Development of thrombosis is regarded as a consequence of several conditions involving endothelial disruption, altered blood flow or blood stasis, or imbalance in clotting factors.\(^1\) Referred to as Virchow’s triad, these risk factors were described more than 100 years ago and are still useful in the assessment of feline and canine thromboembolic disease.

A number of thromboembolic diseases have been described in veterinary patients, including arterial thromboembolism (ATE), pulmonary thromboembolism (PTE), portal vein thrombosis, and vena cava thrombosis. ATE is an established complication of cardiomyopathy in cats. Although the pathophysiology of the formation of intracardiac thrombi is not well understood, potential causes include left atrial enlargement, alterations of the endocardial surface, changes in blood flow, and hypercoagulability. Reports of hyperaggregable platelets in cats with acquired heart disease are conflicting.\(^2,3\) Decreased blood levels of vitamin B\(_{12}\) and arginine have been suggested to play a role in cardiomyopathy and ATE of cats.\(^4\) Once dislodged, thrombi are carried into the arterial circulation, where vascular occlusion may result. Vasoactive mediators are released at the site of embolization, causing alteration of blood flow distal to the clot and constriction of collateral vessels. Treatment options have included anticoagulants and thrombolytic agents.\(^5\)

Canine ATE has been sporadically reported in the veterinary literature.\(^6-7\) To date, age, breed, and sex predisposition have not been determined.\(^6\) Conditions that have been associated with ATE in dogs include cardiac disease, renal disease, hypothyroidism, hyperadrenocorticism, neoplasia, nephrotic syndrome, and pancreatitis.\(^6,8-10\) Presenting clinical signs of dogs with ATE include pain, vague or chronic signs of lameness, weakness, and paresis. Treatments have included anticoagulants, surgery, and thrombolytic agents.\(^11\)

Diagnosis of ATE and venous thromboembolism in small animals has traditionally been based on clinical signs. Definitive diagnosis has been challenging, but advances in diagnostic imaging, including abdominal ultrasonography with color flow Doppler, fluoroscopy with selective angiography, and nuclear perfusion...
scans, have improved identification of thrombi. D-dimers are specific degradation products of cross-linked fibrin and reflect active clot lysis. The presence of elevated D-dimer levels may provide additional evidence of thromboembolic disease.

**MECHANISM OF ACTION OF THROMBOLYTIC AGENTS**

Plasmin is a natural antagonist of uncontrolled coagulation, and fibrinolysis begins with the conversion of plasminogen to plasmin. As plasmin digests the clot, fibrin is removed, resulting in the production of fibrin degradation products. Thrombolytic agents augment fibrinolysis by increasing the conversion of plasminogen to plasmin and by overwhelming plasmin inhibitors (Figure 1). Plasmin itself is inhibited by the serine protease inhibitor antiplasmin. Plasminogen activator inhibitors 1 and 2 inhibit activators of plasminogen, which results in the production of less plasmin.

Thrombolytic agents are infused systematically or locally at the site of the thrombosis. Thrombolytic agents used in human medicine include urokinase, prourokinase, streptokinase, anisoylated plasminogen-streptokinase activator complex, tissue plasminogen activator (tPA), and recombinant tissue plasminogen activator (rtPA). Although classification of thrombolytic agents is variable, fibrin specificity and origin of the agent (human or bacterial) are two important characteristics. A common feature of all thrombolytic agents is the ability to directly or indirectly catalyze the conversion of the inactive proenzyme plasminogen to the active serine protease plasmin. Research and development of newer thrombolytic agents are directed toward increasing fibrin specificity and improving resistance to inactivation by plasminogen activator inhibitor 1. Thrombolytic agents with greater fibrin specificity have increased efficacy for lysis of clots of longer duration as well as a decreased risk of inadvertent hemorrhage. A potential advantage of a more fibrin-specific agent would be that the drug could be administered in a single bolus, which would improve lysis of older clots and decrease the risk of bleeding.

**OVERVIEW OF THROMBOLYTIC AGENTS**

**Streptokinase**

Streptokinase was the first thrombolytic agent approved for clinical use, and it has been used extensively. Streptokinase is a purified bacterial protein isolated from Lancefield group C strains of β-hemolytic streptococci. By binding plasminogen noncovalently to form a 1:1 complex, streptokinase can activate the conversion of other plasminogen molecules to plasmin. The action of streptokinase is species restricted, meaning that streptokinase preferentially activates plasminogen from the animal species infected by the streptococcal strain that produced it. Streptokinase is not fibrin specific and has a long half-life in humans.

Due to its bacterial origin, streptokinase stimulates an immune response and the production of antibodies in humans. Because circulating (neutralizing) antibodies can inactivate the drug, streptokinase cannot be readministered for at least 6 months. Additionally, streptokinase can cause an allergic reaction and hypotension in humans. The risk for an allergic reaction in humans can be the result of presensitization from previous infections with Lancefield group C β-hemolytic streptococci.

Streptokinase is supplied in 250,000- and 750,000-IU vials. The cost per 250,000 IU is approximately one-tenth that of a vial of rtPA, so streptokinase is relatively inexpensive compared with other thrombolytic agents.

**Tissue Plasminogen Activator and Recombinant Tissue Plasminogen Activator**

tPA is a naturally occurring glycoprotein synthesized primarily by endothelial cells. tPA directly converts plasminogen to plasmin. It is fibrin specific, but in humans, it has the shortest half-life of all the thrombolytic agents. Under normal circumstances, a low concentration of tPA is maintained in the human circulation. The concentration can be dramatically increased with exercise, venous occlusion, or an epinephrine surge. Compared with other thrombolytic agents, the enzymatic activity of tPA is greatly enhanced in the presence of fibrin.

Human rtPA is derived from mammalian cell tissue culture, but because tPA is synthesized endogenously, rtPA has not been reported to stimulate an immune response in humans. rtPA is dispensed in 50- and 2-mg vials, which cost approximately $1,100 and $150 per

**Key Points**

- The benefit of thrombolytic agents for the treatment of thrombi in small animals remains largely unknown.
- The administration of thrombolytic agents results in thrombolysis by favoring the fibrinolytic cascade.
- Hemorrhage, reperfusion syndrome, and allergic reactions are all possible complications when administering thrombolytic agents in small animals.

---

August 2007

**COMPENDIUM**
vial, respectively. Modified tPAs, which are tPA mutations that involve amino acid deletions or substitutions or folding variants, have recently been developed. Although the modified tPAs have longer half-lives, allowing bolus administration, they do not have improved fibrin specificity or inhibitor susceptibility.

Urokinase

Two-chain urokinase exists in high molecular weight and low molecular weight forms. Prourokinase, or single-chain urokinase-type plasminogen activator, is the precursor to urokinase. Urokinase directly converts plasminogen to plasmin. Urokinase is found in urine and can be produced from human neonatal renal parenchymal cells. Commercially available urokinase is derived from kidneys donated from neonates (birth to 28 days) who have died from a noninfectious cause. The cells are grown in tissue culture. Similar to tPA, urokinase can be made using recombinant DNA technology.

Urokinase is supplied in 250,000-IU vials, and the cost per vial is approximately one-half that of rtPA. In humans, urokinase is indicated to treat pulmonary embolism. Obtaining prothrombin time (PT) and activated partial thromboplastin time (APTT) before administration is recommended only if the patient has a known coagulopathy or has been treated previously with another anticoagulant or thrombolytic therapy. The drug, which mostly contains the low molecular weight form of urokinase, is given intravenously. The recommended dosage in humans is an initial loading dose of 4,400 IU/kg given over 10 minutes, followed by a constant rate infusion (CRI) of 4,400 IU/kg/hr over 12 hours.

Urokinase is fibrin specific and has a plasma half-life of about 16 minutes in humans. The biologic and thrombolytic properties of the different forms of urokinase have been investigated in several mammalian species.
In dog models, different forms of urokinase have been used for studying clot dissolution.25–30

**POTENTIAL ADVERSE EFFECTS OF THROMBOLYTIC THERAPY**

The most common complication of thrombolytic therapy in human medicine is hemorrhage. In cats, death from presumptive ischemia-reperfusion injury is the most common complication. Ideally, coagulation testing (PT, APTT) should be conducted before drug administration to identify the potential risk for bleeding. Accepted guidelines for the administration of thrombolytic therapy have not been determined in veterinary medicine. Because no consensus exists, the individual clinician should evaluate laboratory test results and determine the potential benefits and risks of thrombolytic administration.

Inadvertent hemorrhage resulting from thrombolytic therapy requires correction with transfusions of cryoprecipitate or fresh frozen plasma. In humans, aminocaproic acid has been administered when other measures have failed. Aminocaproic acid binds to fibrin, competitively inhibiting the binding of plasminogen. Administration of aminocaproic acid reduces the fibrinolytic state.

Ischemia-reperfusion injury occurs when reestablishment of blood flow to a previously ischemic area results in the production and systemic release of reactive oxygen species into the circulation. Metabolic acidosis and hyperkalemia are common clinical signs and, if severe, can be fatal. Allopurinol and N-acetylcysteine have been used to block the formation of reactive oxygen species.

An allergic reaction can occur when any thrombolytic agent is administered to an animal. Veterinary patients should therefore be monitored closely for any adverse clinical signs during administration.

**THROMBOLYTIC THERAPY IN HUMANS**

The American College of Chest Physicians (ACCP) has established recommendations for the use of thrombolytic agents in humans for venous thromboembolic disease (deep venous thrombosis and PTE), myocardial infarction, and ischemic stroke. Administration of an approved thrombolytic agent is recommended for patients with symptoms of acute myocardial infarction of up to 12 hours in duration and ST elevation or left bundle-branch block. However, a fibrin-specific thrombolytic agent is recommended if the duration of symptoms is less than 6 hours. Thrombolytic agents are not recommended in patients with a history of acute myocardial infarction, intracranial hemorrhage, head trauma, or ischemic stroke occurring within the prior 3 months.

---

**Table 1. Properties of Thrombolytic Agents That Have Been Used in Cats and Dogs**

<table>
<thead>
<tr>
<th>Thrombolytic Agent</th>
<th>Description</th>
<th>Fibrin Specificity</th>
<th>Source</th>
<th>IV Dosages</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>rtPA</td>
<td>Enzyme</td>
<td>Moderate</td>
<td>Mammalian cell tissue culture and recombinant DNA technology</td>
<td>Cats: 0.25–1.0 mg/kg/hr for a total dose of 1.0–10.0 mg/kg&lt;sup&gt;a&lt;/sup&gt;, Dogs: 0.4–1.0 mg/kg at 60-min intervals for 4–10 doses over 1–2 days&lt;sup&gt;b&lt;/sup&gt;</td>
<td>PTE and ATE</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Bacterial protein</td>
<td>Minimal</td>
<td>Lancefield group C β-hemolytic streptococci</td>
<td>Cats and dogs: 90,000 IU over 30 min, followed by a CRI of 45,000 IU/hr&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PTE and ATE</td>
</tr>
<tr>
<td>Urokinase</td>
<td>Enzyme</td>
<td>Moderate</td>
<td>Human neonatal renal parenchymal cells</td>
<td>Cats and dogs: 4,400 IU/kg over 10 min, followed by a CRI of 4,400 IU/kg/hr for ≥12 hr&lt;sup&gt;a&lt;/sup&gt;,&lt;sup&gt;b&lt;/sup&gt;</td>
<td>PTE and ATE</td>
</tr>
</tbody>
</table>

<sup>a</sup>Drug dosages that have been described in veterinary reports
<sup>b</sup>Not peer reviewed
The Use of Thrombolytic Agents

THROMBOLYTIC THERAPY IN CATS

Veterinary reports regarding the use of thrombolytic agents are limited, likely because of the challenge of identifying and treating major thromboembolic events in animals (Table 1). Most events are associated with cardiac disease in cats, although PTE and ATE have been reported in dogs and cats in association with a number of conditions. For example, canine PTE has been treated with thrombolytic therapy both experimentally and clinically. Administration of thrombolytic therapy requires intensive nursing care and monitoring, including continuous electrocardiography, blood pressure, supplemental oxygen, and electrolyte and coagulation panels. For this reason, referral to tertiary care facilities is often recommended.

<table>
<thead>
<tr>
<th>Thrombolytic Agent Administered</th>
<th>Number of Cats</th>
<th>Survival to Discharge (number of cats)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>8</td>
<td>0</td>
<td>Ramsey et al</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>46</td>
<td>33% (15)</td>
<td>Moore et al</td>
</tr>
<tr>
<td>rtPA</td>
<td>6</td>
<td>50% (3)</td>
<td>Pion et al</td>
</tr>
<tr>
<td>Urokinase</td>
<td>12</td>
<td>42% (5)</td>
<td>Whelan et al</td>
</tr>
<tr>
<td>None</td>
<td>83</td>
<td>42% (35)</td>
<td>Smith et al</td>
</tr>
<tr>
<td>None</td>
<td>44</td>
<td>39% (17)</td>
<td>Schoeman</td>
</tr>
</tbody>
</table>

Pion et al described the potential utility of administration of rtPA in six cats with aortic thromboembolism. The cats were administered rtPA intravenously at a rate of 0.25 to 1.0 mg/kg/hr for a total dose of 1.0 to 10.0 mg/kg. Two cats died suddenly within 6 hours of administration of the thrombolytic agent, and one died 22 hours later. The three cats (50%) that survived to discharge were ambulatory. Complications included ischemia-reperfusion injury (hyperkalemia and metabolic acidosis), mild hemorrhage, and fever.

Urokinase

The clinical use of urokinase has been described in 12 cats with arterial thromboembolism. Urokinase infusion was not associated with serious clinical bleeding. Five cats (42%) survived to discharge. The dose used (initial loading dose of 4,400 IU/kg over 10 minutes; CRI at 4,400 IU/kg/hr over 12 hours) was extrapolated from the human literature.

Summary of Thrombolytic Therapy in Cats

To date, a prospective controlled study regarding the use of thrombolytic agents in cats has not been conducted. The clinical dilemma of treatment of thromboembolism in cats with thrombolytic agents remains unanswered. An overall survival rate of 35% was reported in a retrospective study of 127 cats with ATE. Of the 83 cats that were treated but received no thrombolytic therapy, 35 (42%) survived to discharge. Another retrospective study of 44 cats with ATE reported a survival rate of 39%, and none of these cats received thrombolytic agents (Table 2). Without evidence of improved survival in feline ATE, the decision to use thrombolytic therapy should be considered judiciously at this time.

THROMBOLYTIC THERAPY IN DOGS

Streptokinase

Ramsey et al described the effective use of streptokinase in four dogs with thrombosis. Although varying dosages were administered, the authors recommended an intravenous loading dose of 90,000 IU over 20 to 30 minutes, followed by a CRI of 45,000 IU/hr for 7 to 12 hours. The authors stated that three doses may be administered during a 72-hour period, but the efficacy and safety of the use of streptokinase past this time period were not known. In addition, three of the four
cases were treated with allopurinol, a xanthine oxidase inhibitor, which may have decreased or prevented ischemia–reperfusion injury.47

**Tissue Plasminogen Activator**

The successful use of rtPA (1 mg/kg IV bolus q60min for a total of 10 doses over a few days) has been reported in one dog with ATE;86; rtPA was also used successfully in another dog with chylothorax secondary to catheter-associated thrombosis of the cranial vena cava (0.4 mg/kg IV q60min for a total of 4 doses).49

**Urokinase**

The use of urokinase in dogs has been reported in the experimental setting and in four clinical cases (one dog with PTE and three with ATE).28 The dose (initial intravenous loading dose of 4,400 IU/kg over 10 minutes; CRI at 4,400 IU/kg/hr over 12 hours) used was extrapolated from the human literature. Of the dogs with ATE, one died and two were euthanized. The dog with PTE survived and was discharged from the hospital.

**Summary of Thrombolytic Therapy in Dogs**

To date, a prospective controlled study regarding the use of thrombolytic agents in dogs has not been conducted. Again, the clinical dilemma of treatment with thrombolytic agents remains unanswered, and the decision to treat canine ATE with thrombolytic agents should be considered on a per-case basis.

**CONCLUSION**

Because thromboembolic disease continues to be a devastating complication of several common disease processes in animals, treatment options are gaining increasing consideration in veterinary medicine. Improved medical management of many of these diseases will extend veterinary patients’ lives, and the use of thrombolytic agents may be beneficial in certain situations. To date, the reported clinical use of thrombolytic therapy in veterinary medicine has been anecdotal, and prospective clinical trials are needed to determine the true efficacy and usefulness of thrombolytic agents in veterinary patients.

**REFERENCES**


### ARTICLE #2 CE TEST

This article qualifies for 2 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. **Subscribers may purchase individual CE tests or sign up for our annual CE program.** Those who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. **CE subscribers can take CE tests online and get real-time scores at CompendiumVet.com.**

1. **All the following drugs can cause thrombolysis except**
   - a. heparin.
   - b. streptokinase.
   - c. urokinase.
   - d. tPA.
   - e. anisoylated plasminogen-streptokinase activator complex.

2. **________ is the primary complication with the use of thrombolytic agents in humans.**
   - a. Hemorrhage
   - b. Death
   - c. Hypertension
   - d. Allergic reaction

3. **________ is the primary complication with the use of thrombolytic agents in cats.**
   - a. Fever
   - b. Death
   - c. Hypertension
   - d. Allergic reaction
   - e. Hemorrhage

4. **Urokinase is produced for commercial use from**
   - a. animal endothelial cells.
   - b. human endothelial cells.
   - c. animal kidney cells.
   - d. human neonatal kidney cells.
   - e. human adult kidney cells.

5. **Thrombolytic agents can be used to treat**
   - a. canine pulmonary thromboemboli.
   - b. canine arterial thromboembolism.
   - c. canine portal vein thrombosis.
   - d. feline arterial thromboembolism.
   - e. all of the above

6. **The main conversion perpetuated by thrombolytic agents is**
   - a. fibrin to D-dimers.
   - b. prothrombin to thrombin.
   - c. plasminogen to plasmin.
   - d. fibrin to FDPs.
   - e. fibrinogen to fibrin.

(continues on page 486)
The Use of Thrombolytic Agents
(continued from page 482)

7. Production of plasmin is inhibited by
   a. fibrinogen.
   b. plasminogen activator inhibitors 1 and 2.
   c. heparin.
   d. thrombin.
   e. tPA.

8. _______ has the shortest half-life and is fibrin specific in humans.
   a. Anisoylated plasminogen-streptokinase activator complex
   b. rtPA
   c. Streptokinase
   d. Prourokinase
   e. Urokinase

9. Allergic reactions can occur with the use of _______ in small animals.
   a. streptokinase
   b. urokinase
   c. tPA
   d. anisoylated plasminogen-streptokinase activator complex
   e. all of the above

10. The optimal treatment for ATE in small animals is
    a. unknown.
    b. systemic anticoagulants.
    c. local thrombolytic infusion.
    d. thromboembolectomy via balloon catheterization or arteriotomy.
    e. limb amputation.