

APPROACH TO THE PATIENT WITH TE DISEASE

CLINICAL PRESENTATION

Clinical manifestations of TE disease depend on the type and location of vessels obstructed, the duration and degree of vascular obstruction, the extent of tissue damage, and any related complications. Most reported cases involve clots in the distal aorta, heart, brachial or other large systemic artery, pulmonary arteries, cranial vena cava, or portal vein. Multiple sites are affected in some animals. An index of suspicion for TE disease is important for antemortem diagnosis, and is based on the patient's history, physical findings, and concurrent disease(s).

Arterial TE disease in cats usually causes acute and dramatic clinical signs secondary to tissue ischemia. Male cats are at higher risk for thromboembolism, but this gender bias appears related to the prevalence of hypertrophic cardiomyopathy^{15, 41, 61, 62}. Distal aortic embolization occurs in most cases (213–215). Acute hindlimb paresis without palpable femoral pulses is typical. Common clinical findings are summarized in Table 39.

Signs of pain and poor systemic perfusion are usually present. Hypothermia and azotemia are common, even when a site other than the distal aorta is affected⁴¹. A cardiac murmur, gallop sound, or

Table 39 Common clinical findings in cats with arterial thromboembolism.

1) Acute limb paresis:	b) Gallop sounds.
a) Posterior paresis.	c) Arrhythmias.
b) Monoparesis.	d) Cardiomegaly.
c) ± Intermittent claudication.	e) Anorexia.
2) Characteristics of affected limb(s):	f) Lethargy/weakness.
a) Painful.	7) Signs of congestive heart failure (not always present):
b) Cool distal limbs.	a) Pulmonary edema.
c) Pale footpads.	b) Pleural effusion.
d) Cyanotic nailbeds.	8) Hematologic and biochemical abnormalities:
e) Absent arterial pulse.	a) Azotemia (prerenal or renal).
f) Contracture of affected muscles, especially gastrocnemius and cranial tibial.	b) Increased alanine aminotransferase activity.
3) Tachypnea/dyspnea (rule out pain or congestive heart failure).	c) Increased aspartate aminotransferase activity.
4) Vocalization (pain and distress).	d) Increased lactate dehydrogenase activity.
5) Hypothermia.	e) Increased creatine phosphokinase activity.
6) Signs of heart disease (not always present):	f) Hyperglycemia (stress).
a) Systolic murmur.	g) Lymphopenia (stress).
	h) Disseminated intravascular coagulation.



213–215 (213) Acute caudal aortic thromboembolism caused respiratory distress and panting as well as posterior paresis in this 4-year-old male DSH cat with restrictive cardiomyopathy. (214) The cat could ambulate with difficulty by shifting its weight to the forelimbs and dragging the hindlimbs and tail. (215) A cyanotic hindlimb nail bed (lower) from another cat with caudal aortic thromboembolism is compared with the pink nail bed (upper) of a forelimb.



arrhythmia is often noted, but these signs are not always evident even with underlying heart disease. Clinical signs of heart disease prior to the TE event are often absent⁴¹. Tachypnea and open-mouth breathing frequently occur with acute arterial embolization, despite the absence of overt CHF in many cats. This may represent a pain response, although it could be related to increased pulmonary venous pressure⁴¹. Because it is important to determine if CHF underlies the acute respiratory signs, thoracic radiographs should be taken as soon as possible. Motor function in the lower limbs is minimal to absent in most cases, although the cat is usually able to flex and extend the hips. Sensation to the lower limbs is poor. One side may show greater deficits than the other. Emboli are occasionally small enough to lodge more distally in only one limb, which causes paresis of the lower limb alone. Embolization of a brachial artery produces forelimb monoparesis. Intermittent claudication (see below) occurs rarely. Thromboemboli within the renal, mesenteric, or pulmonary arterial circulation may result in failure of these organs and death. Emboli to the brain could induce seizures or various neurologic deficits.

Arterial thromboembolism in dogs appears to have no age, breed, or sex predilections¹⁰. Most dogs with arterial (usually distal aortic) thromboemboli have some clinical signs from 1–8 weeks before presentation. Less than a quarter of cases have peracute paralysis without prior signs of lameness, as usually occurs in cats¹⁰. Most dogs are presented for signs related to the TE event. These include pain, hindlimb paresis, lameness or weakness, which may be progressive or intermittent, and chewing or hypersensitivity of the affected limb(s) or lumbar area. About half of the dogs are presented with sudden paralysis, but this is often preceded by a variable period of lameness¹⁰. Intermittent claudication, common in people with peripheral occlusive vascular disease, can be a manifestation of distal aortic TE disease⁴⁵. This involves pain, weakness, and lameness that develop during exercise. These signs intensify until walking becomes impossible, then disappear with rest. Inadequate perfusion during exercise leads to lactic acid accumulation and cramping. Physical findings in dogs with aortic thromboembolism are similar to those in cats, including absent or weak femoral pulses, cool extremities, hindlimb pain, loss of sensation in the digits, hyperesthesia, cyanotic nailbeds, and neuromuscular dysfunction¹⁰. Occasionally, the brachial or other artery is embolized (216, 217). TE disease involving an abdominal organ causes abdominal pain, along with clinical and laboratory evidence of damage to the affected organ.

Coronary artery thromboembolism is likely to be associated with arrhythmias, as well as ST segment and T wave changes on ECG. Ventricular, or other, tachyarrhythmias are common, but if the AV nodal

area is injured, conduction block can result³². Clinical signs of acute myocardial infarction/necrosis mimic those of pulmonary TE disease; these include weakness, dyspnea, and collapse⁴⁹. Dyspnea may develop from underlying pulmonary disease or left-sided heart failure, depending on the underlying disease and degree of myocardial dysfunction. Some animals with respiratory distress have no radiographically evident pulmonary infiltrates. Increased pulmonary venous pressure before overt edema develops (from acute myocardial dysfunction) or concurrent pulmonary emboli are potential causes. Other findings in animals with myocardial necrosis include sudden death, tachycardia, weak pulses, increased lung sounds or crackles, cough, cardiac murmur, hyperthermia or, sometimes, hypothermia, and, less commonly, gastrointestinal signs⁴⁹. Signs of other systemic disease can be concurrent. Acute ischemic myocardial injury causing sudden death may not be detectable on routine histopathology³¹.

Pulmonary TE disease (see also Chapter 23) has no apparent age or sex predilection in dogs or cats^{54, 55}. Classically, pulmonary TE disease causes dyspnea or tachypnea, but this is not evident in all cases^{11, 50, 54}. Increased lung sounds, a cardiac murmur, and hepatosplenomegaly are also reported in many affected dogs⁵⁴. Hypoxia develops mainly from V/Q mismatch related to aeration of nonperfused lung^{19, 54}.



216, 217 (216) This 6-year-old female Poodle developed acute paresis of the left forelimb because of a TE event soon after surgery for cystotomy. The dog recovered normal function after supportive therapy. (217) Cyanosis of the left forepaw is seen best on the nail of the 3rd digit (arrow); the normal pink right forepaw is to the left of the image.

Unexplained respiratory distress with a high A-a gradient should generate suspicion for pulmonary TE disease. Chest pain and hemoptysis are typical signs in people, but not usually recognized in animals⁵⁴.

Systemic venous thrombosis produces signs related to increased venous pressure upstream from the obstruction. Thrombosis of the cranial vena cava leads to the cranial caval syndrome (see Chapter 12 and 199, p. 128). Pleural effusion occurs commonly. This effusion is often chylous because lymph flow from the thoracic duct into the cranial vena cava is also impaired. Palpable thrombosis extends into the jugular veins in some cases. Because vena caval obstruction reduces pulmonary blood flow and left heart filling, signs of poor cardiac output are common.

LABORATORY TESTS

Results of routine laboratory tests depend largely on the disease process underlying the TE event(s). Systemic arterial TE disease also produces elevated muscle enzyme concentrations from skeletal muscle ischemia and necrosis. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities rise soon after the TE event. Widespread muscle injury also causes increased lactate dehydrogenase and creatine kinase (CK) activities¹⁰. Azotemia is common with arterial thromboembolism, especially in cats. This can be prerenal from poor systemic perfusion or dehydration, primary renal from embolization of the renal arteries or preexisting kidney disease, or a combination of both. Metabolic acidosis, DIC, electrolyte abnormalities, especially low serum sodium, calcium, and potassium, and elevated phosphorus, are common in cats, as is stress hyperglycemia. Hyperkalemia can develop secondary to ischemic muscle damage and reperfusion^{15, 41, 61}.

Myocardial damage from coronary artery embolization increases circulating cardiac troponin levels. Increased AST activity has been reported with myocardial necrosis⁴⁹. Total CK and ALT are variably increased within a few hours of injury; elevated cardiac-specific isoenzyme of CK (CK-MB) is expected but not usually measured in animals⁴⁹. Values peak in 6–12 hours then return to normal within 1–2 days. Continued increase indicates ongoing injury. Other laboratory parameters reflect underlying disease, as is the case with pulmonary TE disease and venous thrombosis. Leukocytosis and increased liver enzymes have been noted commonly with pulmonary thromboembolism and thrombocytopenia with cranial caval thrombosis¹³.

Routine coagulation test results are variable with TE disease. Levels of FDPs may be increased, but this can occur with inflammatory disease and is not specific for a TE event or DIC¹⁹. Cats with arterial TE disease usually have normal coagulation profiles³⁵. Coagulation test results are more variable in dogs with systemic arterial, including coronary, and pulmonary

TE disease. Prolonged coagulation times and thrombocytopenia consistent with DIC are reported in many cases, but results are normal in some dogs^{10, 49}. However, many conditions that underlie TE disease are also associated with DIC. Coagulation profile results have usually been normal with cranial vena cava thrombosis. Shortened coagulation (prothrombin, activated partial thromboplastin, and thrombin) times have not been correlated with thrombosis¹⁹.

D-dimer assays provide a more specific indicator of clot breakdown than FDPs in dogs^{5, 7, 63, 64}. D-dimers are degradation products specific to cross-linked fibrin. FDP assays do not discriminate between breakdown of fibrinogen and stable clots and are not sensitive enough to detect thromboemboli. D-dimer concentrations are elevated with TE disease, with higher concentrations more specific for thromboemboli. Modestly increased D-dimer concentrations occur in other diseases such as neoplasia, liver disease, and IMHA. This could reflect subclinical TE disease or another clot activation mechanism, as these conditions are associated with a procoagulant state^{7, 65}. Body cavity hemorrhage also causes a rise in D-dimers. Because this condition is associated with increased fibrin formation, elevated D-dimers may not indicate TE disease in these cases⁶. The specificity of D-dimer testing for pathologic thromboembolism is lower at lower D-dimer concentrations, but the high sensitivity at lower concentrations provides an important screening tool. D-dimer testing appears to be as specific for DIC as FDP measurement⁶. A number of assays have been developed to measure D-dimers in dogs; some are qualitative or semiquantitative (e.g. latex agglutination, immunochromatographic, and immunofiltration tests), others are more quantitative (e.g. immunoturbidity, enzymatic immunoassays)⁶⁶. It is important to interpret D-dimer results in the context of other clinical and test findings. The applicability of D-dimer testing in cats is not yet clear. Assays for circulating AT III and proteins C and S are also available for dogs and cats. Deficiencies of these proteins are associated with increased risk of thrombosis^{5, 30}. A number of methods are described to test for AT III activity. Sample submission instructions and normal reference values should be obtained from the laboratory performing the testing.

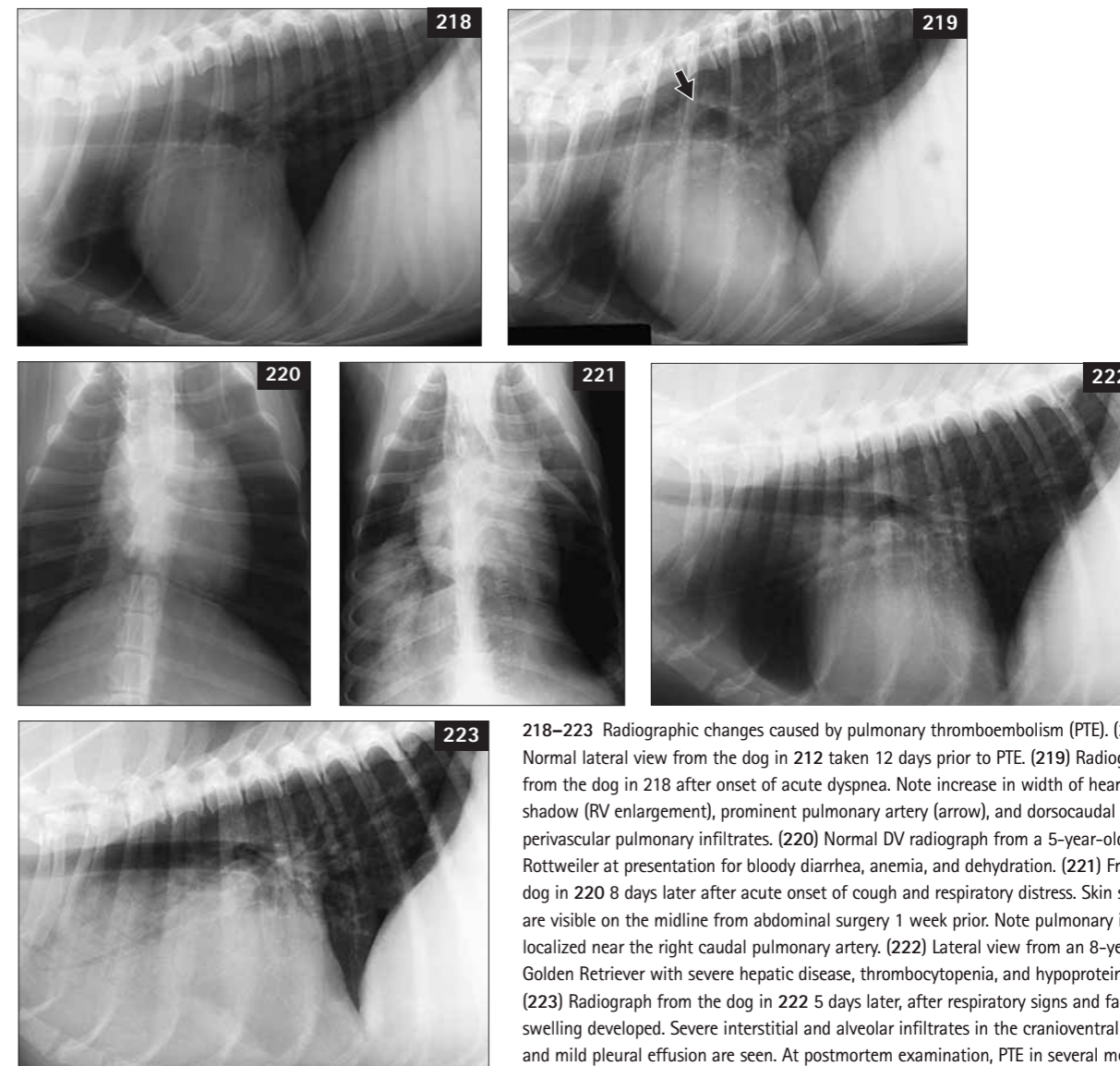
Arterial blood gas analysis is helpful when respiratory signs are severe or persistent (see Chapter 9, p. 114). Animals with pulmonary thromboemboli often have hypoxemia, hypocapnia, and an increased A-a gradient. Hypoxemia usually improves with supplemental O₂ because the mechanism is largely related to V/Q mismatch; however, massive embolization creates a large functional intrapulmonary shunt (venous admixture) and unresponsive hypoxemia. Progressively decreasing PaO₂ despite O₂ therapy suggests intrapulmonary shunting⁵⁴. Cranial vena cava thrombosis with complete caval obstruction also leads to hypocapnia and hypoxemia. Respiratory alkalosis, from

hyperventilation, and metabolic acidosis, possibly from poor tissue oxygenation induced by hypoxemia and low cardiac output, can occur. Partial improvement with O₂ therapy indicates some degree of V/Q mismatch, suggesting concurrent pulmonary thrombo-embolism.

DIAGNOSTIC IMAGING

Thoracic radiography is used to screen for cardiac abnormalities, especially in animals with systemic arterial TE disease, and for pulmonary changes in animals suspected to have pulmonary thromboemboli. Evidence for CHF or other pulmonary disease associated with thromboemboli (e.g. neoplasia, HWD,

or other infections) may also be found. Most cats with arterial TE disease have some degree of cardiomegaly, especially LA enlargement, when cardiomyopathy is underlying (see 46, 47, p. 39, 432–437, p. 302, 466, 467, p. 313, and Chapter 21). A minority of affected cats have no radiographic evidence of cardiomegaly^{15, 67}. Signs of CHF may or may not be present (e.g. dilated pulmonary veins, pulmonary edema, or pleural effusion [see 64–68, p. 45]). Pulmonary TE disease produces variable radiographic findings (218–223). Pleural effusion, truncated lobar pulmonary arteries, alveolar infiltrates, hyperlucent lungs (suggesting reduced pulmonary blood flow), main



218–223 Radiographic changes caused by pulmonary thromboembolism (PTE). (218) Normal lateral view from the dog in 212 taken 12 days prior to PTE. (219) Radiograph from the dog in 218 after onset of acute dyspnea. Note increase in width of heart shadow (RV enlargement), prominent pulmonary artery (arrow), and dorsocaudal perivascular pulmonary infiltrates. (220) Normal DV radiograph from a 5-year-old Rottweiler at presentation for bloody diarrhea, anemia, and dehydration. (221) From the dog in 220 8 days later after acute onset of cough and respiratory distress. Skin staples are visible on the midline from abdominal surgery 1 week prior. Note pulmonary infiltrates localized near the right caudal pulmonary artery. (222) Lateral view from an 8-year-old Golden Retriever with severe hepatic disease, thrombocytopenia, and hypoproteinemia. (223) Radiograph from the dog in 222 5 days later, after respiratory signs and facial/neck swelling developed. Severe interstitial and alveolar infiltrates in the cranioventral lung and mild pleural effusion are seen. At postmortem examination, PTE in several medium sized arteries (but no evidence for bacterial pneumonia), malignant histiocytosis of the liver and spleen, membranous glomerulonephritis, and cranial caval and jugular vein thrombosis were found (see also 199, p. 128).

pulmonary trunk enlargement, and, sometimes, lung atelectasis are described in dogs. But any radiographic pattern is possible^{54, 68}. Cats with pulmonary thromboembolism can also develop pleural effusion, alveolar opacification, peribronchial and interstitial markings, or pulmonary vascular congestion similar to dogs^{55, 56}. Radiographs are sometimes unremarkable, even with clinical signs of respiratory compromise¹⁹.

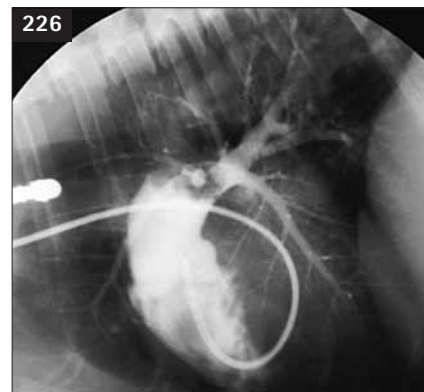
A complete echocardiographic examination is important to define whether heart disease might be present and, if so, what type of heart disease. Thrombi within the left or right heart chambers and proximal great vessels can be readily seen with 2-D echocardiography (224, 225) (see also 454, 455, p. 307, 464, p. 312, and 549, p. 345). Doppler modalities help define abnormal (or lack of) blood flow in affected regions. Most cats with arterial TE disease associated with cardiomyopathy have some degree of LA enlargement. An LA dimension of >20 mm (measured from the 2-D long-axis 4-chamber view) may increase the risk for TE disease^{37, 67}, although over half of aortic TE cases had a smaller LA size in one study⁴¹. The most common site for intracardiac thrombi is the left auricular appendage. Pulmonary TE disease that causes pulmonary hypertension variably produces RV enlargement and hypertrophy, interventricular septal

flattening, and high tricuspid regurgitation jet velocities (see Chapter 23 and 544–552, pp. 345, 346). Sometimes, a clot is identified within the pulmonary artery or RA. Likewise, vena cava thrombosis may be visible ultrasonographically, especially when the clot extends into the RA. Portal vein thrombosis and thromboemboli in the aorta or other large peripheral vessels can also be documented on ultrasound examination (225). In animals with coronary TE disease, the echo examination may indicate reduced myocardial contractility with or without regional dysfunction. Areas of myocardial fibrosis secondary to chronic ischemia or infarction appear hyperechoic compared with the surrounding myocardium.

Angiography can document vascular occlusion when ultrasonography is inconclusive or unavailable, as well as show the extent of collateral circulation. The choice of selective or nonselective technique depends on patient size and the suspected location of the clot. Especially in cats, if echocardiography is unavailable, nonselective angiography can help define the nature of underlying cardiac disease and determine the location and extent of the thromboembolus. Pulmonary angiography can identify major pulmonary flow obstructions (226, 227). Ventilation/perfusion scintigraphy may show unperfused lung regions.



224, 225 (224) Echocardiography revealed a large PTE (arrows) in the main PA of an 8-year-old male mixed breed dog with a 2-week history of exercise intolerance and fainting. CF Doppler showed flow (coded blue) up to and around the edge of the mass. RV dilation and hypertrophy and small LV size were also evident. Severe renal amyloidosis, hypoproteinemia, and low AT III were identified. (225) Abdominal ultrasonography indicated a thromboembolus in the distal aorta of a cat with cardiomyopathy. CF Doppler showed flow (blue) in the descending aorta (DA) just proximal to the obstruction. Flow (red) is also seen in the adjacent vena cava (VC). (Courtesy Dr K Miles.)



226, 227 Lateral (226) and DV (227) pulmonary angiograms from a 7-year-old female mixed breed dog with hypothyroidism, exercise intolerance, and postexercise cyanosis. A large thromboembolus (TE) obstructed flow into the left pulmonary artery (PA) and its branches. PAs serving the right cranial and ventral lung regions are perfused, but another TE obstructed flow to the right caudodorsal lung region. (Courtesy Dr E Riedesel.)

Nuclear scintigraphy can help evaluate perfusion in other obstructed regions as well^{35, 69, 70}. CT and magnetic resonance angiography could also have applicability in delineating TE disease in animals.

GENERAL PRINCIPLES OF THERAPY FOR TE DISEASE

The goals of therapy are 1) to stabilize the patient by supportive treatment as indicated; 2) to prevent extension of the thrombus and additional TE events; and 3) to reduce the size of existing clots and restore perfusion. Management strategies used for TE disease

are outlined in *Table 40*. Supportive care is given to improve and maintain adequate tissue perfusion, to minimize further endothelial damage and blood stasis, and to optimize organ function, as well as to allow time for collateral circulation development. Antiplatelet and anticoagulant therapies are used to reduce platelet aggregation and growth of existing thrombi. Although fibrinolytic therapy is used in some cases, dosage uncertainties, the need for intensive care, and the potential for serious complications limit its use. Correcting or managing underlying disease(s), as far as is possible, is also important.

Table 40 Management of thromboembolic disease.

- | | |
|---|--|
| <p>1) Initial diagnostic tests:</p> <ul style="list-style-type: none"> a) Complete physical examination and history. b) Hemogram, serum biochemical profile, urinalysis. c) Thoracic radiographs (rule out signs of CHF, other infiltrates, pleural effusion). d) Coagulation and D-dimer tests, if possible. <p>2) Initial management:</p> <ul style="list-style-type: none"> a) Analgesia as needed (especially for systemic arterial thromboembolism). b) Morphine: <ul style="list-style-type: none"> ■ Dog: 0.5–2.0 mg/kg IM, SC q3–5h; 0.05–0.4 mg/kg IV q3–5h. ■ Cat: 0.05–0.2 mg/kg IM, SC q3–4h (dysphoria occurs in some cats). c) Oxymorphone or hydromorphone: <ul style="list-style-type: none"> ■ Dog: 0.05–0.2 mg/kg IM, IV, SC q2–4h. ■ Cat: 0.05–0.2 mg/kg IM, IV, SC q2–4h. d) Butorphanol: <ul style="list-style-type: none"> ■ Dog: 0.2–2.0 mg/kg IM, IV, SC q1–4h. ■ Cat: 0.2–1.0 mg/kg IM (cranial lumbar area), IV, SC q1–4h. e) Buprenorphine: <ul style="list-style-type: none"> ■ Dog: 0.005–0.02 mg/kg IM, IV, SC q6–8h. ■ Cat: 0.005–0.02 mg/kg IM, IV, SC q6–8h; can give PO for transmucosal absorption. <p>3) Supportive care:</p> <ul style="list-style-type: none"> a) Supplemental O₂ if respiratory signs. b) IV fluid as indicated (and not in CHF). c) Monitor for and correct azotemia and electrolyte abnormalities. d) Manage CHF if present (see Chapters 16 and 21). e) External warming if persistent hypothermia after rehydration. f) Identify and manage underlying disease(s). g) Nutritional support if persistent anorexia. | <p>4) Further diagnostic testing:</p> <ul style="list-style-type: none"> a) Complete cardiac evaluation, including echocardiogram. b) Other tests as indicated (based on initial findings and cardiac exam) to rule out predisposing conditions (see <i>Table 38</i>, p. 148). <p>5) Prevent extension of existing clot and new TE events:</p> <ul style="list-style-type: none"> a) Antiplatelet therapy: <ul style="list-style-type: none"> ■ Aspirin: <ul style="list-style-type: none"> • Dog: 0.5 mg/kg PO q12h. • Cat: 81 mg/cat PO 2–3 times a week; low-dose, 5 mg/cat q72h (see text). ■ Clopidogrel: <ul style="list-style-type: none"> • Cat: ?18.75 mg/cat PO q24h (dose not well established). b) Anticoagulant therapy: <ul style="list-style-type: none"> ■ Sodium heparin: <ul style="list-style-type: none"> • Dog: 200–250 IU/kg IV, followed by 200–300 IU/kg SC q6–8h for 2–4 days or as needed. • Cat: same. ■ Dalteparin sodium: <ul style="list-style-type: none"> • Dog: 100–150 U/kg SC q(12)–24h (see text). • Cat: 100 U/kg SC q(12)–24h (see text). ■ Enoxaparin: <ul style="list-style-type: none"> • Dog: same as cat? • Cat: 1 mg/kg SC q12–24h (see text). <p>6) Thrombolytic therapy (pursue only with caution, see text):</p> <ul style="list-style-type: none"> a) Streptokinase: <ul style="list-style-type: none"> ■ Dog: 90,000 IU infused IV over 20–30 minutes, then at 45,000 IU/hour for 3 (or more) hours (see text). ■ Cat: same. b) rt-PA: <ul style="list-style-type: none"> ■ Dog: 1 mg/kg bolus IV q1h for 10 doses (see text). ■ Cat: 0.25–1 mg/kg/hour (up to a total of 1–10 mg/kg) IV (see text). |
|---|--|

Fluid therapy is used to expand vascular volume, support blood pressure, and correct electrolyte and acid/base abnormalities depending on individual patient needs. However, for animals with heart disease, and especially CHF, fluid therapy is given only with great caution, if at all. Specific therapy for heart diseases, CHF, and arrhythmias is provided as indicated (see Chapters 16, 17, and other pertinent chapters). In patients with acute respiratory signs, it is important to determine if CHF is the cause or if pain or pulmonary thromboembolism is responsible. Diuretic or vasodilator therapy could worsen perfusion in animals without CHF.

Acute arterial embolization is particularly painful, so analgesic therapy is important in such cases, especially for the first 24–36 hours (Table 40, p. 157). Acepromazine is not recommended for animals with arterial thromboembolism, despite its alpha-adrenergic receptor-blocking effects. Improved collateral flow has not been documented, and hypotension or exacerbation of dynamic ventricular outflow obstruction, particularly in cats with hypertrophic obstructive cardiomyopathy, are potential adverse effects. Propranolol is also avoided in cats with cardiomyopathy and arterial thromboembolism. Propranolol's nonselective beta-blocking effect may contribute to peripheral vasoconstriction from unopposed alpha-receptors, and the drug has no antithrombotic effects at clinical doses.

Loosely bandaging the affected limb(s) to prevent self-mutilation may be needed in some animals with aortic TE disease. Hypothermia that persists after circulating volume is restored can be addressed with external warming. Renal function and serum electrolyte concentrations are monitored daily or more frequently if fibrinolytic therapy is used. Continuous ECG monitoring during the first several days can help the clinician detect acute hyperkalemia associated with reperfusion (see Chapter 4, p. 64). Nutritional support may become important if anorexia persists after the initial treatment period. Supplemental O₂ improves hypoxemia related to V/Q mismatch and alveolar hypoventilation. This is especially important with pulmonary TE events but may be helpful with other TE disease also.

ANTIPLATELET THERAPY

Aspirin (acetylsalicylic acid) is used commonly to block platelet activation and aggregation in patients with, or at risk for, TE disease. Aspirin irreversibly inhibits cyclo-oxygenase, which reduces prostaglandin and thromboxane A₂ synthesis and, therefore, subsequent platelet aggregation, serotonin release, and vasoconstriction. Because platelets cannot synthesize additional cyclo-oxygenase, this reduction of procoagulant prostaglandins and thromboxane persists for the platelet's lifespan (7–10 days). Endothelial production of prostacyclin (also via the cyclo-

oxygenase pathway) is reduced by aspirin, but only transiently as endothelial cells synthesize additional cyclo-oxygenase. Aspirin's benefit may relate more to *in situ* thrombus formation; efficacy in acute arterial thromboembolism is unknown³⁵. Adverse effects of aspirin tend to be mild and uncommon, but the optimal dose is unclear. Cats lack an enzyme (glucaronyl transferase) needed to metabolize aspirin, so less frequent dosing is required compared with dogs. In cats with experimental aortic thrombosis, 10–25 mg/kg (1.25 grains/cat) given PO once every (2–)3 days inhibited platelet aggregation and improved collateral circulation²⁷. However, low-dose aspirin (5 mg/cat q72h) has also been used with fewer GI side-effects, although its efficacy in preventing TE events is unknown⁴¹. Aspirin therapy is started when the patient is able to take food and oral medications.

Other antiplatelet drugs are being studied. The thienopyridines inhibit ADP binding at platelet receptors and subsequent ADP-mediated platelet aggregation. Clopidogrel (18.75 mg/cat PO q24h) appears to have significant antiplatelet effects; dosing every other day may be possible⁷¹. The related drug ticlopidine caused a high rate of anorexia and vomiting at the effective antiplatelet dose in a preliminary study in cats⁷². Another group of antiplatelet agents block gp IIb/IIIa receptors, which interferes with binding of platelets and fibrinogen. A preliminary study showed that pretreatment with the gp IIb/IIIa receptor-blocker abciximab (0.25 mg/kg IV bolus, followed by 0.125 µg/kg/min CRI) plus aspirin was more effective than aspirin alone in reducing platelet aggregation and *in vivo* thrombosis in cats, although there was much intercat variability⁷³. Clinical studies are needed to verify whether the drug is useful for acute TE disease management. A similar drug, eptifibatide, caused unpredictable CV collapse and death in an experimental cat study and is not recommended⁷⁴. Other drugs have antiplatelet effects via calcium-blocking or phosphodiesterase-inhibiting mechanisms.

ANTICOAGULANT THERAPY

Heparin is indicated to limit extension of existing thrombi and prevent further TE episodes; it does not promote thrombolysis. Unfractionated heparin and a number of low-molecular-weight heparin (LMWH) products are available. Heparin's main anticoagulant effect is produced through AT III activation, which in turn inhibits factors IX, X, XI, and XII and thrombin⁷⁵. Unfractionated heparin binds thrombin as well as AT III. Heparin also stimulates release of tissue factor inhibitor from vascular sites, which helps reduce (extrinsic) coagulation cascade activation. Optimal dosing protocols for animals are not known. Unfractionated heparin is usually given as an initial IV bolus followed by SC injections (Table 40, p. 157). Heparin is not given IM because of the risk for

hemorrhage at the injection site. Heparin doses (from 75–500 U/kg) have been used with uncertain efficacy^{41, 76}. Monitoring the patient's activated partial thromboplastin time (aPTT) has been recommended, although results may not accurately predict serum heparin concentrations³⁵. Pretreatment coagulation testing is done for comparison, and the goal is to prolong the aPTT to 1.5–2.5 times baseline. Activated clotting time is not recommended to monitor heparin therapy. Hemorrhage is the major complication. Protamine sulfate can be used to counteract heparin-induced bleeding. Fresh frozen plasma may be needed to replenish AT III⁷⁶. Heparin treatment is continued until the patient is stable and has been on antiplatelet therapy for a few days³⁵.

LMWH products are a diverse group of depolymerized heparins that vary in size, structure, and pharmacokinetics. Their smaller size prevents simultaneous binding to thrombin and AT III. LMWHs have more effect against factor Xa by catalyzing AT III inhibition of factor Xa. They have minimal ability to inhibit thrombin, so are less likely to cause bleeding. LMWHs have greater bioavailability and a longer half-life than unfractionated heparin when given SC, because of lesser binding to plasma proteins as well as endothelial cells and macrophages⁷⁵. LMWHs do not markedly affect coagulation times, so monitoring aPTT is generally not necessary^{76, 77}. The LMWH effect can be monitored indirectly by anti-Xa activity⁷⁷. An anti-Xa activity level of 0.3–0.6 U/ml is considered sufficient in people. The most effective dosage for the various LMWHs is not clearly established in dogs and cats. Dalteparin sodium has been used (100–150 U/kg SC q[12–]24h), but some animals may need q8h dosing^{35, 77, 78}. Enoxaparin has been used (1 mg/kg SC q12[–]24[h]).

FIBRINOLYTIC THERAPY

Drugs used to promote clot lysis include streptokinase and human recombinant tissue plasminogen activator (rt-PA). These agents increase conversion of plasminogen to plasmin to facilitate fibrinolysis. Veterinary experience with these agents is quite limited. Although they effectively break down clots, complications related to reperfusion injury and hemorrhage, high mortality rate, cost of therapy, intensive care required, and lack of clearly established dosing protocols have prevented their widespread use^{19, 79, 80}. If used, this therapy is best instituted within 3–4 hours of vascular occlusion. An intensive care setting, including continuous serum potassium concentration (or ECG) monitoring to detect reperfusion-induced hyperkalemia, is recommended.

Streptokinase is a nonspecific plasminogen activator that promotes the breakdown of fibrin as well as fibrinogen. This leads to the degradation of fibrin within thrombi and clot lysis, but also potentially leads to systemic fibrinolysis, coagulopathy, and bleeding⁸¹. Streptokinase also degrades factors V and

VIII, and prothrombin. Although its half-life is about 30 minutes, fibrinogen depletion continues for much longer⁷⁹. Streptokinase has been used with variable success in a small number of dogs with arterial thromboembolism⁷⁹. The reported protocol for dogs and cats is 90,000 IU of streptokinase infused IV over 20–30 minutes, then at a rate of 45,000 IU/hour for 3 hours (up to 8–12 in dogs)³⁹. Dilution of 250,000 IU into 5 ml saline, then into 50 ml to yield 5,000 IU/ml for infusion with a syringe pump has been suggested for cats³⁵. Adverse effects are minor in some cases and bleeding may respond to discontinuing streptokinase⁸¹; however, there is potential for serious hemorrhage and the mortality rate in clinical cases is high^{39, 61, 81}. Acute hyperkalemia, secondary to thrombolysis and reperfusion injury, metabolic acidosis, bleeding, and other complications are thought to be responsible for causing death⁶¹. Streptokinase can increase platelet aggregability and induce platelet dysfunction. It is unclear if lower doses would be effective with fewer complications. Streptokinase combined with heparin therapy can increase the risk of hemorrhage, especially when coagulation times are increased. Streptokinase is potentially antigenic, as it is produced by beta-hemolytic streptococci. No survival benefit has been shown for streptokinase compared with 'conventional' (aspirin and heparin) treatment in cats³⁵.

rt-PA is a single-chain polypeptide serine protease with a higher specificity for fibrin within thrombi and a low affinity for circulating plasminogen. Although the risk of hemorrhage is less than with streptokinase, there is potential for serious bleeding as well as other side-effects. rt-PA is also potentially antigenic in animals because it is a human protein. Like streptokinase, rt-PA induces platelet dysfunction but not hyperaggregability. Experience with rt-PA is very limited and the optimal dosage is not known⁷⁹. A dose of 0.25–1 mg/kg/hour up to a total of 1–10 mg/kg IV was used in a small number of cats; although signs of reperfusion occurred, there was a high mortality rate⁸². The cause of death in most cats was attributed to reperfusion (hyperkalemia, metabolic acidosis) and hemorrhage, although CHF and arrhythmias were also involved⁸². In dogs, rt-PA has been used as 1 mg/kg boluses IV q1h for 10 doses, with IV fluid, other supportive therapy, and close monitoring⁸⁰. The half-life of t-PA is about 2–3 minutes in dogs, but effects persist longer because of binding to fibrin. The consequences of reperfusion injury present serious complications to thrombolytic therapy. The iron chelator deferoxamine mesylate has been used in an attempt to reduce oxidative damage from free radicals involving iron⁸⁰. Allopurinol has also been used but with uncertain results⁸¹.