



Prospective evaluation of tissue plasminogen activator in 11 cats with arterial thromboembolism[☆]

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The purpose of this study was to evaluate the clinical response and side effects of tissue plasminogen activator (tPA) for the treatment of feline arterial thromboembolism (ATE). Previous reports of conservative and thrombolytic therapy were used to provide a historical control group of cats with ATE. The study was terminated due to a high frequency of adverse outcomes. tPA was administered to 11 cats with clinical signs of ATE for a median duration of 4.0 h (range 2–12 h) prior to treatment. Pulses were restored in 40% of limbs within 4 h and 53% within 24 h. Motor function was restored to 33% of limbs within 24 h. Adverse effects were seen in 11/11 cats following administration of tPA including azotemia ($n = 5$), neurological signs ($n = 5$), cardiac arrhythmias ($n = 5$), hyperkalemia ($n = 4$), acidosis ($n = 2$) and sudden death in one cat. Ultimately, three cats (27%) were discharged alive from the hospital. While signs compatible with thrombolysis were noted in many cats following tPA administration, a high rate of side effects and low rate of hospital discharge were noted in this study.

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Feline arterial thromboembolism (ATE) is a devastating event associated with acute ischemic necrosis of one or more limbs. Although ATE is reported in less than 1% of the overall cat population,^{1,2} ATE occurs in 13–48% of cats with cardiomyopathy.^{2–7} ATE affects both hind limbs in 23–89% of cats.^{2,7,8}

Aortic thromboembolism in cats has been treated either by conservative methods such as supportive care and antithrombotics^{2,3,8–10} or by more aggressive strategies such as surgical thromboectomy¹¹ or administration of thrombolytic agents.^{7,12–15} Thrombolytics and thromboectomy may be associated with severe reperfusion injury manifested as metabolic acidosis, electrolyte disturbances and cardiac arrhythmias.^{7,12,14,15} Conservative management and supportive care, while awaiting endogenous thrombolytic pathways or the development of collateral circulation, was associated with ischemic necrosis of the distal extremities in 9% of cats in one study,² which may necessitate amputation. Regardless of the treatment method, the rate of survival to hospital

discharge has been reported to be between 0 and 50%.^{2,3,7–9,11–15}

In people with arterial thromboembolic disease, tissue plasminogen activator (tPA) is used both systemically and locally to re-canalize occluded vessels. In contrast to other thrombolytic agents, tPA is relatively specific for the dissolution of cross-linked fibrin rather than circulating fibrinogen, and thus more effectively directed against the specific thrombus. In acute human limb ischemia, tPA administered by either systemic or local methods resulted in more rapid thrombolysis than other thrombolytic agents,¹⁶ with successful thrombolysis in 88–91% of patients.^{17,18} Studies in people have shown tPA to be rapidly effective in restoring arterial patency in a variety of thrombotic or embolic diseases.^{19–24} tPA is particularly effective when administered within 3–6 h of myocardial infarction and acute ischemic stroke after the development of clinical signs consistent with an embolus.^{19–24} Current evidence based guidelines from the American College of Chest Physicians recommend thrombolytic therapy be administered immediately to patients with clinical signs of myocardial infarction and recommend tPA over other thrombolytics in patients with less than a 6 h duration of clinical signs.²⁵ The use of two different dosing protocols has been evaluated in myocardial infarction with a documented

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30-day survival benefit and increased infarct-related arterial patency as soon as 90 min and up to 24 h after starting a 90 min bolus infusion.²⁰ A 100 mg total dose is used in both the 90 min bolus infusion and the 3 h constant rate infusion (CRI) protocol in humans, which is 1.4 mg/kg for the average 70 kg human. A preliminary trial describing tPA use in six cats with ATE reported that pulses returned to most cats yet only 50% of the treated cats survived the study period due to severe hyperkalemia and metabolic acidosis.^{12,13} Thus, based upon that study, tPA is often recommended anecdotally, but no further clinical trials have been reported in cats with ATE.

The purpose of this study was to evaluate the clinical response and side effects of two different dosing protocols of tPA as a non-operative treatment of ATE.

Material and methods

Cats presented to the emergency service at the Foster Hospital for Small Animals at the Tufts University Cummings School of Veterinary Medicine with clinical signs of ATE were eligible for inclusion. Clinical signs that were considered consistent with ATE included an acute onset of paresis in a limb or limbs, which was accompanied by lack of a palpable pulse, pain, pallor and a loss of warmth in the extremity. Cats were excluded if clinical signs were present for greater than 12 h or if one of the investigators (KW, ER) was not immediately available to enroll the cat in the study. The study was approved by the Institutional Animal Care and Use Committee and informed consent of risks was obtained from owners.

Cats were randomly allocated to one of two treatment groups using a computer generated random numbers system. Treatment with tPA was planned to start within 1 h of hospital presentation. Group A cats were assigned to receive a CRI of tPA over 4 h totaling 5 mg tPA per cat. Group B cats were assigned to receive an accelerated dosing protocol (1 mg IV bolus, 2.5 mg IV over 30 min, 1.5 mg IV over 1 h) totaling 5 mg tPA per cat. For cats with a continued lack of pulse to one or more limbs 4 h after initiation of tPA, the study protocol allowed for the investigator to administer an additional 5 mg of tPA, as a CRI over 4 h, if there was no evidence of side effects from initial treatment.

Continuous electrocardiogram (EKG) monitoring with telemetry was performed to monitor for ectopy or for evidence of severe hyperkalemia. The study

protocol specified that all cats should be treated with narcotic analgesics, and the dose and frequency were at the discretion of the attending clinician. In cats with concurrent congestive heart failure, treatment with supplemental oxygen and diuretics was permitted. Antiplatelet and anticoagulant drugs were not permitted during the 24 h study period.

Samples for electrolytes and venous blood gas analysis were collected at admission and at 12 h. Further blood samples could be collected at the investigators' discretion if there was suspicion of a clinically important abnormality.

Cats were evaluated for arterial pulses and motor function at baseline and at 4, 12 and 24 h following initiation of tPA. In addition to qualitative evaluation of arterial pulses and motor function (ie, no motor, weak motor, strong motor), cats were scored for limb function using the limb scoring system displayed in Table 1. Each affected limb was independently scored, therefore, a maximum limb score was four for each affected limb. Cats were monitored in an intensive care unit environment for side effects including altered mentation, hemorrhage, biochemical changes and EKG abnormalities at baseline and at 4, 12, and 24 h following initiation of tPA.

The study concluded 24 h after admission to the hospital. The primary outcome variables were return of pulses and motor function (ie, limb score). Secondary outcome variables were 24-h survival and discharge from the hospital. After the conclusion of the study period, cats were treated at the attending clinician's discretion.

Previous reports of conservative and thrombolytic therapy were used to provide a historical control group of cats with ATE.

Statistics

Data are presented as mean \pm SD (for normally distributed data) or median (range; for skewed data). Data were analyzed using commercial statistical software (SPSS 16.0, SPSS, Chicago, IL).

Results

Eleven cats were prospectively enrolled into the study over a 6-month period. The study was terminated before enrollment of the planned 24 cats due to a high frequency of adverse outcomes. The mean age of cats was 8.1 years (\pm 3.5). Eight cats were castrated

Table 1. Limb scoring system.

	1	2	3	4
Limb function Score*	Pulse and strong motor	Pulse and weak motor	Pulse but no motor	No pulse, no motor

*1 score per affected limb.

males and three were spayed females. There were nine domestic breeds (four domestic shorthair, one domestic medium hair, four domestic longhair), one Burmese and one Sphinx. Only one cat had a previous diagnosis of cardiomyopathy; this cat was being treated with atenolol (6.25 mg/day) and aspirin (20 mg every 3 days). One cat had recently been receiving oral amoxicillin for suspected pancreatitis and one cat had a prior history of undiagnosed cough. The remaining eight cats had no history of prior medical problems.

Table 2 details clinical findings, limb scores, adverse effects and outcome of the 11 cats in the study. The median duration of clinical signs prior to study inclusion was 4.0 h (range 2–12 h). Ten cats had bilateral pelvic limb signs and one cat had unilateral right forelimb signs. Two of the cats with bilateral pelvic limb signs had clinical signs that were more pronounced on one of the pelvic limbs. At study inclusion, there were 21 affected limbs.

The median rectal temperature of all cats prior to treatment was 99.7°F (range, 92.0–102.7°) [37.6°C; 33.3–39.3°]. Eight of 11 cats were hypothermic (median rectal temperature of 98.2°F (range, 92.4–99.9°) [36.7°C; 33.5–37.7°]. Three of 11 cats had metabolic acidosis (pH < 7.337) and two cats were azotemic (creatinine \geq 1.6 mg/dl [141.4 μ mol/l]) at presentation. No cats were hyperkalemic (>4.9 mEq/l [4.9 mmol/l]) prior to treatment. No cats had evidence of ventricular arrhythmia or hemorrhage prior to treatment.

Seven cats were randomly allocated to group A and were treated with a CRI of tPA. Four cats were allocated to group B and received an accelerated dosing protocol. Four cats (two cats in group A and two cats in group B) received an additional dose of tPA at 4 h after one or more limbs continued to have no pulse or motor function.

At study inclusion, 15/21 limbs (71% of affected limbs) had no pulse and no motor function. Nine of the 11 cats had at least one limb with no pulse and no motor function. For the cats remaining in the study at 4 h post-tPA administration, 6/12 limbs with no pulse prior to tPA administration now had a palpable arterial pulse. For the seven cats remaining in the study at 24 h after tPA administration, an arterial pulse was palpable in 10/13 limbs; this arterial pulse was not present at baseline in 8/10 limbs. Prior to tPA administration, only 3/11 cats had evidence of motor function in one or more affected limbs, while at 24 h 4/7 cats had evidence of motor function in one or more limbs.

At the conclusion of the 24-h study period, 7/11 cats were alive. Of the seven cats that survived the 24-h study period, four cats did not survive to hospital discharge. Two cats were euthanased independent of tPA side effects; one for failure to improve, and the second cat, which had regained enough function to walk, developed a suspected second thrombus and accompanying acute worsening of pelvic limb signs. Two additional cats developed cardiac arrest at 27 h

and 42 h and died. The relationship between cardiac arrest >24 h after completion of tPA therapy and the tPA therapy itself is unknown. Three cats (27%) were discharged from the hospital. One of the surviving cats is currently alive greater than 1.5 years after discharge from the hospital. The other two surviving cats survived 110 and 210 days after hospital discharge. The cat that died 110 days after therapy was euthanased for congestive heart failure and a suspected thrombus and the cat that died 210 days after therapy died suddenly at home with no known preceding clinical signs.

Adverse effects that might have been directly attributable to tPA administration were seen in 11/11 cats. The median creatinine of the cats that developed azotemia during the study period was 2.7 mg/dl [238.7 μ mol/l] (range 1.6–5.1 mg/dl [141.4–450.8 μ mol/l]) and the median potassium of the cats that developed hyperkalemia during the study period was 5.75 mEq/l [5.75 mmol/l] (range 5.25–6.59). Neurological signs included nystagmus, anisocoria, mental dullness, cervical ventroflexion, head bobbing and circling which progressed to respiratory arrest in three cases. Sudden cardiac arrest occurred 30 min after initiation of tPA in a cat that was moribund at study admission. Hemorrhagic complications including pigmenturia ($n=4$), scleral hemorrhage ($n=2$) and rectal bleeding ($n=1$) were also recorded.

One cat with neurological signs prior to cardiac arrest underwent necropsy which documented a residual 1.5 \times 0.5 \times 0.5 cm thrombus in the distal aorta, but no intracranial hemorrhage or other central nervous system lesion to explain the neurological abnormalities. The remaining seven non-surviving cats did not undergo post mortem examination.

Discussion

The results of this study demonstrate that tPA administration was associated with the return of pulses and improved limb scores in 6/9 cats within 12 h of drug administration. However, side effects were common and the survival to discharge was generally not higher than that reported in the literature with other therapies.

Previous reports of survival following ATE range from 0% to 50% of thrombolytic treated cats.^{7,12–15} Cats treated with supportive measures are reported to have a 39–45% survival rate, with death accompanying subsequent emboli or following euthanasia.^{2,8–10}

One study described rheolytic thrombectomy in affected cats, and reported a 50% survival.¹¹ Rheolytic thrombectomy, a specialized technique involving fluoroscopic mechanical thrombolysis and removal of the thrombus through an arterial catheter, is unlikely to be widely available to affected cats.

Other less specific thrombolytic agents have been previously evaluated in cats, including streptokinase and urokinase.^{7,15} Streptokinase, which is no longer commercially available, resulted in return of pulses

Table 2. Summary of clinical findings, adverse effects and outcome.

Cat	Limbs affected	Rectal temperature (°F)	Limb score*					Adverse effects					24-h survival	Outcome
			0 h	4 h	12 h	24 h	Additional tPA dose at 4 h [†]	Hyperkalemia >4.9 mmol/l	Neurologic signs	Arrhythmia	Azotemia creatinine >1.6 mg/dl	Acidosis pH <7.337		
1	HL	92.4	8	6	—	—	Yes	Yes	Yes	No	Yes	Yes	No	Died
2	HL	99.9	6	4	4	4	No	No	No	Yes	No	No	No	Died
3	RFL	99.5	4	1	1	1	No	No	Yes	Yes	No	No	Yes	Discharged
4	HL	96.5	8	8	8	6	Yes	Yes	No	Yes	Yes	Yes	No	Died
5	HL	98.2	7	3	2	2	No	No	No	Yes	No	No	Yes	Died
6	HL	102.7	8	6	6	—	No	Yes	Yes	No	Yes	No	Yes	Died
7	HL	102.6	6	5	5	5	No	No	Yes	No	No	No	Yes	Discharged
8	HL	100.0	4	7	7	7	Yes	Yes	No	No	No	No	Yes	Died
9	HL	92.0	8	—	—	—	No	No	No	No	No	No	No	Died
10	HL	98.7	8	8	8	—	No	No	Yes	No	Yes	No	Yes	Died
11	HL	96.0	8	8	8	8	Yes	No	No	Yes	Yes	No	Yes	Discharged

HL = bilateral hind limbs affected; RFL = right forelimb affected.

*Limb score detailed in Table 1.

[†]For cats with continued lack pulse to one or more limbs 4 h after initiation of treatment, an additional 5 mg tPA was administered as a continuous rate infusion.

in 50% (23 cats) within 24 h and return of motor function occurred in approximately 30% of affected cats within 6 days of therapy. Severe reperfusion injury occurred in 35% (16 cats) and 33% (15 cats) survived to discharge.⁷

Urokinase therapy has been evaluated in a single abstract in cats with ATE.¹⁵ Fifty-six percent of cats (5/9) regained voluntary motor function and 27% (3/11) of cats had return of pulses. Reperfusion injury occurred in three cats and five cats survived to hospital discharge.

Overall, these small clinical trials of thrombolytic agents have failed to demonstrate a markedly improved survival of cats with ATE compared to conservative therapy, although evidence of a thrombolytic effect has been consistently reported. The thrombolysis associated with tPA administration in our cats was evidenced by return of pulses; however, the high rate of side effects limits the utility of this dose of tPA.

Previous survival data demonstrate that the outcome for bilaterally affected cats is worse than for unilaterally affected cats.^{2,3,7-11,14} Ten of 11 (90.9%) cats in the current study were bilaterally affected and only one cat had a right forelimb thromboembolism. The unilaterally affected cat in the study reported here survived.

Azotemia and hypothermia were previously reported to be negatively associated with survival in ATE.^{2,7} In the current study, the small study size and small number of cats that survived to discharge limited our ability to identify factors associated with outcome. The current study attempted to preliminarily evaluate the effects of two separate protocols of tPA administration; however, statistical analysis was limited due to early termination of the study and the small numbers of cats in each treatment arm.

In the study reported here, pulses were restored to one or both limbs within 4 h of treatment in 67% (6/9 cats). In comparison, 54% (25 cats) treated with streptokinase⁷ with no pulses on presentation regained pulses within 24 h as did 27% (three cats) treated with urokinase.¹⁵ Cats treated with tPA in the current study had rapid restoration of perfusion which may explain the relatively high percentage of cats in this study who regained motor function within 12 h. In the current study, voluntary motor function returned in 63% (7/11 cats) within 12 h of treatment. In comparison, 30% (14 cats) treated with streptokinase⁷ and 56% (five cats) cats treated with urokinase¹⁵ regained motor function after treatment. In a study of six cats treated with tPA, Pion et al¹² reported that perfusion was improved in 7/11 affected limbs, and 3/6 of treated cats were discharged from the hospital. Reperfusion injury, evidenced by hyperkalemia and acidosis, was seen in 2/6 cats in the Pion study.³

We were not able to demonstrate any relationship between the time from the onset of the ATE until the time of administration of thrombolytic therapy. Based on studies in people indicating that rapid initiation of

thrombolytic agents is associated with improved outcomes, we designed the study to only include cats that presented less than 12 h after the onset of clinical signs. The median time to initiation of tPA was 4 h in the current study, similar to that reported in the Moore et al study.⁷

Five cats (45%) had ventricular ectopy and five (45%) developed hyperkalemia during the 24 h period. There is no previous reported incidence of ventricular arrhythmias in past thrombolytic studies. In previous reports of cats with ATE that were treated with thrombolytics, hyperkalemia was documented in 25–70%.^{7,12,13,15} Other complications seen in the current study included hemorrhage in 27%, pigmenturia in 36%, and neurologic signs in 45% of cats. Previous reports identified clinical signs of bleeding in 24% of cats with three cats requiring transfusion,⁷ and pigmenturia was reported in 41% of cats.¹⁵ Forty-five percent (5/11 cats) in the current study had acute neurologic signs including nystagmus, anisocoria, mental dullness, cervical ventroflexion, head bobbing and circling. Acute neurologic signs were previously reported only by Ramsey et al¹⁴ and occurred in 2/8 cats treated with streptokinase in that study. Intracranial hemorrhage is a known side effect of thrombolytic therapy in humans. It is possible that these cats had acute intracranial hemorrhage or cerebrovascular thromboembolism, however the one cat with acute neurologic signs that underwent necropsy examination had no evidence of either abnormality.

The cat which experienced cardiac arrest 30 min after starting of tPA infusion had the longest duration of clinical signs (12 h) of any cat in the current study. This cat was moribund at the time of hospital admission and the role of tPA in the development of cardiac arrest in this cat is unclear. No abnormal EKG findings were recorded in advance of cardiac arrest. There was no evidence of bleeding or hyperkalemia which might indicate that the sudden cardiac arrest was related to tPA administration. Sudden death was reported to occur in one cat in the Pion et al study¹² and 100% (8/8) of cats in the Ramsey et al study.¹⁴ Ramsey identified that electrolyte abnormalities occurred in 3/8, acute respiratory changes in 4/8 and acute neurologic signs in 2/8 immediately prior to cardiac arrest. Of the cats that underwent necropsy in the Ramsey study, the cause of death was not identified in 4/5 cats and one cat had evidence of ventricular myocardial infarction. Similarly, the cause of death was not identified in the single cat that underwent post mortem examination in the current study.

Several limitations exist in the current study. Although this was a prospective randomized clinical trial intending to compare two tPA dosing protocols, no control group exists to compare the results of this small study to a group of cats with ATE who were not treated with a thrombolytic. Previous retrospective studies of ATE in larger populations provide some basis for comparison of complications and

survival data.^{3,7-10} The outcome in this study was similar to that previously reported with tPA, urokinase, and streptokinase.^{7,12,15} The use of 5 mg of intravenous tPA, with these dosing strategies, does not appear to be superior to other thrombolytics or conservative management for treatment of ATE in cats. The findings of this study support the hypothesis that tPA does lead to restoration of pulses and motor function in cats with ATE, however, the survival to hospital discharge in the current study does not appear to be superior to that reported in other studies evaluating thrombolytic medications in cats with ATE. Future studies involving a lower dose of tPA as a CRI or local tPA administration at the site of the thrombus, as it is commonly undertaken in humans, may result in fewer systemic side effects and a different outcome. Our study design excluded the use of other antiplatelet drugs and anticoagulants during the 24 h study in order to evaluate the effects of tPA alone. Previous administration of antithrombotics was not a criterion for exclusion and only 1/11 cats had received a potential antithrombotic. The effect of concurrent aspirin therapy on outcome in the one cat in this study is unknown; however, future studies might be designed to evaluate concurrent thrombolytics and antithrombotic drugs in cats with ATE. Long-term success in treatment of ATE includes prevention of rethrombosis; future studies of antithrombotic treatment after the initial thrombus has been addressed with thrombolytic or supportive care may result in a decrease in the rate of rethrombosis. Finally, pairing thrombolytics with advances in treatment of reperfusion injury may result in better outcomes for cats affected with ATE.

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