Thrombosis is clot formation within a cardiac chamber or vascular lumen. Embolization results from dislodgement of a clot fragment or other foreign material into a vessel.

**Pathogenesis**

Thrombosis requires one or more of the following conditions: 1) local vessel or tissue injury, 2) circulatory stasis, and 3) altered blood coagulability. The cardiomyopathies predispose to LA or LV endothelial injury and blood stasis from atrial dilation and impaired function. Together, these factors predispose cats to thromboembolism. Moreover, collateral circulation is modulated by vasoactive substances (e.g., serotonin and others) released by the clot as well as by endothelial substrates. These chemicals decrease collateral circulation and exacerbate ischemia.

**Clinical Presentation**

Clinical consequences depend upon: 1) site of embolization, 2) severity and duration of occlusion, 3) degree of functional collateral circulation, 4) state of myocardial function, and 5) development of serious complications. CHF (dyspnea, tachypnea, anorexia) or syncope may occur concurrently. Clinical signs result from CHF and specific tissues or organs that are embolized (e.g., azotemia from renal infarction, bloody diarrhea from mesenteric infarction, posterior paresis from saddle embolus). More than 90% of affected cats present with lateralizing posterior paresis caused by a saddle clot at the distal aortic trifurcation. Clinical signs are characterized by the 4 P's: Paralysis; Pain; Pulselessness (lack of palpable femoral arterial pulses); and Polar (e.g., cold distal limbs and pads) extremities. Anterior tibial and gastrocnemius muscles become firm from ischemic myopathy by 10 to 12 hours post aortic embolization. These soften 24 to 72 hours later. Acutely affected cats drag their back legs by flexing and extending the hip but can not flex and extend the hock. Invariably, one leg is more severely effected. Nail beds are cyanotic and distal limbs are swollen. Embolus to a single brachial artery (usually right front leg) may cause monoparesis. When intermittent claudication occurs, arterial pulses may be palpated, foot pads feel warm (normal), and nail beds are not cyanotic. This frequently precedes severe subsequent thromboembolism. Less common sites include renal, mesenteric, pulmonary, coronary, and cerebral arteries (embolic “showers”). Most cats are clinically dehydrated and hypothermic.

**Diagnostic Workup**
Thoracic radiographs, ECG, echocardiogram, biochemical profile, and urinalysis provide the initial data base. Affected cats have creatine phosphokinase enzymes elevated shortly after embolization; BUN/creatinine, serum alanine aminotransferase and aspartate aminotransferase (SGOT) elevate by 12 hours of presentation, and peak by 36 hours post embolization. Hyperglycemia, mature leukocytosis, lymphopenia, and hypocalcemia may be present. Acute hyperkalemia can result from skeletal muscle reperfusion injury downstream from the embolus. Hypokalemia accompanies anorexia and diuretic therapy. Coagulation abnormalities may occur. Echocardiography characterized heart structure and function and detects intracardiac and vascular thrombi. Spontaneous echo contrast (“smoke”) in the LA or LV is associated with blood stasis, and is a harbinger for increased thromboembolic risk. Scintigraphy, MRI, high definition CT, and angiography may have clinical application in some cases.

Treatment Goals

Therapies are directed to 1) manage concomitant CHF or serious arrhythmias (especially associated with hyperkalemia), 2) patient support (nutritional supplementation, correct hypothermia, prevent self mutilation), 3) acute pain amelioration, 4) measures to limit thrombus growth/ formation, 5) critical monitoring, and 6) prevention of repeated events.

Management of Heart Failure

Therapies may include furosemide, supplemental O₂ administration, ACE inhibitors, inotropes or inodilator’s, nutraceuticals, arrhythmia control, mechanical fluid removal, and other measures as needed.

Patient Support

Measures include correction of dehydration, acid/base/electrolyte alterations, hypothermia, and nutrition. Aspirin during the first 48 hours relieves muscle pain from ischemic myopathy. For anorexia, placement of a nasoesophageal feeding tube provides alimentation, particularly during the first week of therapy. Maintain hydration, electrolyte balance, and nutritional support. To prevent self mutilation (excessive licking or chewing) of distal limbs devitalized by an occlusive saddle embolus which is common during convalescence, apply a loose-fitting bandage, stockinet, or other barrier. Avoid indwelling venous catheters into legs devitalized by embolus.

Pain Management

Pain is usually most intenst within the first 24 hours of thromboembolism and appears to subside rapidly thereafter. One must take care to avoid excessive medications that would blunt the ability to clinically assess
physical status, mentation, and appetite. Some commonly used agents include butorphanol (0.2-0.4mg/kg SQ q6-8 hours), hydromorphone (0.05-0.1mg/kg SQ), or fentanyl patches.

Thrombolytic Therapy

Streptokinase
(or urokinase) acts by generating the nonspecific proteolytic enzyme plasmin through conversion of the proenzyme plasminogen. This causes a generalized lytic state (beware of bleeding complications). Dose- 90,000IU over 20 minutes followed by 45,000 IU CRI for 2-24h.

Recombinant tissue-type plasminogen activator (p-ta)
Has a lower affinity for circulating plasminogen and does not induce systemic fibrinolysis. It binds to fibrin within the thrombus, converts entrapped plasminogen to plasmin, and initiates local fibrinolysis. Severe hyperkalemia occurs in half of treated cats. Dose (cats with thromboembolism)- 0.25 to 1.0 mg/kg/hr IV; total IV dose, 1-10 mg/kg.

Anticoagulant Therapy

Heparin
Binds to lysine sites on plasma antithrombin III, enhancing its ability to neutralize thrombin and activated factors XII, XI, X, IX, preventing activation of the coagulation process. Efficacy has never been established. Bleeding is a major complication of unfractionated heparins. Compared with unfractionated heparins, low molecular weight heparins (LMWH) provide greater safety and bioavailability, longer plasma half life, and can be given as a fixed, daily, subcutaneous dose. Dose- Unfractionated heparin: initial IV dose (100-200 IU/kg), then 50-100 IU/kg subcutaneously q6 to 8 hours; adjust dose to prolong PT 1.5 - 2 times pretreatment values. LMWH: Fragmin (100 U/kg q12-24hr SQ) or enoxaparine (1mg/kg q12-24hr SQ).

Coumarin
Impairs hepatic vitamin K metabolism, a vitamin necessary for synthesis of procoagulants factors II or prothrombin, VII, IX, and X. Dose- warfarin initial oral daily dosage (0.25 to 0.5 mg/cat) is adjusted to prolong the PT time to twice the normal value; alternatively, it is adjusted by the international normalization ratio (INR) to maintain a value of 2.0 to 3.0. as follows: INR=[(Cat Prothrombin Time) Control Prothrombin Time]. The laboratory should provide an index of sensitivity of the thromboplastin reagent called an international sensitivity index (ISI). Some overlap warfarin and heparin therapies several days (in man, the level of protein C, a naturally occurring antithrombotic protein, is decreased when coumarin treatment is initiated, creating a thrombogenic potential; overlapping heparin therapy theoretically counteracts this transient
procoagulant effect before other vitamin K-dependant factors (factors II, IX, and X) are affected by warfarin.

**Critical Monitoring**

Hyperkalemia can occur acutely as a result of re-perfusion injury. Continuous ECG monitoring is valuable during the first 3 days of hospitalization. Periodic evaluation of BUN and electrolytes during this interval are useful.

Prevention of Repeated Thrombosis Drugs intended to prevent thrombosis include antiplatelet agents and anticoagulants.

**Antiplatelet Agents**

Antiplatelet therapy may be considered when there is severe left atrial enlargement, when spontaneous echo contrast is evident in the LA or LAV, or when cats have have had previous thromboembolic episodes.

**Aspirin**

Is a commonly use to drug administered for its theoretical effect to limit further thromboembolic events. Aspirin induces a functional platelet defect by irreversibly inactivating (through acetylation) cyclo-oxygenase. In the platelet, cyclo-oxygenase converts arachidonic acid to thromboxane A2 which induces platelet activation (through release of platelet adenosine diphosphate), and which stimulates vasoconstriction [in the vascular wall cyclo-oxygenase converts arachidonic acid to prostacycline which inhibits platelet aggregation and induces vasodilatation]. Aspirin-induced acetylation of the cyclo-oxygenase enzyme is irreversible. It persists for the life of the platelet (7 to 10 days), reducing platelet aggregation and release response to various agonists. Dose in cats - 25 mg/kg, or 1/4 of a 5-grain tablet q48 - 72h PO effectively inhibits platelet function for 3 to 5 days, and is relatively safe. Investigators could not demonstrate a survival difference between high dose (>40mg/cat) versus low dose (5mg/cat) aspirin, although morbidity was reduced using the low dose. There is no evidence that aspirin prevents first time or recurrent thromboembolism. Adverse effects include anorexia and emesis.

**Clopidogrel (Plavix)**

Is a new potent antiplatelet agent currently under evaluation to prevent or treat arterial thromboembolism. It is an irreversible antagonist of platelet adenosine diphosphate receptor ADP_{2Y12}. It inhibits primary and secondary platelet aggregation, impairs platelet-release reaction, decreases release of proaggregating and vasoconstrictive agents (eg, serotonin and ADP), and prolongs mucosal bleeding time. Anti-platelet effects occur by three days post-administration. Dosage is one quarter of a 75 mg tabletop q 24 hrs. adverse effects can occur in 10% of cases and include anorexia and emesis, and diarrhea.
Anticoagulants

These agents interfere with one or more coagulation factors and disrupt the coagulation cascade.

Low Molecular Weight Heparin

Several agents have become available, though optimal doses are uncertain. Two particular agents, enoxaparin (Lovenox) and dalteparin (Fragmin), have received the most attention. Both drugs are expensive but appear to have a far greater safety margin than unfractionated heparin. Fragmin (100 U/kg q 12-24hrs SQ) or enoxaparine (1mg/kg q 12-24 hrs SQ) have been used relatively safely. The dose of fragmin, while safe, may be low for maximal efficacy, and merits further study (administration rates of every 6 to 8 hours are generally impractical).

Coumarin (see above).

This has largely fallen into disfavor. Beware potential bleeding side effects.

Modulation of Hypercoagulability

Hyperhomocysteinemia is a risk factor for thromboembolism in people and may occur in some cats. Folic acid and B12 supplementation might be beneficial in cats with hyperhomocysteinemia or recovering from thromboembolism.

Indicators of a Relatively Favorable Prognosis-Arterial TE

Favorable signs: 1. resolution of CHF and/or control of serious arrhythmias, 2. Lack of LA/LV thrombi or spontaneous echo contrast, 3. Reestablished appetite, 4. Relatively normal BUN/creatinine/ electrolytes, 5. Return of limb viability/function (e.g., loss of swelling; return of normal limb temperature; return of motor ability), 6. Return of femoral arterial pulses and pink nail beds, 7. Lack of self mutilation.

Indicators of a Grave Prognosis- Arterial TE

Grave prognosis: 1. Refractory CHF or development of malignant arrhythmias, 2. Acute hyperkalemia, 3. Declining limb viability (e.g., progressive hardening of gastrocnemius and anterior tibial muscle group; failure of these muscles to soften 48-72 hours after presentation; distal limb necrosis), 4. Multiorgan/multisystemic embolization (CNS signs, bloody diarrhea, acute renal failure), 5. History of previous embolic episodes, 6. Presence or development of LA/LV thrombus or spontaneous echo contrast, 7. Rising BUN/creatinine, 8. Disseminated intravascular coagulation, 9. Unresponsive hypothermia, 10. Severe LA enlargement with arrhythmia and myocardial failure.