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PATHOPHYSIOLOGY OF THROMBOEMBOLISM (TE)

Alterations in blood flow are one component leading to TE. Abnormalities in blood flow are common in patients with cardiac disease. Stasis of blood allows increased contact between platelets and coagulation factors with the endothelium, thus promoting coagulation. Turbulent flow may cause a denuding endothelial injury and also promote coagulation.

Under normal conditions, the endothelium has an anticoagulant function. An abnormal endothelium is another promoter of hypercoagulability. The presence of atherosclerotic plaques is a well-known risk factor for TE in humans and hypothyroid dogs have been shown to have TE secondary to atherosclerosis.

Hypercoagulability is the third factor in the development of TE. Changes in coagulation have been identified in dogs and cats with TE. In canine Cushing’s disease, which often results in pulmonary thromboembolism, an increase in coagulation factors II, V, VII, IX, X, XII and fibrinogen coupled with a decrease in the natural anticoagulant antithrombin III were identified in dogs with Cushing’s disease compared to normal control dogs. Several coagulation abnormalities have been identified in cats with aortic thromboembolism. Platelets from some cardiomyopathic cats have been shown to be hyperaggregable in response to ADP in an in vitro system. Coagulation profiles in cases of FATE are consistent with DIC. Cats with aortic thromboembolism have also been shown to have elevated blood levels of an amino acid homocysteine when compared to cats with cardiomyopathy, but not aortic thromboembolism. Hyperhomocysteinemia is a risk factor for thromboembolic disease in humans.

### Inherited Hypercoagulable States

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Clinical disorder</th>
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<tbody>
<tr>
<td>Protein C deficiency</td>
<td>Hypercoagulable thoroughbred colt</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Not in veterinary patients</td>
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<tr>
<td>Factor V Leiden</td>
<td>Not in veterinary patients</td>
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</tbody>
</table>

### Acquired Hypercoagulable States

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Clinical disorder</th>
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<tbody>
<tr>
<td>Antithrombin III deficiency</td>
<td>Nephrotic syndrome</td>
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<tr>
<td>Immune mediated hemolytic anemia</td>
<td>Canine pulmonary thromboembolism</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Feline aortic thromboembolism</td>
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<tr>
<td>Thrombocytosis</td>
<td>Feline bronchoaveolar carcinoma</td>
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<tr>
<td>Neoplasia</td>
<td>PTE in lymphoma, carcinoma, sarcoma</td>
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<tr>
<td>Hyperthyroidism</td>
<td>Atherosclerosis</td>
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<tr>
<td>Hyperadrenocorticism</td>
<td>PTE</td>
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<tr>
<td>Antiphospholipid syndrome</td>
<td>Canine IMHA, nephrotic syndrome, PTE</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
<td>Secondary to enterotoxin?</td>
</tr>
</tbody>
</table>

### VENOUS THROMBOEMBOLISM

Thrombi formed in the venous circulation under low blood flow conditions are composed of fibrin and erythrocytes. The most common site of venous thromboembolism in animals is pulmonary arteries which are actually more like veins than arteries. Deep venous thrombosis, a major risk factor for pulmonary thromboembolism in over 90% of cases in humans is not a risk factor in animals and the causes of PTE in animals varies widely. Pulmonary TE occurs secondary to several hypercoaguable states: nephrotic syndrome, immune mediated hemolytic anemia, hyperadrenocorticism, thrombocytosis, cardiac disease, sepsis, DIC, heartworm disease and neoplasia. The presence of multiple concurrent disorders in a patient with TE is common. For example, 47% of cats with necropsy confirmed pulmonary thromboembolism had multiple concurrent disorders predisposing to TE.

### DIAGNOSIS

The diagnosis of TE is made based on a combination of clinical signs, laboratory parameters and a site specific evaluation for the presence of TE. The underlying disease present in the patient will dictate the scope of the medical evaluation.

### CLINICAL SIGNS AND SITE SPECIFIC DIAGNOSTIC EVALUATION

#### Feline Aortic Thromboembolism (FATE)

The hallmark clinical signs of FATE are pain, paresis and pulselessness of the hind limbs. Typically these clinical findings coupled with a diagnosis of congestive heart failure on radiographs or significant cardiac disease on echocardiography are all that is required for a diagnosis of FATE. Thromboembolism occasionally occurs in the right forelimb, but not the left. Nonselective angiography can be used to confirm thromboembolic disease, but is risky for the patient due to their cardiopulmonary instability.

Aortic thromboembolism also occurs in canine patients. There are frequently emboli in other vascular systems such as the pulmonary and portal systems. Clinical signs responsible for presentation to a veterinary hospital are similar to those in FATE. Unlike cats, dogs with aortic TE do not predominantly have cardiac disease and suffer from disorders such as renal disease, hypercortisolism, cancer, hypothyroid induced atherosclerosis, all of which are known causes of hypercoagulability.

#### Pulmonary Thromboembolism (PTE)

Clinical signs of PTE vary widely and range from none to acute death. Underdigation is frequent in PTE since simple, readily available diagnostic tests are not available to
clinicians and a lack of awareness of the disorder exists since it occurs infrequently. PTE should be suspected when a patient exhibits an acute onset of dyspnea, hypoxemia and hypocapnia. Tachycardia is also common. A split second heart sound can sometimes be ausculated as a consequence of pulmonary hypertension. When right ventricular failure occurs, distended jugular veins, jugular pulses and ascites can be found. Placement of an intravenous catheter has been associated with PTE in dogs with IMHA, but not in other causes of PTE. Cats with PTE commonly have underlying cardiac disease, neoplasia, corticosteroid administration and DIC. Clinical signs are nonspecific and include lethargy, anorexia and weight loss. Dyspnea was seen in less than half the cats studied.

Thoracic radiography is rarely diagnostic for PTE, but still provides important clinical information. In dogs with PTE, signs of congestive heart failure or cardiomegaly are common. Regional hypoperfusion of the pulmonary parenchyma results in a hypolucent area in the lung fields. The other common finding in dogs with necropsy confirmed PTE was a patchy alveolar infiltrates. Pruning and asymmetric filling of vessels are suggestive of PTE. Pleural effusion is also commonly seen. Radiographic findings in cats with necropsy confirmed PTE are abnormalities in pulmonary vessels, pleural effusion and peripheral pulmonary parenchyma consolidation.

EKG may show cor pulmonale and echocardiography may demonstrate a thrombus in the right heart in cases of PTE.

Ventilation-perfusion scanning is a frequently used diagnostic technique in humans with PTE. The availability in veterinary medicine is limited, but its utility has been shown in dogs with PTE. Angiography, both nonselective and selective are other techniques for the diagnosis of PTE which require skill and equipment to perform and interpret and may carry an increased risk of complications in the critically ill PTE patient.

LABORATORY PARAMETERS

Blood Gas Analysis

Normal results are possible on routine blood gas analysis in pets with pulmonary thromboembolism if only a small amount of pulmonary parenchyma is affected. When hypoxemia occurs, a reflex tachypnea results and hypocarbia and metabolic alkalosis ensue. Severe hypoxemia will result in metabolic acidosis. An increased alveolar-arterial oxygen difference is frequently present.

Coagulation Testing

A routine coagulation profile will often be abnormal in dogs and cats with TE since DIC is a common abnormality predisposing to TE.

D-Dimer

When plasmin acts on fibrin, one of the resulting subunits is a dimer of the D fragment. Various test methodologies available to measure D dimer have been evaluated in healthy dogs and dogs with DIC. Latex agglutination D dimer test was most sensitive and specific in dogs. Comparison of titers cannot be made between the various tests methods. Although D dimer is more specific for the diagnosis of DIC, this test can also be positive in cases of pulmonary thromboembolism, deep venous thrombosis, liver disease and neoplastic disease. High titers (>1000 ng/ml) are consistent with thromboembolism in the dog.

TREATMENT

Supportive Care

Strict cage rest and oxygen therapy are intended to decrease the demand on the compromised cardiopulmonary system. Fluid therapy has been advocated to maintain hydration and facilitate blood flow. A significant risk of volume overload exists if right heart function is compromised. Dextrose containing fluids should be avoided as they may cause endothelial damage, promoting thrombosis.

Thrombolysis

Streptokinase binds plasminogen and the complex transforms other plasminogen molecules into plasmin. Plasmin binds to fibrin and causes thrombolysis. Streptokinase binds both free and clot associated plasminogen. It also degrades factors V, VIII and prothrombin which can result in a massive systemic coagulation defect.

Streptokinase has been used to treat aortic thromboembolism in cats with varying degrees of success. In one study of 46 cats, 15 were discharged from the hospital following streptokinase therapy. Median survival was 51 days. Single limb ATE may carry a better prognosis. Cats with azotemia at the time of admission to the hospital for streptokinase therapy were less likely to survive than those with normal values and more likely to develop hyperkalemia. Cats with hypothermia were less likely to survive than normothermic cats, but those who did survive rectal temperature normalized in 12 hours following hospitalization. Eleven of the cats developed clinical hemorrhage after streptokinase therapy. In 3 cats, hemorrhage was significant enough to require transfusion. The data on conservative management (treatment of heart failure and coumadin or aspirin) of FATE suggests a hospital discharge rate of 28%, which may not be different that in cats treated with thrombolytic agents.

Hemodialysis catheter associated right atrial thrombosis has been reported in cats and dogs. Urokinase and streptokinase have been used in the lumen of the catheter to lyse thrombin in or around the catheter in an attempt to prevent migration to the right atrium or pulmonary vasculature. Short term (1-3 hours) continuous infusions of streptokinase have been used to treat hemodialysis catheter associated thrombi as well.

One recommended dose of streptokinase for dogs and cats with TE is 90,000 U IV over 20-30 minutes followed by a maintenance infusion of 45,000 U for 7-12 hours. Infusions may be repeated over a total of 3 days. Monitoring for coagulation abnormalities and hemorrhage is essential. Hypotension and allergic reactions are seen in humans treated with streptokinase secondary to anti-streptokinase antibodies. Occurrence of antibodies have not be documented in cats or dogs. Reperfusion injury following thrombolysis has been reported in approximately 35% of cats treated with streptokinase for FATE. The resulting hyperkalemia and metabolic acidosis is frequently fatal.

Tissue plasminogen activator (t-PA) is a serine protease produced by recombinant DNA technology. A complex forms between t-PA and fibrin and that complex preferentially activates thrombus associated plasminogen resulting in rapid fibrinolysis. Fibrinolysis results in an increase in plasma FDP.

Like all medications that interfere with coagulation, t-PA has significant side effects. Bleeding is a number one
ACUTE ANTICOAGULATION

Heparin is the mainstay of acute anticoagulation and is typically used with thrombolytic agents since those agents do not prevent additional clots from forming and anticoagulants such as heparin and coumadin do not dissolve clots. Coumadin therapy is initiated after adequate heparinization has been achieved.

Heparin is not an anticoagulant, but functions as a cofactor with antithrombin III. This complex exerts its effect by neutralizing factor X and thrombin. Heparin must be administered by injection because gastrointestinal enzymes inactivate it. Heparin is administered to prolong the baseline aPTT 1.5-3.0 times. The aPTT or ACT does not correlate well with heparin levels in cats and dogs and measurement of plasma heparin levels may be more useful. Doses of heparin required to achieve adequate heparin levels in cats with TE ranged from 175 U/kg q 6hr to 475 U/kg q 8hr SQ. In normal dogs the dose of heparin required to achieve adequate heparin concentrations was 250 U/kg q 6hr SQ. The most common side effect of heparin therapy is hemorrhage, which can be fatal.

Low molecular weight (LMW) heparin is produced from unfractionated heparin. Its anticoagulant effect is limited to blocking the activity of factor X. Because LMW has a lower antithrombin effect than unfractionated heparin, LMW heparin does not have an effect on the PT or PTT. Measurement of factor X activity is used to assess the effect of LMW heparin. One advantage of LMW heparin is that it has a lower risk of hemorrhage than conventional heparin therapy. The effective dose determined in normal beagles was 150 U LMW heparin SQ q 8 hr.

CHRONIC ANTICOAGULATION

Coumadin or warfarin sodium functions as an anticoagulant because it interrupts the activation of coagulation factors II, VII, IX and X as well as natural anticoagulants protein C and S. It is used in humans who have experienced deep venous thrombosis in an attempt to prevent further clot formation. It has also been used in cats with FATE. Because coumadin inhibits the anticoagulants protein C and S before it inhibits factors II, VII, IX and X, it induces a transient hypercoagulable effect and the standard recommendation in human medicine is to use heparin for 2 days prior to initiating coumadin therapy and continuing heparin for 2 days following coumadin initiation.

A loading dose of 6 mg for a dog weighing 25-30 kg has been recommended in dogs and should be decreased to a maintenance rate of 3 mg after 2 days. A dose of 0.25-1.0 mg per cat has been recommended. The dose is then adjusted to attain adequate anticoagulation. More than one recommended target level of anticoagulation has been recommended. Early recommendations were to maintain the PT 1.5 times the precoumadin value. More recent recommendations suggest attaining an international normalized ratio (INR) of 2-3. INR is calculated by the formula (patient PT/control PT)^ISI. The ISI is a value specific to the tissue thromboplastin used in the laboratory measuring the PT. Coumadin is continued on a long term basis to prevent recurrent TE. Studies documenting optimal dose and efficacy in dogs and cats are lacking and the optimal duration of coumadin therapy is unknown.

The use of coumadin is not without risks. The major risk is fatal hemorrhage, which occurs acutely and unexpectedly. Pets maintained on coumadin should live indoors and be well supervised to prevent trauma and to monitor for hemorrhage. Periodic measurement of the PT should be done to ensure adequate dosing without overdosage. Coumadin interacts with many drug and addition of medications to the treatment regimen of a pet on coumadin should be done cautiously as certain drugs will raise the activity of coumadin and predispose patients to bleeding. Some of these drugs are: phenylbutazone, metronidazole, trimethoprim sulfa and second and third generation cephalosporins. Barbiturates will decrease coumadin anticoagulant effect.

Aspirin is successful in preventing thrombotic strokes in humans. A small, unpublished trial of aspirin in normal cats was unable to demonstrate prolongation of buccal mucosal bleeding time as an indicator of platelet inhibition. Clinically, aspirin at a dose of 25 mg/kg q 3d has also been unsuccessfully used as an inhibitor of platelet function in cats undergoing hemodialysis and with FATE, suggesting other prophylactic treatments should be investigated.

concern. The half life of t-PA in dogs is 2-3 minutes; consequently, if bleeding occurs, stopping the infusion will result in the drug being cleared from the system in 5-10 minutes. Because t-PA causes rapid thrombolysis, the risk of reperfusion syndrome is significant; 50% of cats with FATE died acutely during t-PA therapy. Death was attributed to hyperkalemia, severe anemia and renal hemorrhage.

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