸

These recommendations were mainly based on the FAT CAT study, a multicentric, prospective, randomized investigation published in 2015,¹⁷ as well as expert opinion. The FAT CAT study demonstrated that clopidogrel was superior to aspirin for prevention of recurrence of FATE, as well as for overall survival. However, a criterion for enrollment into the study was a cardiogenic FATE that had been stable for between 1 and 3 months.¹⁷ Since then, the SUPER-CAT study, a similarly designed investigation comparing clopidogrel with rivaroxaban, has been performed, with preliminary results presented at the 2023 American College of Veterinary Internal Medicine (ACVIM) forum (B Brainard, personal communication, 2023). In that study, there were no statistically significant differences in the recurrence rate of FATE between rivaroxaban (median 513 days) and clopidogrel (median 663 days), nor in the median time to death between rivaroxaban (296 days) and clopidogrel (335 days).

In recent studies, cats with FATE and cardiac thrombi or ‘smoke’ present in the left atrium showed an excellent response to the use of clopidogrel/rivaroxaban dual therapy, with a synergistic effect being noted between the two drugs.^{15,24} Median survival time from the initiation of therapy was 257 days for all cats, and 502 days for cats with FATE. The FATE recurrence rate in cats on dual therapy was 16.7%, while no cat newly developed FATE while on dual therapy.¹⁵ On the basis of these findings,

KEY POINTS

- ❖ FATE is a syndrome that warrants reconsideration by the veterinary community.
- ❖ Recent years have seen advancements in preventive as well as in-hospital treatments, including thrombolytic therapies and promising thromboprophylactic treatments.
- ❖ Although the prognosis should remain guarded, there are now options available to clinicians for the treatment of FATE. Approximately 40% of cats will survive, with some single centers reporting 80–90% survival rates for bilateral FATE, and prospective and retrospective studies showing median survival times of up to 500 days.
- ❖ Treatment of cats with FATE nevertheless remains challenging and complications are common. A team approach to decision-making involving the client is important.



it seems logical to adopt a dual therapy approach using clopidogrel and a novel oral anticoagulant such as rivaroxaban or apixaban, although more research is need to assess clinical efficacy more broadly.

Supplementary material

The following supplementary material files are available at go.jfms.com/3WHYiMo:

- ❖ Video 1: Right parasternal short-axis ventricular (‘mushroom’) view in a cat with HCM. Courtesy of Kaitlin Abbott-Johnson.
- ❖ Video 2: Right parasternal short-axis view at the level of the heart base showing an increased LA:Ao ratio in a cat with HCM. Courtesy of Kaitlin Abbott-Johnson.
- ❖ Video 3: Right parasternal long-axis view showing the right ventricle and right atrium in the near field, and left atrium and left ventricle in the far field, in a cat with HCM. Courtesy of Kaitlin Abbott-Johnson.
- ❖ Video 4: Cat (featured in ‘Case Notes 2’) at admission showing clinical signs of FATE. Videos 5–7 document the clinical progression.
- ❖ Video 5: Full echocardiography performed on the cat in Video 4 shows severe HCM with spontaneous echo contrast and two organized thrombi in the left atrium.
- ❖ Video 6: Clinical signs and ambulation status in the cat in Videos 4 and 5, at 6 h post-thrombolysis with TPA.
- ❖ Video 7: Clinical signs and ambulation status in the cat in Videos 4–6, at 72 h post-thrombolysis with TPA.
- ❖ Video 8: Cat (featured in ‘Case Notes 3’) ambulating on his pelvic limbs after treatment with supportive care without thrombolysis.



Ongoing care for a cat following a FATE episode may be best suited to a 24/7 veterinary facility with solid expertise in nursing care and a multispecialty medical team.

Case notes 3

Gus, a 6-year-old male castrated domestic shorthair cat, presented out of hours to the emergency service having been referred for a suspected aortic thromboembolism.



Relevant history Gus had presented to his primary care veterinarian early in the evening of day 1 after his owners returned from work to find him unable to use his hindlimbs. They reported that he had been normal in the morning, but they were absent all day. The referring veterinarian found that Gus was not overly painful, but his hindlimbs were cold to the touch and non-mobile. His temperature on presentation was 36.6°C (97.8°F). Gus was immediately referred.

Presentation On presentation, Gus was bright, alert, responsive and did not appear painful (image a). His temperature, heart rate and respiratory rate were 36.6° (97.8°F), 190 bpm and 70 breaths per min, respectively. He weighed 3.95 kg. Principal physical examination findings were no palpable femoral pulses, cyanotic nail beds and cold hindlimbs with no motor function bilaterally. No murmur or pulmonary crackles were auscultated.

Triage and initial assessment

FATE was confirmed using thermal imaging (image b). As Gus was stable, a FATE work-up was performed with blood work, T-POCUS and chest radiography. A mild thrombocytopenia (125,000/ μ l) and normal creatinine (0.8 md/dl) were determined, with T-POCUS and chest radiography findings being consistent with a cardiogenic FATE.

Initial treatment Since the time of onset of FATE was unknown, use of thrombolytic medications was

deemed not ideal, so hospitalization with supportive care was recommended, which the owners agreed to. Gus was given clopidogrel and enoxaparin therapy, with fentanyl as needed. He was also started on intravenous fluids (lactated Ringer's solution) at 2 ml/kg/h.

Hospitalization On day 2, Gus was bright, alert and comfortable. He still did not have femoral pulses but was able to ambulate on his pelvic limbs with a crouched hindlimb stance (see Video 8 in the supplementary material). Chest radiographs were interpreted by a board-certified radiologist as being consistent with left-sided CHF with moderate to marked generalized cardiomegaly and left ventricular and left atrial enlargement.

Blood work results were good (PCV 31%, total protein 6.2 g/dl, potassium 3.5 mmol/l, creatinine 0.9 mg/dl). Echocardiographic

examination revealed HOCM with a trace of pericardial effusion, and intravenous fluids were immediately stopped. Clopidogrel was continued and enoxaparin was replaced with apixaban (0.625 mg PO q12h). Transmucosal buprenorphine (0.09 mg q8h) was started. A single furosemide dose (2 mg/kg IV) was given.

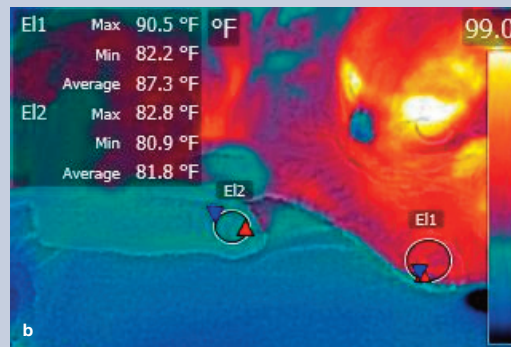
On the evening of day 2, Gus suffered an acute neurological event. He was found in his cage non-responsive but breathing, with marked obtundation, slow pupillary light reflexes and non-visual. Abdominal POCUS, T-POCUS and C-POCUS did not reveal free fluid in any of the three body cavities. Venous blood gas analysis showed an increase in creatinine (1.5 mg/dl) and mild hypokalemia. A cerebrovascular event, such as an acute ischemic stroke, was suspected. After initial stabilization and assessment, the owners were consulted regarding treatment options, including conservative management and thrombolysis with TPA, and elected to go forward with TPA treatment. Gus received 1 mg/kg of TPA, with 10% being given as a bolus and the remainder over 1 h.

Neurological findings improved during the course of the TPA infusion, with Gus becoming visual, and able to stand and turn around. His mentation improved more slowly but, within 1 h, he was back to normal and able to eat, drink and use the litter box.

On the basis of a further increase in creatinine (1.9 mg/dl) later that evening, with a potassium level of 3.0 mmol/l, an AKI was suspected.

On day 3, Gus was still anorectic, with static motor function in his pelvic limbs. On morning blood work, creatinine and potassium were 3.3 mg/dl and 4.7 mmol/l, respectively, with a PCV of 41% and total protein of 7.0 g/dl. Furosemide was discontinued, and he was started on 0.45% sodium chloride at 10 ml/h, increasing to 12 ml/h.

Mirtazapine therapy (1.5 inch transdermal ointment strip applied to an aural pinna q24h) was instigated. Early afternoon blood work revealed a further increase in creatinine (4.7 mg/dl), with normal potassium. Given the rapid progression of AKI, despite fluid therapy, the owners elected for humane euthanasia.



Digital and thermal images confirming FATE. Note the decrease in temperature in the distal pelvic limbs

✦ What this case demonstrates: Gus was referred very quickly to allow a tertiary referral center to provide full diagnostic and treatment options. Thromboprophylaxis was initiated, but not thrombolysis because the timing of the onset of FATE was unknown. Motor function recovered relatively quickly, which is unusual without thrombolysis in the author's experience. However, Gus went on to suffer a suspected cerebrovascular event. Although this was successfully treated with thrombolysis, he then developed an AKI and was euthanized. Necropsy confirmed an organized left atrial thrombus. No aortic thrombus was found – possibly as a result of spontaneous or TPA-induced thrombolysis. Also, no thrombus was found in the kidneys, supporting the idea that FATE-induced AKI may not necessarily be related to bilateral renal thrombosis.

Conflict of interest

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Ethical approval

This work did not involve the use of animals and therefore ethical approval was not specifically required for publication in *JFMS*.

Informed consent

This work did not involve the use of animals (including cadavers) and therefore informed consent was not required. No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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