Thrombolysis with tissue plasminogen activator (TPA) in feline acute aortic thromboembolism: a retrospective study of 16 cases

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Abstract

Objectives  Thrombolytic therapy is a treatment of choice for people with acute ischemic events, but is uncommonly administered for feline aortic thromboembolism (FATE). This study reports selected clinical data and outcomes of acute FATE treated with tissue plasminogen activator (TPA). A reference group treated with current standard of care (SOC) was analyzed for comparison.

Methods  This was a retrospective study of FATE in two academic hospitals. TPA-treated cats with two or more limbs (n = 16) affected were compared with a SOC-treated group with two or more limbs affected (n = 38). A limb score based on motor function and pulse quality was calculated for each group.

Results  Limb score and proportion of congestive heart failure at admission was similar in both groups. Time from FATE to admission was shorter in the TPA group, with a median of 3 h (range 0–6 h) vs 6 h (range 0–48 h; P = 0.0004). The most common regimen received for TPA was 1 mg/kg over 1 h. Other treatments were similar to those of the SOC group and included analgesia, thromboprophylaxis and furosemide. Documented complications for TPA-treated cats included reperfusion injury (5/10) and acute kidney injury (AKI; 3/10). Discharge proportion rate was 44% (TPA) vs 29% (SOC; P = 0.351). There were no differences in short-term survival rate (56.2% vs 39.5%; P = 0.369), clinical improvement (56.2% vs 31%; P = 0.122), rates of reperfusion injury (50% vs 50%; P = 1.00) or AKI (30% vs 27%; P = 1.00) between the TPA-treated and SOC groups, respectively.

Conclusions and relevance  Survival and complication rates of TPA-treated cats and SOC-treated cats for acute FATE were similar.

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Introduction

The clinical syndrome of feline aortic thromboembolism (FATE) is mainly initiated by the sudden migration of a left atrial thrombus into the systemic arteries.1 This leads to an acute disorder characterized by pain, paralysis, lack of pulse and eventual rhabdomyolysis in the affected limb(s). Approximately 90% of cats have underlying cardiomyopathy, which can lead to higher comorbidity.2-4 Prognosis for FATE is considered poor, with euthanasia as high as 90% in some reports.2-4 With the current standard treatments used for FATE (analgesia and thromboprophylaxis), the prognosis is still guarded, with a reported survival with treatment of 27–45%.2-6

Both mortality and functional outcome improve in people treated with intravenous tissue plasminogen activator (TPA) within 6 h of an acute ischemic stroke.7 TPA causes direct fibrinolysis by stimulating plasminogen
conversion to plasmin, with TPA preferentially inducing the dissolution of cross-linked fibrin rather than circulating fibrinogen. Although thrombolysis represents the standard of care for thromboembolism in people with acute ischemic stroke or acute myocardial infarction, it is infrequently offered in FATE. A recent study in people suggested that patients treated with TPA up to 6 h after the event and surviving the initial 7 days had a significantly better 3 year survival than those treated with standard of care (SOC) alone. However, in veterinary medicine, thrombolysis in FATE has been considered unrewarding. Lack of efficacy and risks of reperfusion injury (RI) with hyperkalemia are commonly expressed concerns surrounding thrombolysis in this syndrome. However, only two reported studies of TPA in cats included a time frame of treatment or a regimen for administration of TPA that vastly differed from recent human studies. Moreover, these studies were observational and did not include case controls or comparison groups representing current SOC (analgesia and thromboprophylaxis). The purpose of this retrospective study is to report clinical data and outcomes associated with the early use and short-term infusion of TPA in FATE vs a reference group of cats that received only SOC without TPA. We hypothesized that short-term outcome and short-term complication rates with TPA would not differ to SOC.

Materials and methods
A retrospective study was conducted by searching the electronic medical record databases from two academic hospitals – The Ohio State University and Lyon VetAgroSup – from June 2005 to March 2015. Inclusion criteria were hospitalized cats having an episode of confirmed FATE. A diagnosis was made based on clinical observation of any limbs affected by all of the following five criteria: pale, cold, lack of pulse, painful and lack of motor function. Additional criteria used to confirm the diagnosis included any of the following: lack of Doppler flow on affected limbs, glucose or lactate differential between affected limb and non-affected limb, vascular ultrasound or necropsy. If multiple episodes of FATE were identified for the same patient, only the first episode was recorded. In order to study a more homogeneous and clinically relevant patient population, only TPA-treated patients with two or more limbs affected were included in this study. That sample was compared with a control group of patients that had two or more limbs affected and which received SOC without thrombolysis at the same veterinary medical centers during the same period. The main exclusion criterion involved patients where no attempts of treatment were made besides analgesia and resulted in euthanasia shortly after admission. Other exclusion criteria were miscoded or incomplete medical records.

The primary outcome was the proportion of cats that survived to discharge. Secondary outcomes were 48 h survival, as well as clinical improvement or development of complications during hospitalization. Short-term outcomes were chosen because the short half-life and action of thrombolytics would theoretically only affect short-term outcome, and it reduces the risks of non-thrombolysis factors influencing outcome.

Demographics, physical examination, clinicopathological variables, complications and outcomes were recorded. The time from onset of FATE to admission was determined based on the history, such as when the cat was last seen as normal or the onset of the client hearing vocalization. The time from onset to admission was estimated to the nearest hour. All patients were retrospectively assigned a previously described limb score, based on physical examination findings (Table 1).

Clinical improvement was defined as improved motor function or limb score if available. Congestive heart failure (CHF) was defined by the presence of clinical signs consistent with pulmonary edema (eg, pulmonary crackles), or diagnosis of pulmonary edema on thoracic radiographs, reviewed by a Diplomate of the American College of Veterinary Radiology or a Diplomate of the European College of Diagnostic Imaging. Cardiogenic cause of FATE was diagnosed based on echocardiographic findings by a trained cardiologist. Cases without echocardiographic examination were deemed suspected cardiogenic if clinical signs, such as the presence of CHF, gallop rhythm or heart murmur, were present. Cardiogenic shock was defined as any of the following criteria: systemic hypotension (systolic blood pressure <90 mmHg), hyperlactatemia in a non-affected limb (>4 mmol/l) or the need for intravenous constant rate infusion of positive inotrope (eg, dobutamine). Acute kidney injury (AKI) was defined as a 100% increase of serum creatinine concentration between two time points, corresponding to a stage 2 AKI. RI was defined as an increase in serum potassium above our laboratory reference interval (ie, 5.4

<table>
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<th>Table 1 Limb score</th>
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<td>Limb function score</td>
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<td>Pulse present</td>
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Score only for affected limb. Minimum would be 2 (if only two limbs minimally affected) to 12 (if three limbs are severely affected).
mEq/L for Ohio State University and 5.8 mEq/L for Lyon VetAgroSup, without a concurrent rise in blood urea nitrogen and creatinine). When a rise in creatinine preceded a rise in potassium, it was classified as AKI. When a rise in potassium preceded the rise in creatinine, it was classified as RI. If both rises were concurrent or too challenging to be appropriately timed, it was classified as both AKI and RI.

Statistical analysis

Normality of continuous data were tested using the d’Agostino–Pearson test. Normally distributed data are presented as mean ± SD and non-normally distributed data are presented as median (range). Data are presented as median (range) if one of the groups (ie, TPA-treated or SOC) was non-normally distributed. Differences in nominal data between TPA-treated patients and SOC group were tested using Fisher’s exact test for categorical data. Continuous, normally distributed data were compared using Student’s t-test or the Mann–Whitney–Wilcoxon test as appropriate. Statistical significance was set at P <0.05.

Results

Demographics and history

Nineteen cats received TPA between 2011 and 2015. Sixteen cats affected in both pelvic limbs were included in the study (in one the right forelimb was also affected). Three cats with single-limb involvement had only the left pelvic limb (n = 2) or the right forelimb (n = 1) affected and these three cats were not analyzed further. Five of the cases treated with TPA were from The Ohio State University and 11 cases were from Lyon VetAgroSup. In TPA cats that had FATE confirmed with additional diagnostics, six had a vascular ultrasound, four had differential lactate measurements, two had differential glucose measurements and two cases were confirmed during necropsy. Affected breeds included 12 domestic shorthairs and one each of the following breeds: Ocicat, Bengal, Pixie-Bob and Ragdoll. Twelve cats were male castrated. Fourteen cats in the TPA group had confirmed or suspected heart disease, one cat had liver disease and the remaining cat had an unknown cause of FATE. The time from suspected onset of FATE to admission had a median of 3 h (range 0–6 h).

The comparison group included 38 cats that had two or more limbs affected by FATE. These cats received current SOC defined as analgesia, treatment of underlying disease and thromboprophylaxis but without thrombolysis. There were 15 from Ohio State University and 23 from Lyon VetAgroSup. In SOC cats that had FATE confirmed with additional diagnostics, seven had a vascular ultrasound, six had differential lactate measurements, two had differential glucose measurements and two were confirmed during necropsy. Time from suspected onset of FATE to admission for SOC cats was a median of 6 h (range 0–48 h). The clinical characteristics and results of diagnostic tests for the TPA and the SOC groups are presented in Tables 2 and 3.

Compared with the SOC group, there were no differences regarding sex (P = 0.749) or cardiogenic origin of FATE (P = 1.000). Compared with the SOC group, cats in the TPA group were more likely to be presented sooner that the SOC cats (P = 0.0004).

Patient characteristics

Physical examination and clinicopathologic data of the TPA and SOC groups are presented in Tables 2 and 3. Limb score did not differ between TPA and SOC groups (median 8; range 6–10 for TPA and 3–10 for SOC [P = 0.324]; Table 2). Proportion of CHF or cardiogenic shock did not differ between TPA and SOC groups (11 [69%] vs 22 [58%] for CHF [P = 1.0]; 3 [19%] vs 7 [18%] for cardiogenic shock [P = 1.000]; Table 3). Levels of serum sodium, potassium, lactate, packed cell volume and total proteins at admission are reported in Table 2. There were no significant differences between the groups.

Thoracic radiographs were performed in 11 (69%) and 26 (68%) cats in the TPA and SOC groups, respectively. Pulmonary edema was diagnosed in 9/16 and 16/38 of the TPA and SOC group cats, respectively. Two cats in the TPA and one cat in the SOC group also had pleural effusion. Three cats in the SOC group had pleural effusion only. Twelve cats in the TPA group (75%) and 23 in the SOC group (61%) echocardiography performed. Cardiac disease was confirmed in 11 cats in the TPA group (69%) and 22 in the SOC group (58%). In the TPA group, 10 of the cardiomyopathic cats (91%) were diagnosed with hypertrophic cardiomyopathy vs 73% in the SOC group. Restrictive cardiomyopathy was diagnosed in 9% in both groups. Other cardiac diseases in the SOC group included 13.5% with unclassified cardiomyopathy (n = 3) and 4.5% with a mass in the left auricle with no sign of cardiomyopathy (n = 1). In the TPA group, 67% of the cats had spontaneous echogenic contrast reported during echocardiography, and 17% had changes consistent with a physical left atrium thrombus vs 35% and 4% in the SOC group.

An additional three cats (19%) in the TPA group and 10 cats (26%) in the SOC group were suspected to have cardiogenic FATE as defined above. The remaining cat that underwent echocardiography and was not diagnosed with cardiogenic FATE in the TPA group was suffering from liver failure, whereas the remaining cat that underwent echocardiography without cardiogenic FATE in the SOC group had pulmonary neoplasia. Two cats in the TPA group and six cats in the SOC group had no definitive cause for FATE.
Treatment

For cats in the TPA group, the mean time between admission and TPA administration was 1.5 ± 0.6 h. Eleven cats received 1 mg/kg TPA intravenously over 1 h. Four of 16 received 10% of the 1 mg/kg dose over 1 min intravenously as a loading dose. The remaining cat received 17% of a 1 mg/kg dose over 1 min, 46% over 30 mins and 37% over 1 h.

All cats in both groups received supportive care, including treatment for cardiac disease if applicable, pain medications (many with multimodal analgesia) and thromboprophylaxis (Table 4). Doses were at the discretion of the attending clinician.

Complications and short-term outcome

Median length of hospitalization was 2.0 days (range 0–11 days) for the TPA group and 1.5 days (range 0–7 days) for the SOC group. Nine cats in the TPA group (56.3%) showed clinical improvement during their hospitalization vs 11 (28.9%) in the SOC group (P = 0.122) (Table 3). Although ambulation status was reassessed during hospitalization in all cats, limb scores were
Treatments may add up to more than the total number of cats in each group because of multimodal treatment or change of medications during hospitalization. TPA = tissue plasminogen activator.

Table 4  Treatment data of 16 cats with feline aortic thromboembolism (FATE) with two or more limbs affected compared with a control group (n = 38) treated with standard of care

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TPA group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>Cardiac disease</td>
<td>Furosemide (n = 11), oxygen (n = 4), pimobendan (n = 3), thoracocentesis (n = 1), lidocaine (n = 1), sotalol (n = 1), dobutamine (n = 1)</td>
<td>Furosemide (n = 19), oxygen (n = 5), aural nitroglycerin (n = 4), dobutamine (n = 3), enalapril (n = 2), pimobendan (n = 2), atenolol (n = 1), benazepril (n = 1)</td>
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<td>Pain medication</td>
<td>Methadone (n = 10), fentanyl (n = 6), buprenorphine (n = 4), morphine (n = 3)</td>
<td>Morphine (n = 19), fentanyl (n = 14), methadone (n = 10), butorphanol (n = 6), lidocaine (n = 5), buprenorphine (n = 4), ketamine (n = 1), hydromorphone (n = 1)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Enoxaparin (n = 6), unfractionated heparin (n = 5)</td>
<td>Unfractionated heparin (n = 13), enoxaparin (n = 9), nadroparin (n = 8)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>Clopidogrel (n = 9), aspirin/clopidogrel (n = 7)</td>
<td>Clopidogrel (n = 13), aspirin (n = 5), aspirin/clopidogrel (n = 5)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Acepromazine (n = 7), mirtazapine (n = 2), methimazole (n = 1), intravenous fluid therapy (n = 1), ondansetron (n = 1), metronidazole (n = 1), clindamycin (n = 1), silymarin/S-adenosyl (n = 1), ursodiol (n = 1), flucanazole (n = 1), amoxicillin/clavulanic acid (n = 1), diazepam (n = 1), tolfenamic acid (n = 1)</td>
<td>Acepromazine (n = 5), albuterol (n = 2), intravenous fluids (n = 2), sodium bicarbonates (n = 2), antibiotics (n = 2), calcium gluconate (n = 1), insulin/dextrose (n = 1), ondansetron (n = 1), maropitant (n = 1), meloxicam (n = 1), mirtazapine (n = 1), midazolam (n = 1), surgical thrombectomy (n = 1)</td>
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Rechecked in only five (31%) in the TPA group and two (5%) in the SOC group. For seven of the TPA cats, improvement was noted within 12 h. Three TPA cats showed improvement in motor function within 3 h of treatment. In comparison, no SOC cats had clinical improvement within 12 h of starting hospital treatment.

Ten TPA cats and 22 SOC cats had clinical laboratory tests re-evaluated. Of those, three TPA-treated cats were diagnosed with RI during hospitalization vs eight in the SOC group, and one TPA cat was diagnosed with AKI vs three in the SOC group. Two TPA cats and three SOC cats were diagnosed with combined AKI and RI. Complications of AKI and RI were similar between the TPA and the SOC groups, with a 30% rate of AKI in TPA-treated cats (vs 27% in SOC cats; P = 1.00) and 50% rate of RI (vs 50% in SOC cats; P = 1.00).

The main study outcomes and the complications seen in cats with FATE treated with TPA plus SOC were not statistically different than those recorded from a reference group treated with SOC, although the small number of cats in each group certainly affected the power to identify statistical differences. We focused on patients with two or more limbs affected, which represent 74–80% of the clinical syndrome, and compared these with a reference group of 38 patients with two or more limbs affected treated with SOC only. The comparison SOC group was not a true case-control group but represented typical cats treated with analgesia, antithrombotic drugs and supportive care.

Follow up
Long-term follow-up was available for all seven cats discharged in the TPA treatment group. Median follow-up time was 148 days (range 61–1366 days). Four of the seven cats had reoccurrence of FATE, with a median time of 106 days (range 34–483 days) before reoccurrence. Long-term follow-up was not recorded for the SOC group.

Discussion
The main study outcomes and the complications seen in cats with FATE treated with TPA plus SOC were not statistically different than those recorded from a reference group treated with SOC, although the small number of cats in each group certainly affected the power to identify statistical differences. We focused on patients with two or more limbs affected, which represent 74–80% of the clinical syndrome, and compared these with a reference group of 38 patients with two or more limbs affected treated with SOC only. The comparison SOC group was not a true case-control group but represented typical cats treated with analgesia, antithrombotic drugs and supportive care.

Survival to discharge
In the TPA group, short-term (48 h) survival (including client-directed euthanasia) was 56.3%. Seven cats (43.8%) were successfully discharged in that group. Of the nine non-surviving cats, five (55.6%) were euthanized and four (44.4%) died spontaneously. This discharge proportion for TPA-treated cats (43.8%) was not significantly different from that of SOC-treated group (28.9%; P = 0.351). The euthanasia rate vs spontaneous death was similar in both groups (55.55% for TPA-treated vs 66.7%; P = 0.693). Short-term (48 h) survival proportion were not different between groups (56.25% in the TPA-treated vs 39.5%; P = 0.369) (Table 3).
Male castrated cats represented the majority of patients, consistent with previous studies. Our study showed similar proportions of documented underlying cardiomyopathies and heart failure to previous FATE studies, which report rates of cardiomyopathies from 23–76.4% and rates of heart failure between 45.6% and 66.7%. However, standardized echocardiograms and thoracic radiographs were not obtained for all cats, which can be explained by the emergent clinical situation posed by these cases, times of admission and the retrospective nature of the study.

All TPA-treated cats received TPA within 3 h of admission, with a median time to treatment of 1.25 h. This short time frame indicates that this disease is easily identifiable and treatment can be initiated quickly in the case of a client-witnessed event; however, it also shows room for improvement, with TPA treatment being delayed 3 h for one patient in our study.

This study is the first to report cases where TPA treatment was initiated shortly after FATE. In an abstract on six patients with FATE, TPA-treated cats had a median length of clinical signs associated with thromboembolism of 17 h (range 5–29 h) and TPA was used at 0.25–1 mg/kg/h intravenous continuous rate infusion for a total of 1–10 mg/kg. Both the timing of thrombolysis and the dose are very different from the current human recommendations. In that report, 43% of the cats were discharged and the re-embolization risk on aspirin prophylaxis was 50–90% within 3 months. Another study prospectively investigated TPA administration in 11 patients with FATE. Cats were enrolled within 12 h of the onset of clinical signs; however, no control group was available and two different TPA administration protocols were compared. An additional 4 h of TPA was administered to 36% of the cases. Return of pulses and improved limb function occurred in 67% of the cats, similar to our findings. Five of their cats had documented azotemia, two of which were azotemic on presentation and 4/11 developed hyperkalemia. However, only 20% of cats with two or more limbs affected were discharged from the hospital vs 43.8% in our study, suggesting that time to administration of TPA and dosing regimen might have an impact on outcome. In people, TPA regimen is standardized, using a 0.9 mg/kg dose with 10% given as a bolus and the remaining 90% over the next hour. The vast majority of our patients received a similar dose regimen and none received a second dose.

When we compared TPA-treated cats with a group treated with SOC only, the only statistical difference between the two groups was time between FATE event and admission. Those patients that were treated with TPA were more likely to present within 6 h because most veterinary emergency clinicians who administered TPA therapy are likely to follow the 6 h guidelines reported in the human literature. The impact of time to presentation on survival is difficult to assess, and has not been identified as a prognostic indicator in veterinary medicine. Because 30% of FATE cats hospitalized and treated will die or be euthanized in the first 24 h, and cats in the SOC group presented up to 48 h after the event, it is possible that some cats in the SOC group represent a more stable group more likely to survival. However, that would bias the SOC group toward improved survival compared with the TPA group, which is not consistent with our findings, and the survival proportion in our SOC group is consistent with historical data on bilateral FATE.

The present study identified complications associated with SOC treatment, and the first to specifically describe AKI and RI in association with SOC. This is an important distinction as AKI and RI were previously considered risks of TPA therapy. We showed that in the SOC group 25% and 50% developed AKI and RI, respectively, values not statistically different to the TPA-treated group. As many clinicians are concerned about RI with thrombolysis, this information is clinically noteworthy. These results were similar to previous studies that report clinical findings suggestive of AKI and RI with SOC for FATE with percentages ranging from 33–45%. Similarly, the rate of spontaneous death in our SOC group (33.3%) is similar to previously published spontaneous death.

Although most of our cats were discharged on clopidogrel, the 44% reoccurrence rate with a median time for reoccurrence of 3.5 months is similar to previously published retrospective data. When in-hospital death or euthanasia was added to the complication proportion, overall in-hospital complication proportion in our study was 62.5%, which is similar to previous reports. Studies by Schoeman and Smith et al report a rate of in-hospital death or euthanasia of 55–61%, but no further details were provided. One report noted severe azotemia and hyperkalemia in some cats. Another report suggested that 2/6 developed RI, as evidenced by hyperkalemia and acidosis. The uncontrolled study of Welch et al described complications in 100% of their cases, including azotemia (45%) and hyperkalemia (36%), as well as sudden death, metabolic acidosis, neurological abnormalities and bleeding disorders.

Potential complications associated with thrombolysis are a concern, based on data from human stroke patients and previously published veterinary studies and reports. In people, intracranial hemorrhage is by far the most common complication, followed by systemic bleeding, and hypersensitivity reactions being less common. However, an important difference between human and feline patients is the typical location of thromboembolism (brain vs distal aorta), as well as species differences. Compared with cats, it is rare for humans to have distal aortic thromboembolism with approximately 150 reports published.
There are limitations to the present report, largely related to its retrospective nature and lack of a true control group, as well as the relatively small sample sizes, lack of consistent data obtained from each cat, and individual patient differences and client motivations, which were not addressed in this study. Although the timing of presentation was a main decision factor regarding administration of TPA by clinician, the decision-making process regarding the administration of TPA is unknown and could have created some bias in case recruitment, in both the treated and control groups. Lastly, as our study was not powered for outcomes, it is probable that some type II statistical errors occurred as a result of low statistical power. Fifty-two subjects in each group would have an 80% power for detecting a clinical improvement due to TPA of 30% (from 60% in the control group) using Fischer’s exact test with a P value of 0.05.

Conclusions
We showed that outcomes and complications of acute thrombolysis with TPA were not statistically different compared with a control population treated with SOC only. A larger, randomized, multicentric, placebo-controlled study is needed to assess the impact of thrombolysis in acute FATE.

Conflict of interest
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