CHAPTER **181**

Arterial Thromboembolism

DANIEL F. HOGAN, *West Lafayette, Indiana*

Background

Arterial thromboembolism (ATE) is a sudden interruption of arterial blood flow caused by thrombotic material that is derived from a distant site. This obstruction leads to infarction of tissues served by that arterial bed. Localized arterial thrombosis is associated with abnormalities of the vascular endothelium or vascular wall and may stem from high-shear flow within a narrowed blood vessel. This condition seems relatively rare in dogs and cats. Conversely, ATE occurs commonly in small animals.

In some cases of ATE, the site of the originating thrombus is either known or reliably suspected. For example, cardiogenic embolism (CE) typically results from thrombi located within a dilated left atrium or auricle, whereas septic cardioemboli develop with valvular or mural endocarditis. However, in other cases, such as neoplasia, protein-losing nephropathy, hyperadrenocorticism, and immune-mediated hemolytic anemia, the thrombus source cannot be determined. It has been suggested that in some cases of ATE where a source of the arterial thrombus cannot be identified, systemic venous thrombi may be the source of the embolic material, causing paradoxical (right-to-left) ATE. In human patients paradoxical ATE often is associated with deep venous thrombosis in which thrombotic material crosses a congenital cardiac defect from the right to the left side of the circulation, often across a patent foramen ovale (PFO). Cryptogenic stroke (a stroke of uncertain origin) is three times more likely in human patients with a PFO, and human patients with a PFO are 34 times more likely to experience silent brain infarction. Paradoxic embolism has been reported in veterinary medicine and in one recent study (Hogan and Meltzer, 2011) evidence of right-to-left shunting at the atrial level was identified in approximately 50% of dogs with congenital heart disease using agitated saline contrast echocardiography. Such findings could explain the relatively high frequency of silent renal infarcts on abdominal ultrasonography in cats and dogs and the development of systemic ATE in veterinary patients with hypercoagulable disorders.

Pathogenesis

In the normal healthy state, there is an equilibrium between thrombus formation and thrombus dissolution, which prevents unregulated thrombus formation. Primary hemostasis occurs when platelets are exposed to subendothelial collagen. This leads to platelet adhesion and activation, with subsequent aggregation and release of proaggregating and vasoconstrictive substances. Platelet release products, in conjunction with circulating factors within the plasma, initiate the coagulation cascade. Fibrinolytic and antithrombotic mechanisms are activated simultaneously to break down the developing hemostatic plug, which prevents excessive thrombus formation. Pathologic thrombosis can result from any combination of impaired or overwhelmed antithrombotic mechanisms, increased function of prothrombotic mechanisms, or impaired fibrinolysis.

The development of pathologic thrombosis classically has been linked to Virchow's triad, which includes endothelial injury, blood stasis, and the presence of a hypercoagulable state, with each arm adding to the risk of thrombosis (cumulative thrombotic risk). Examples of endothelial injury are a dilated left atrium in a cat with hypertrophic cardiomyopathy, a damaged aortic valve in a dog with subaortic stenosis, and tumor invasion of the arterial tree. Blood stasis is associated with dilated or poorly contracting cardiac chambers, restricted blood flow from tumor growth, or sluggish venous flow. The hypercoagulability arm of the triad has been poorly defined in domestic animal species, although there are known clinical conditions associated with thrombosis in animals (see Chapter 166).

Known hypercoagulable states in humans include inherited abnormalities in the procoagulant factors IIa (thrombin), Va, and VIIIa as well as the antithrombotic proteins antithrombin (AT), protein C, and protein S. Additional hypercoagulable states include platelet hypersensitivity and increases in homocysteine, lipoprotein (a), plasminogen activator inhibitor, and thrombin-activatable fibrinolysis inhibitor. Suspected hypercoagulable states in dogs and cats include platelet hypersensitivity, decreased AT and protein C activity, and increased levels of in factors II, V, VII, VIII, IX, X, XII, and fibrinogen.

Early pathologic thrombus composition is classified as platelet rich but progressively becomes more fibrin rich as the thrombus continues to grow. As the thrombus ages, superficial portions can break off forming emboli that cause infarction in distant arterial beds. The clinical signs that result from the arterial infarction depend on the site and completeness of the arterial obstruction, the availability of arterial anastomoses and collateral circulation, and the metabolic demands of the tissues. Platelet-released vasoactive substances reduce the collateral flow around the site of obstruction and contribute to the clinical signs of ischemic neuromyopathy. This is similar to what is observed in humans with thrombotic stroke, cardiogenic embolism, and pulmonary embolism. In experimental feline models of aortic ATE, pretreatment with the antiserotonergic drug cyproheptadine and clopidogrel

(which inhibits platelet activation and has a vasomodulating effect) maintains the collateral network and reduces the signs of ischemic neuromyopathy.

Clinical Signs

The type and severity of clinical signs relates to the location and completeness of the arterial obstruction. Organs often have a collateral network that can be recruited to provide blood flow around a site of arterial obstruction, but flow through these networks appears to be impaired with acute thrombotic infarction.

Renal infarction can present with renal pain and acute renal failure, whereas infarction of the cranial mesenteric artery can result in severe abdominal pain, vomiting, and diarrhea. Nonspecific signs of lethargy, anorexia, vomiting, and diarrhea have been reported with splenic infarction. The clinical signs of cerebrovascular accidents or stroke can be profound, depending on the neural location of the infarction and the territory served by the affected artery. Signs can include paresis, vestibular dysfunction, cranial nerve deficits, and seizures.

Infarction caused by obstruction of the distal aortic trifurcation (a saddle thromboembolus) accounts for the majority of ATE cases in dogs and cats and results in a loss of blood flow to the pelvic limbs, causing ischemic neuromyopathy. Paresis or paralysis of the pelvic limbs with absence of segmental reflexes, firm and painful pelvic limb musculature, and cold and pulseless limbs with cyanotic nail beds are typical features. These findings can be bilateral and symmetric, or unilateral and asymmetric, depending on the degree of infarction and blood flow through collateral vessels. The tail often is involved. Cats appear to be more severely affected with ischemic neuromyopathy than are dogs, which may be indicative of species differences in platelet function or preservation of the collateral circulation. The clinical signs of ischemic neuromyopathy are peracute in onset and can worsen, but usually remain stagnant or improve over the following several days to 3 weeks.

Infarction of the subclavian artery, typically the right subclavian, is the second most common site for ATE in cats and occasionally is seen in dogs. The clinical signs associated with infarction at this site are essentially identical to those for infarction of the aortic trifurcation, although the signs are confined to the affected forelimb.

Clinical Thrombotic Conditions

There are a number of clinical conditions in which thrombotic complications are commonly recognized, increase morbidity and mortality, may require acute treatment, and should initiate consideration for antithrombotic therapy. For this discussion, systemic ATE and pulmonary ATE are included in the pathologic process of ATE.

Immune-Mediated Hemolytic Anemia
Pulmonary embolism has been identified in 30% to 80% of dogs with immune-mediated hemolytic anemia (IMHA) at necropsy and often is speculated to be the

cause of death. Altered hemostatic parameters, including prolonged coagulation times and increased levels of fibrinogen, D-dimers, and fibrin degradation products as well as reduced AT levels, have been noted. Oxidative stress and platelet hyperactivation appear to be associated with thrombosis in humans with IMHA. One study identified an eightfold increase in P-selectin expression in dogs with IMHA, which suggests that dogs with the disorder have an increase in circulating activated platelets (Weiss and Brazzell, 2006).

Hyperadrenocorticism
Pulmonary embolism appears to occur in up to 18% of dogs with hyperadrenocorticism, and increases in the procoagulant factors II, V, VII, IX, X, XII, and fibrinogen have been noted. There is a fourfold increase in pulmonary embolism in humans with hyperadrenocorticism, and as in dogs, elevations in procoagulant factors II, V, VII, IX, X, and XII have been identified.

Protein-Losing Nephropathy
Thromboembolic complications have been reported to occur in over 20% of dogs with protein-losing nephropathy. Reduced circulating AT levels are thought to result from loss through the damaged glomerular tuft; a correlation also has been noted between platelet hypersensitivity and hypoalbuminemia. This platelet hypersensitivity appears to resolve with increases in albumin concentration following therapy. The incidence of thromboembolic disease in humans with nephrotic syndrome is approximately 1% per year, and risk is related to the degree of proteinuria and hypoalbuminemia. In addition to loss of AT, other possible causes of hypercoagulability in humans include increased thrombin-activatable fibrinolysis inhibitor and reduced protein C activity.

Neoplasia
The reported frequency of neoplasia in dogs and cats with ATE ranges from 2.5% to 30%. Suspected causes include an unknown hypercoagulable state, paraneoplastic thrombocytosis, tumor embolization, and local tumor extension. Thrombosis is seen in up to 15% of human cancer patients, and there are a number of proposed causes for the hypercoagulable state, including the presence of a cysteine proteinase (cancer procoagulant factor), acquired protein C resistance, and increased P-selectin levels.

Cerebrovascular Accidents (Strokes)
Although representing fewer than approximately 2% of all neurologic cases in dogs, cerebrovascular accidents or strokes have become more widely identified clinically with the advent of advanced brain imaging. Apparent clinical associations include hypothyroidism, diabetes mellitus, hypertension, and suspected but undefined hypercoagulable states. Cavalier King Charles spaniels and greyhounds, breeds with known platelet abnormalities, appear to be overrepresented.

Cardiogenic Embolism
Thromboembolic complications associated with cardiac disease probably are the most common cause of ATE in

veterinary medicine, with cats affected far more commonly than dogs. The frequency of CE in cats with cardiac disease has been reported to be between 6% and 17%. Males are overrepresented, and breeds that appear to have an increased risk are Ragdoll, Birman, Tonkinese, and Abyssinian. Possible markers of hypercoagulability have been identified in cats with a previous history of CE and include platelet hypersensitivity as well as reductions in AT and protein C activity. Survival rates with an initial ATE event range from 33% to 39%. Survival is dramatically better with single-limb infarction than with bilateral infarction (68% to 93% versus 15% to 36%, respectively) and is negatively impacted by hypothermia, reduced heart rate, and absence of motor function. Reported median survival times range from 51 days to 443 days with recurrence rates of 17% to 75% over the first year (Laste and Harpster, 1995; Smith et al, 2003). A recent trial comparing clopidogrel with aspirin demonstrated significant improvement in survival with clopidogrel (Fat Cat trial, Hogan et al, 2013).

Clinical Management

Key elements in the acute management of ATE include preventing continued thrombus formation associated with the embolus, improving blood flow to the infarcted tissues, and managing pain.

Reduce Thrombus Formation

Unfractionated heparin (UFH) is a group of heterogeneous molecules with a mean molecular weight of approximately 15,000 D. Heparin molecules contain a pentasaccharide sequence that binds to AT, which facilitates the inhibition of factors IIa, Xa, IXa, and XIIa. Thrombin-catalyzed activation of factors V and VIII is inhibited as well. UFH also exhibits a mild antiplatelet effect in normal humans. Objective studies evaluating the bleeding risk with UFH therapy in dogs and cats are unavailable, but clinically relevant bleeding has been observed in both species. There is no documented report of heparin-induced thrombocytopenia in dogs or cats, although this severe condition has been reported in up to 10% of human patients receiving UFH. Ideally, coagulation testing including platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) should be performed before heparin therapy is begun. Adequate dosing of heparin in dogs and cats has been shown to be quite variable, and dosing requirements may change over time because of a decrease in AT levels. Dosing guidelines call for an initial dose of 250 to 375 IU/kg followed by 150 to 250 IU/kg q6-8h SC for cats, and an initial dose of 200 to 300 IU/kg IV followed by 200 to 250 IU/kg q6-8h SC for dogs. Constant-rate infusions also are used by some clinicians (see Chapter 166). Serial measurement of the aPTT can be used to monitor heparin therapy with a target of 1.5 to 2.0 times the baseline value.

The *low-molecular-weight heparins* (LMWHs) are smaller in molecular size than UFH and can be used in lieu of UFH. The cost of these agents is considerably more than that of UFH (approximately $3 to $5 per dose) and there is no clear indication of clinical benefit over UFH in the

acute management period. Dalteparin (Fragmin) and enoxaparin (Lovenox) have been used in dogs and cats at 100 IU/kg q12h SC and 1.0 to 1.5 mg/kg q12h SC, respectively, during the acute management period.

Improvement of Blood Flow

Thrombolytic Therapy

Thrombolytic drugs have been used in dogs and cats to dissolve emboli and reestablish arterial blood flow. These should be administered as soon as possible after the embolic event, with many clinicians considering 6 hours a reasonable therapeutic window, although effective therapy has been documented as late as 18 hours after initial clinical signs of ATE. Severe and potentially fatal adverse effects can be associated with thrombolytic therapy; therefore caution should be exercised when considering these drugs. The sudden resumption of arterial flow to infarcted organs can result in the rapid development of life-threatening hyperkalemia and metabolic acidosis (reperfusion injury), and this is most likely to occur with complete aortic occlusion and severe infarction of rear limb muscles. The reported frequency of reperfusion injury following thrombolytic therapy in cats with CE is from 40% to 70% with reported survival rates from 0% to 43%, and some of these fatality rates are higher than those observed with more conservative therapy (heparin, pain management, time for reperfusion). Because of potential adverse effects and cost, the author considers thrombolytic therapy only in cases in which the loss of arterial flow makes survival unlikely.

Tissue plasminogen activator (t-PA) forms an intimate relationship with plasminogen within thrombi, resulting in a relative fibrin-specific conversion of plasminogen to plasmin. However, when t-PA is administered at clinical doses, a systemic proteolytic state and bleeding can be seen.

Although there is overall little experience with the use of human recombinant t-PA (Activase) in dogs and cats, it has been administered intravenously either as a constant-rate infusion in cats (0.25 to 1 mg/kg/hr IV for a total dose of 5 mg/kg) or multiple-bolus therapy in dogs (1 mg/kg IV). The success rate in two isolated case reports of dogs was variable. There is one reported clinical trial of t-PA therapy in six cats with CE that recorded a 50% survival rate. Perfusion was restored within 36 hours and motor function returned within 48 hours in 100% of surviving cats. Complications included minor hemorrhage from catheter sites (50%), fever (33%), and reperfusion injury (33%).

Urokinase, similar to streptokinase, is no longer commercially available, and is considered relatively fibrin specific. Urokinase has been administered to cats and dogs for treatment of ATE using a protocol of 4400 IU/kg IV as a loading dose given over 10 minutes followed by 4400 IU/kg/hr IV for 12 hours. There is one published study in cats (Whelan et al, 2005a), which reported a 42% survival rate; 30% regained pulses, 60% regained motor function, and 25% developed reperfusion injury. The published clinical experience in dogs (Whelan et al, 2005b) has been much less encouraging, with a mortality rate of 100% in treated dogs.

Improvement of Collateral Blood Flow

Increasing perfusion to the infarcted organ has been attempted by administering drugs that may potentially increase flow through the collateral arterial network. The use of vasodilators such as acepromazine has not been demonstrated to be effective and may have a negative clinical impact by inducing hypotension, which further reduces perfusion. The platelet-release products serotonin and thromboxane have been implicated as factors involved in loss of collateral circulation. Clopidogrel (Plavix) has been shown to reduce serotonin release from activated platelets in cats and improve collateral flow, with reduced clinical signs of ischemic neuromyopathy in a cat model of aortic thromboembolism. Maximal platelet inhibition is achieved within 72 hours at dosage of 1 to 4 mg/kg q24h PO in dogs and cats, but an oral loading dose of 10 mg/kg in dogs resulted in comparable effects within 90 minutes with no adverse effects. Daily administration of 1 to 2 mg/kg in cats (approximately 18.75 mg) is well tolerated and is not associated with adverse effects. Therefore the author administers a loading dose of 75 mg of clopidogrel PO upon presentation with ATE in an attempt to improve collateral flow and reduce thrombus formation.

Pain Management

ATE can result in severe pain that must be treated aggressively, especially within the initial 24 to 36 hours after the event when pain is most severe. Opiates generally are selected for this purpose. These include *butorphanol tartrate* (0.1 to 0.4 mg/kg q1-4h SC, IM, or IV for dogs and cats), *hydromorphone* (0.08 to 0.3 mg/kg q2-6h SC for dogs and cats), *buprenorphine hydrochloride* (0.005 to 0.02 mg/kg q6-12h SC, IM, or IV for dogs and cats), *oxymorphone hydrochloride* (0.05 to 0.2 mg/kg q1-3h SC, IM, or IV for dogs and cats), and *fentanyl citrate* (4 to 10 µg/kg IV bolus followed by 2 to 10 µg/kg/hr IV infusion for dogs and cats). The use of these drugs is discussed more fully in Chapter 12 of this book. In general, strong mu agonists (such as fentanyl or hydromorphone) provide the best analgesia, compared with partial (butorphanol) or mixed (buprenorphine) analgesics, and should be considered for initial therapy. Availability of specific opiates within the practice may influence the selection of drugs.

Prevention

Primary prevention of ATE is defined as preventing the first event in an animal at risk of ATE. Although primary prevention would be an ideal and logical goal, there is a poor understanding of thrombotic risk in dogs and cats. The greatest body of evidence relates to CE in cats. Cats appear to be at a greater risk of ATE if they have an increase in left atrial size or evidence of stagnant left atrial blood flow ("smoke") or diminished left auricular emptying as evidenced by echocardiography. Therefore prophylactic antithrombotic therapy should be considered in cats with these risk factors.

Secondary prevention is defined as preventing a recurrent ATE event, and the largest body of evidence again relates to CE in cats. However, these data are problematic because they are based on retrospective, non–placebo-controlled studies of individual antithrombotic agents. Thus there is no scientific basis for conclusions that any antithrombotic agent is effective, completely ineffective, or superior to another agent. Reported recurrence rates for cats receiving some antithrombotic drug range from 17% to 75%, with a 1-year recurrence rate of 25% to 50%.

Antithrombotic Drugs

Due to their direct effect on thrombus formation, antithrombotic agents have become a mainstay for primary and secondary prevention of ATE in dogs and cats. However, it should be emphasized that the goal of complete prevention of recurrent embolic events in animals with chronic diseases such as cardiac disease or nephrotic syndrome is unrealistic.

Antiplatelet Agents

Antiplatelet agents inhibit some aspect of platelet function and impair the formation of the initial platelet-rich thrombus. Some of these drugs also exhibit vasomodulating effects by reducing the release of or interfering with the activity of vasoactive substances released by platelets.

Aspirin irreversibly acetylates platelet cyclooxygenase, preventing the formation of thromboxane A_2, a potent proaggregating and vasoconstrictive molecule. Aspirin is considered a modest and indirect antiplatelet agent. The standard dosage in cats is 81 mg q72h PO, but adverse effects such as anorexia and vomiting have been reported in up to 22% of treated cats. A low-dose protocol of 5 mg q72h PO has been associated with reduced adverse effects. Reported recurrence rates of ATE in aspirin-treated cats range from 17% to 75%, regardless of aspirin dose. There has been very little published regarding the clinical use of aspirin for the prevention of thrombosis in dogs, but 0.5 mg/kg q24-12h PO generally is used, and one study reported an increased survival in dogs with IMHA.

Clopidogrel, which must undergo hepatic biotransformation to form the active metabolite, induces specific and irreversible antagonism of the adenosine diphosphate P2Y12 receptor along the platelet membrane and results in more potent platelet inhibition than aspirin. The vasomodulating effects of clopidogrel already have been mentioned. Unlike aspirin, clopidogrel is not associated with gastroduodenal ulceration. When dosed at 1 to 3 mg/kg q24h PO in cats and dogs, maximal antiplatelet effects are seen by 3 days of drug administration and are lost within 7 days after drug discontinuation. Because of the size of the commercially available tablet, the typical cat dosing protocol is 18.75 mg per cat q24h PO. There have been anecdotal reports of sporadic vomiting in cats receiving clopidogrel clinically. Administering clopidogrel in a gel capsule or with food appears to reduce this occurrence dramatically. Preliminary analysis of an ongoing trial indicated that clopidogrel confers a survival benefit over aspirin in cats that had previously survived a cardiogenic embolus (Hogan et al, 2013). Clopidogrel sometimes is combined with aspirin in human patients,

but whether this combination might be effective in dogs and cats is unknown.

Anticoagulant Agents

Anticoagulant drugs inhibit the coagulation cascade by interfering with the formation of one or more active coagulation factors. Some of these drugs also exhibit relatively minor antiplatelet effects.

Warfarin inhibits the formation of the vitamin K–dependent coagulation factors II, VII, IX, and X as well as the anticoagulant proteins C and S. Numerous studies in humans have demonstrated superior efficacy of warfarin over antiplatelet drugs for primary and secondary prevention of CE in patients with atrial fibrillation. Warfarin therapy is adjusted by monitoring the international normalized ratio (INR), which normalizes an individual animal's PT for a given laboratory. The pharmacokinetics and pharmacodynamics of warfarin have been evaluated in dogs and cats, and wide interindividual and intraindividual variability have been noted. Published dosing protocols call for 0.06 to 0.09 mg/kg q24h PO for cats and 0.05 to 0.2 mg/kg q24h PO for dogs. Warfarin is not evenly distributed throughout the tablet, so it is best to have it compounded by a pharmacist if partial-pill dosing is required. Careful monitoring of the INR (with a target value of 2 to 3) or PT (with a target value of 1.3 to 1.6 times baseline) is required, and owners should be aware of this requirement for frequent blood draws and dosing adjustments. Warfarin dosing changes are often accomplished by changing the total weekly dose (as opposed to daily dose) in response to INR monitoring. Published CE recurrence rates for warfarin-treated cats in retrospective studies range from 42% to 53% with estimated mean survival times of 210 to 471 days. Bleeding is the most common complication and is seen in 13% to 20% of cats, with fatal hemorrhage reported in up to 13% of cats. Because of the difficulty in dosing accurately, wide variability in drug response, and requirement for diligent monitoring, warfarin rarely is used for prevention of ATE in cats. Warfarin is easier to administer to dogs, and there are small retrospective studies demonstrating practical clinical use in this species.

The *LMWHs* are smaller in molecular size than UFH but maintain the pentasaccharide sequence that binds to AT, so that they inhibit factor Xa but have a greatly reduced inhibition of factor IIa. Recommended dosing protocols are dalteparin 100 IU/kg q24-12h SC for cats and dogs and enoxaparin 1.0 to 1.5 mg/kg q24-12h SC for cats and dogs (see Chapter 166). Although some have advocated monitoring LMWH therapy by measuring anti–factor Xa activity, it has been shown that anti–factor Xa activity does not correlate with thrombus inhibition in cats, so monitoring is not indicated in the author's opinion. The ATE recurrence rate in cats treated with dalteparin is similar to that in cats given warfarin, but bleeding rarely is experienced. The major limiting factors for these drugs are that they must be administered by injection and are quite expensive.

Future Directions in Prevention

Most recently a number of drugs have been developed that selectively inhibit factor Xa (*Xa inhibitors*). These drugs are some of the first to have been proven to be at least as effective as warfarin for the prevention of CE in humans. They also are being used for the prevention of venous thromboembolism in humans. This group includes the drugs fondaparinux, rivaroxaban, and apixaban. Most of these drugs can be given orally and generally do not require monitoring. The development of a drug that is as efficacious as warfarin for ATE, can be given orally, and does not require clinical monitoring would be the greatest advancement in ATE prevention to date.

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