Aortic Thromboembolism Associated with Feline Hypertrophic Cardiomyopathy

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ABSTRACT: Thromboembolism (TE), often with recurrent episodes, is a devastating complication of hypertrophic cardiomyopathy. Such clinical signs as acute paraplegia and excruciating pain are distressful to both animals and clients. Clinicians must be familiar with the available treatment options for TE in order to provide clients with the necessary information to make well-informed decisions. Although the prognosis is guarded, recovery from TE with considerable disease-free intervals is possible with proper management.

Cats with hypertrophic cardiomyopathy (HCM) are predisposed to thromboembolism (TE).1-5 Thrombus formation usually occurs in the left atrium with subsequent embolization into the systemic circulation. Thrombi form less frequently in the left ventricle and right side of the heart.1-4 Most commonly, embolization occurs in the distal aortic trifurcation (Figure 1) but may also occur in the brachial, visceral, and cerebral arteries. Factors that predispose patients to thrombus formation include localized endocardial injury, circulatory stasis, and increased blood coagulability.1-3,6 Left atrial enlargement causes stretching of the endocardium, which can alter the endothelium and expose surfaces for platelet adherence, thereby initiating thrombosis.1-3,7-9 Left atrial enlargement and mitral regurgitation can also lead to blood stasis and turbulence.4,9 Some cats with HCM may have platelets that are hypercoagulable.6 Treatment of feline aortic TE is aimed at preventing further thrombus formation, promoting circulation to ischemic tissues, managing pain, and (potentially) dissolving the existing embolus.
**PREVENTION OF THROMBOEMBOLISM**

**Heparin Therapy**

Heparin acts by complexing with antithrombin III leading to the inactivation of clotting factors II, IX, X, XI, and XII (serine proteases). The goal of heparin therapy is to prevent the formation or expansion of thrombi and allow thrombolytic processes to dissolve the existing embolus. Heparin sodium is initially given at 100 to 200 IU/kg IV followed by 100 IU/kg SC qid until the patient is discharged (Table 1). An activated partial thromboplastin time of approximately 1.5 to 2.0 times baseline should be maintained.

**Table 1. Agents Used to Treat Thromboembolism**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Uses/Indications</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Long-term therapy to prevent thrombus formation</td>
<td>81 mg PO q48–72h</td>
<td>May cause gastrointestinal upset</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Long-term therapy to prevent thrombus formation</td>
<td>0.25–0.5 mg PO sid</td>
<td>May cause hemorrhage; may interact with many other drugs</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Used to prevent thrombus formation (usually in an acute crisis)</td>
<td>100–200 IU/kg IV followed by 100 IU/kg SC qid</td>
<td>May cause hemorrhage; monitor partial thromboplastin time; desired prolongation is 1.5 to 2.0 times baseline</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Dissolves existing thrombus</td>
<td>90,000 U over 20–30 min followed by CRI of 45,000 U/hr for 3 hr</td>
<td>Nonspecific plasminogen activator that can cause systemic fibrinolysis/hemorrhage; monitor for reperfusion injury (hyperkalemia and acidosis)</td>
</tr>
<tr>
<td>Tissue-plasminogen activator</td>
<td>Dissolves existing thrombus</td>
<td>1–10 mg/kg IV at CRI of 0.25–1.0 mg/kg/hr</td>
<td>Specific for fibrin-bound plasminogen, thus may have less chance of causing hemorrhage; monitor for reperfusion injury (hyperkalemia and acidosis)</td>
</tr>
</tbody>
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CRI = constant-rate infusion.

Recently, there has been some interest in the use of fractionated heparins, also known as low-molecular-weight heparins, for the treatment and/or prevention of TE in cats. In many parts of Europe and recently in North America, the use of low-molecular-weight heparins in humans has become the standard when using heparin for antithrombotic therapy. Because of the smaller molecular size and structure of fractionated heparins, they have much less specificity for inhibiting clotting factor II (thrombin) but retain their specificity for factor X. Additionally, due to less binding of low-molecular-weight heparins to proteins, endothelial cells, and macrophages, they have much better bioavailability, more predictable excretion, and a longer half-life when compared with unfractionated heparin. These properties result in less potential for hemorrhage and allow a once- or twice-daily subcutaneous dose, which can be given at home. Another desirable feature that has made this class of drugs popular in human medicine is that laboratory monitoring is unnecessary because of the agent's predictable antithrombotic effect and pharmacokinetics. However, because low-molecular-weight heparins are mainly excreted through the kidneys, patients with renal insufficiency should be monitored for unwanted prolongation of activated partial thromboplastin times. A preliminary study in cats that examined the effect of low-molecular-weight heparin on coagulation suggests that dalteparin sodium can be given effectively at a dose of 100 IU/kg SC sid. Some veterinary cardiologists and institutions have begun using fractionated heparins, such as dalteparin, in cats with HCM. Published data are necessary to make objective recommendations regarding the use of...
fractional heparins in cats with TE or those that are at high risk.

**Warfarin and Aspirin**

Warfarin may be used as long-term therapy to prevent further TE episodes.\(^1\)\(^{-3}\)\(^{15}\)\(^{16}\) Warfarin acts by preventing synthesis of vitamin K–dependent clotting factors II, VII, IX, and X. The goal is to achieve a degree of anticoagulation considered therapeutic in order to prevent thrombus formation. Warfarin is usually given at a starting dose of 0.25 to 0.5 mg PO sid.\(^1\)\(^{-3}\)\(^{15}\) Prothrombin time should be prolonged to 1.5 to 2.0 times baseline and should be monitored frequently or when any changes in medications are made.\(^1\)\(^{-3}\)\(^{15}\) Warfarin is known to have multidrug interactions, and its anticoagulant effect can be either enhanced or diminished by other drugs.\(^1\)\(^{15}\) Hemorrhage is a major concern when instituting warfarin therapy. Owners of animals on warfarin must be committed to their animal's care and monitor for such signs as melena, hematuria, epistaxis, pale mucous membranes, or bruising. If an owner is unwilling to make frequent follow-up visits or if finances are a concern, warfarin should not be used.

Aspirin can be used as an alternative for long-term prophylactic anticoagulant therapy. Aspirin works by inhibiting cyclooxygenase-1–derived thromboxane \(A_2\), thus reducing platelet aggregation and thromboxane \(A_2\)–induced vasoconstriction.\(^1\)\(^{-3}\)\(^{11}\)\(^{16}\) Aspirin’s effectiveness is questionable in preventing future TE episodes, and some feel it is inferior to warfarin for this purpose.\(^15\) The usual dose is 81 mg (baby aspirin) q48–72 h.\(^1\)\(^{-3}\) The most common side effect is gastrointestinal upset.\(^3\)\(^{-5}\)

**MANAGEMENT OF THROMBOEMBOLISM**

**Promoting Circulation**

Placing warm compresses on affected limbs has been suggested to promote circulation.\(^4\) Additionally, vasodilator therapy can be attempted to promote collateral circulation because vasoconstriction is thought to play an important role in ischemia.\(^1\)\(^{-3}\) Acepromazine and hydralazine have been used for this purpose,\(^3\)\(^4\) but care must be taken to avoid hypotension and/or excess sedation. An alternative therapy to promote collateral circulation is the use of an angiotensin-converting enzyme (ACE) inhibitor. In a study evaluating the effect of ACE inhibitors on collateral blood flow in rats that had undergone experimental femoral artery ligation, collateral blood flow to the limbs and muscles was increased by 33% to 46% compared with that of untreated controls.\(^1\)\(^7\) Studies evaluating the use of these drugs to promote collateral circulation in cats with naturally occurring TE are needed to make definitive recommendations.

**Analgesic Therapy**

Because cats suffering from TE are usually in pain, some form of analgesic therapy is appropriate. Aspirin can be used as an analgesic in cats at a dose of 81 mg q48 h.\(^1\)\(^2\) and may also be beneficial at preventing platelet aggregation.\(^1\)\(^{-3}\)\(^{3}\) Opioids are excellent analgesics and can be given to cats with cardiovascular disease. When used properly, opioids have minimal effects on myocardial contractility, preload, and afterload.\(^1\)\(^8\) Oxymorphone can be used at a dose of 0.05 mg/kg for moderate to severe pain,\(^1\)\(^{19}\) and butorphanol can be used at a dose of 0.2 to 0.4 mg/kg for mild to moderate pain.\(^1\)\(^{11}\)\(^{17}\) Both of these drugs can be given SC, IM, or IV q4 h as needed to control pain. Opioids can potentially cause respiratory depression and bradycardia, but most critically ill patients tolerate analgesic doses of these drugs with few side effects.\(^19\)

**Thrombolytic Drugs**

Unlike heparin, warfarin, and aspirin, thrombolytic drugs have the potential to dissolve a thrombus or embolus. The two drugs currently used are streptokinase and tissue-plasminogen activator (t-PA).\(^1\)\(^{16}\)\(^{20}\) It is recommended that thrombolytic therapy be initiated within 4 hours of clinical signs to maximize clot dissolution and reperfusion.\(^3\)\(^{21}\) Streptokinase is a nonspecific thrombolytic agent that activates circulating plasminogen. Plasminogen is converted to its active form, plasmin, which subsequently degrades fibrin into fibrin-split products. In cats with thrombi, this can lead to dissolution of the clot with restoration of perfusion to affected tissues. However, since streptokinase is not specific for fibrin-bound plasminogen, a state of systemic fibrinolysis can lead to a coagulopathy. Hence, a major complication of streptokinase therapy is hemorrhage.\(^1\)\(^{2}\)\(^{20}\) The dose of streptokinase is 90,000 U over 20 to 30 minutes followed by a constant-rate infusion of 45,000 U/hour for 3 hours.\(^1\)\(^{3}\)\(^{20}\) t-PA is an enzyme that converts fibrin-bound plasminogen to plasmin, leading to dissolution of the thrombus. Because t-PA is more specific for plasminogen that is bound to the thrombus, it has less chance of activating circulating plasminogen, thus preventing systemic fibrinolysis.\(^1\)\(^{2}\)\(^{16}\) The dose of t-PA in cats is 1 to 10 mg/kg IV administered at a rate of 0.25 to 1.0 mg/kg/hour.\(^1\)\(^{-3}\)\(^{16}\) Due to the specificity of t-PA, there is less chance for hemorrhage compared with streptokinase.\(^3\)\(^{5}\)\(^{16}\) Nonetheless, both drugs have equal potential for causing reperfusion-associated complications.\(^1\)\(^{-3}\)\(^{16}\)\(^{20}\) Life-threatening hyperkalemia and metabolic acidosis are primary concerns. In one report of using t-PA to treat cats for TE, 70% of complications resulting in fatalities were due to metabolic acidosis and hyperkalemia.\(^16\) When treating a
cat with TE, these potential complications must be kept in mind and the patient monitored carefully using clinical assessment, biochemical analysis, and electrocardiographic monitoring. If life-threatening hyperkalemia or acidosis occurs, patients must be treated promptly and aggressively. We recommend the use of thrombolytic agents only at referral institutions or critical care centers capable of intensive monitoring and 24-hour observation.

PROGNOSIS

Cats with HCM that form a thrombus are generally regarded as having a guarded prognosis. However, in a retrospective study of 100 cats with TE, animals that survived the initial episode and were released from the hospital had an average life expectancy of 11.5 months. In this study, cats had a 34% chance of surviving the initial episode of TE but 32% of cats were euthanized because of a guarded prognosis rather than a specific recommendation from the clinician. Therefore, the chance of recovery was likely greater than 34%.

REFERENCES


ARTICLE #4 CE TEST

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose the best answer to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium*.

1. Heparin exerts its anticoagulant effect by
   a. decreasing platelet numbers.
   b. impairing vitamin K metabolism.
   c. complexing with antithrombin III, which leads to inactivation of the serine proteases.
   d. impairing platelet function.
   e. decreasing antithrombin III levels.

2. When warfarin is combined with other drugs,
   a. its anticoagulant activity may be enhanced.
   b. its anticoagulant activity may be diminished.
   c. frequent coagulation tests should be conducted.
   d. there is little need for concern.
   e. a, b, and c

3. Therapies that may be used on a long-term basis in an attempt to prevent TE are
   a. acetaminophen and ivermectin.
   b. warfarin, aspirin, and low-molecular-weight heparins.
   c. diuretics and digitalis glycosides.
   d. cardiac pacemakers and decreased exercise.
   e. ACE inhibitors and diuretics.
4. Which of the following is a major difference between t-PA and streptokinase for the use of actively dissolving a thrombus?
   a. There are no major differences between these drugs.
   b. Streptokinase is specific for fibrin-bound plasminogen, whereas t-PA nonselectively activates plasminogen.
   c. t-PA is specific for fibrin-bound plasminogen, whereas streptokinase nonselectively activates plasminogen.
   d. Streptokinase can be used with little concern for hemorrhage compared with t-PA.
   e. Streptokinase is administered orally, while t-PA is given subcutaneously.

5. When trying to reperfuse tissue previously compromised by a thrombus, it is important to monitor for life-threatening.
   a. hypoglycemia and hypothermia.
   b. hypernatremia and hypercalcemia.
   c. hypophosphatemia and anemia.
   d. hypokalemia and metabolic alkalosis.
   e. hyperkalemia and metabolic acidosis.

6. When treating pain associated with acute aortic TE,
   a. opioids should be avoided because they will likely further compromise the patient.
   b. opioids are an appropriate choice.
   c. analgesics should be avoided because they may mask clinical signs.
   d. steroids are the drugs of choice.
   e. analgesics should be provided only if pain is considered severe.

7. Heparin therapy may be effective at
   a. dissolving the existing thrombus.
   b. preventing the formation or expansion of thrombi.
   c. relieving pain.
   d. preventing reperfusion injury.
   e. treating pulmonary edema.

8. Aspirin is sometimes used as a chronic anticoagulant because it
   a. reduces platelet aggregation by inhibiting the platelet cyclooxygenase-1 enzyme.
   b. inhibits the intrinsic coagulation system.
   c. inhibits the extrinsic coagulation system.
   d. binds to antithrombin III and thus potentiates its effect.
   e. relieves chest pain associated with coronary disease.

9. The major complication associated with warfarin therapy is
   a. vomiting.
   b. diarrhea.
   c. inappropriate urination.
   d. aggressiveness.
   e. hemorrhage.

10. Which factor(s) predispose patients to TE?
    a. endocardial injury
    b. circulatory stasis
    c. hypocoagulability
    d. hypercoagulability
    e. a, b, and d