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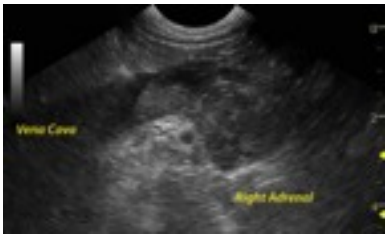
THROMBOEMBOLIC DISEASE (TED) – 4 PAGES



Thrombosis is clot formation within a vascular or cardiac lumen, while embolization occurs when a foreign body or clot fragment lodges within a lumen. Thromboembolic disease can be arterial (ATE) or venous (vena cava, portal vein). The most prominent site of arterial embolization is the distal *aortic trifurcation* (saddle thrombus) causing hind limb ischemia, myalgia and contraction, cold limbs and cyanotic nail beds. However, other frequent sites include *renal* parenchyma causing azotemia and hematuria due to infarction, *coronary arteries* inducing myocardial ischemia and frequently inducing arrhythmias, *mesenteric arteries* causing gastrointestinal symptoms and bacterial translocation, *cerebral vessels* inducing cns symptoms +/- sudden death, caval syndrome inducing front body edema, *portal vein thrombosis* due to pancreatitis, hepatitis, neoplasia, or peritonitis, *hepatic* ischemia signified by a rapid ALT rise, *muscle* ischemia with ↑ CPK, lactate, and potassium, as well as *brachial arteries* causing front leg lameness and ischemia. *Microcirculation* thrombosis and reperfusion injury is also a complicating factor. This is a painful disease causing acute abdomen when viscera is involved and self-mutilation when extremities are afflicted. According to Dr Alwood (ACVIM 2008) Studies report a survival rate of approximately 40% with treatment (with approximately 35% being euthanized without attempted treatment). If cats survive the initial embolic event, re-embolization represents a common cause of future morbidity and mortality

Causes of TED from an **arterial** standpoint include ***congestive heart failure*** (frequently in cats, occasionally in dogs) subsequent to endocardial damage and blood stasis, ***protein losing diseases*** (nephropathy, enteropathy), ***hypertension***, ***neoplasia***, ***hyperadrenocorticism***, ***SIRS*** (systemic inflammatory response syndrome), and ***atherosclerosis*** due to hypothyroidism. **Pulmonary thromboembolism** (**PTE** → V/Q mismatch and hypoxemia) occurs as a complication to immune mediated hemolytic anemia (***IMHA***), disseminated intravascular coagulation (***DIC***), ***renal*** disease, ***pancreatitis***, ***neoplasia***, ***sepsis***, ***heartworm***, ***hyperadrenocorticism***, and ***hypothyroidism***.

The **pathophysiology** of TED is complex but essential to diagnose and treat adequately. Here is an attempt at simplifying the phenomenon:

A) **Vessel endothelial lesion** → vWF(8)+ fibrinogen → platelet activation/aggregation

B) Fibrinogen formation depends on:

1) ***Intrinsic pathway (aPTT):*** factors 12,11,9
2) ***Extrinsic pathway (PT):*** Tissue factor, 7

3) ***Common pathway (TT):*** 10,1, 2 end result = thrombin → <u>fibrinogen</u> →insoluble fibrin

C) **<u>Anticoagulation Team</u>** (**SAC-3T**): **S** protein, **Antithrombin III** (responsible for 80% of activity), **C** protein, **T**FPI-1, **T**hrombomodulin, **t-**PA (from endothelium) → plasminogen → plasmin → fibrinolysis.

D) **Clot/thrombus breakdown markers**: Fibrinogen → FDPs, D-Dimers

E) Virchow's Triad of prothrombotic state:

1) ***Altered endothelial structure/function***: endothelin → activation of coag. cascade; activation of platelet aggregation by ADP, Fibrinogen, Thromboxane A2.
2) ***Blood stasis***
3) ***Hypercoagulable state:*** **<u>↓ATIII</u>** (PLN, PLE, liver dysfunction)(normally AT3 + heparin binds thrombin blocking F9-12), ↓ t-PA, ↓urokinase, ↓ plasminogen, ↓ Protein C, ↓ S, ↑PAI-1, ↑ platelet aggregation.

F) **Thrombus** → ischemia/inflammation, effect is size dependent. Clots are firmly attached to Vessel walls as opposed to post mortem clots that are not attached.

Thrombus destiny:

1) Fibrinolysis and dissolution
2) Organization & recanalization
3) Clot propagation
4) Dislodgement and embolization

The core problem/marker of a hypercoagulative state is the loss/lack of production of ATIII. Glomerular disease and protein losing nephropathy (PLN) (immune complex/amyloid) dumps ATIII in the urine due to its small size (65,000 Daltons). This also occurs in protein losing enteropathy (PLE) but during PLN other coagulation factors are lost, whereas PLE lesions tend not to dump the larger proteins as easily as PLN does. Moreover, diseases that cause PLN increase fibrinogen and thromboxane levels (reasoning for aspirin tx in PLN) further predisposing the patient to TED. **<u>ATIII levels</u>** are essential in evaluating a hypercoagulable state. **50-75% ↓ in ATIII level = MODERATE TED risk; 75% ↓ = SEVERE TED risk.**

Recent studies compiled by Tobias and Smith have demonstrated that the vast majority (97%) of cats present with signs of ATE as the first indication of disease, and most had no prior history of diagnosed cardiac disease. Prodromal signs were rare or absent, however 16 % of these patients do display vomiting before the onset of acute limb paralysis. Predominant **symptoms** include pain related vocalizing, licking affected limbs, lameness, lateralizing paresis, firm and contracted (10-12 hrs) then soft (24-72 hrs) and cold limbs, cyanotic nail beds, and organ specific signs (hematuria, diarrhea, respiratory distress, seizures). Marked tachypnea is often noted, and patients may display open-mouthed breathing. It should be noted that this does not correlate to the presence of congestive heart failure; therefore thoracic radiographs are imperative in furthering the diagnosis. Respiratory signs relate not only to pain, but also to metabolic aberrations such as acid-base imbalances. Azotemia from renal ischemia, acute hyperkalemia from muscular reperfusion followed by hypokalemia from diuresis and anorexia, ALT and AST elevations (max 36 hrs post embolus), elevated CPK, hyperglycemia and leukocytosis are the prominent serum biochemistry and hematological parameters.

Smith et al. (ACVIM 2002) recently demonstrated a body temperature correlation to **<u>prognosis in cats</u>**. Patients demonstrated a ***73% survival rate with a body temp 100°F, 50% at 99°F, and 25% at 97°F.*** Moreover, 68% survival rate with 1 limb affected and 38% with 2+ limbs affected was also demonstrated. Better prognosis was also found with front limb infliction as opposed to hind limb due to less tissue necrosis due to ischemia.

<u>Diagnosis</u>

Multiple modalities are necessary to confirm the diagnosis of thromboembolic disease. Although it is most commonly associated with cardiac disease, the second most common correlating condition is *neoplasia.* Of the types of neoplasia seen to relate to thromboembolic disease, Pulmonary Carcinoma is the most common, and can be recognized both radiographically and by postmortem evaluation of tumor cells present within the thrombus. Other neoplasia associated with ATE includes hepatocellular carcinoma, squamous cell carcinoma and vaccine-site associated sarcoma (Smith et al 2003). It should be noted that occasionally no cause is identified despite thorough medical evaluation.

Further research into **thromboelastography (TEG)** derived from human studies may allow for earlier detection of hypercoagulable states but is not widely available at the moment. For now clinical signs and traditional coagulation panel alterations are utilized to arrive at the presumptive diagnosis.

Echocardiography is essential to assess cardiac function and the presence of "smoke" (indicator of blood stasis) and clots in chambers as well as myocardial infarcts and extent of cardiac remodeling should CHF be the underlying cause. Otherwise, history, clinical assessment, blood work, urinalysis, viral assessment, radiographs, and ECG can all be helpful.

Diagnosis of TED can be achieved by symptoms, cbc/chem. ultrasound of major vessels (portal vein, cvc, aortic trifurcation…) and heart, as well as an elaborate coagulation profile:

1) Platelet aggregation (followed by thrombocytopenia as DIC approaches), **short PT/aPTT times** (followed by long times when factors are exhausted and the patient approaches DIC),

2) ↑ D-dimer, Fbrinogen, FDP, PAI-1,

3) ↓ ATIII, protein C, S, t-PA are consistent with a hypercoagulable state

Therapy is aimed at **battling Virchow's triad**, **support for hypothermia**, ensuring proper nutrition, correcting hemodynamically significant arrhythmias (>20-30/min), managing CHF (if present) (nitro, lasix, oxygen), **IV fluid balance and reestablishing microcirculation**, **pain management** (pain prolongs recovery), and **clot prevention and dissolution**. **Anticoagulant therapy** by heparin is controversial with variable dosages and outcomes reported. ***Unfractionated heparin*** given SQ at concentrations of 0.35-0.70 U/ml (most efficacious in human trials) was advocated for **dogs** at **250 U/kg SQ q6hr** and at **200 U/kg SQ q 8hrs for cats** by Smith et al. at the University of Minnesota. The first dose of heparin may be given IV in cases of shock. ACT of 15-20 seconds over normal and APTT increase by a factor of 1.5-2.5 are used as target assessments for effective therapy. Higher cost low molecular weight heparins (LMWH) are less associated with bleeding in experimental human and animal studies. A starting dose of 100 U/kg SQ q12-24hrs has been suggested by the same group. ***Aspirin*** theoretically is administered inducing deficient platelet aggregation to prevent further TED episodes at **5 mg/cat every 72 hours** once the patient is eating.

Aspirin can be compounded to suit this small dosage. Heparin may then be discontinued slowly over 2-3 days once the patient is hemodynamically stable and taking oral aspirin. Slow discontinuation is recommended as human studies indicate a hypercoagulable state can occur with rapid discontinuation. Note that the use of *coumadin displays no improved effect on survival when compared to aspirin*, but does carry a high risk of fatal hemorrhage; therefore it is currently not a recommended drug of choice unless nothing else is available. ***Folic acid*** and ***B12*** supplementation has also been advocated in experimental studies. The anitplatelet aggregate **Clopidogrel (Plavix)** (18.75 mg/cat from 75 mg tablet at 4$/tablet = 30$/month) has recently been reported to be a favorable **replacement for aspirin** to increase collateral circulation and reduction of clinical signs when administered at the time of symptoms as compared to placebo in limited trials. In addition, use of **analgesia**, ideally opioids such as Buprenorphine (0.01-0.02 mg/kg sublingual) or Fentanyl (25 micrograms/hr transdermal) should be instituted. The FAT CAT study is underway blindly examining the efficacy of aspirin (81 mg Q72hr) versus Clopidrel (18.75 mg/ Q24hrs) in cats but the study is still underway. The good news is that side effects at these dosages for both medications have been negligible.

For open checkbook clients and to generate a good debate between clinicians regarding cost/utility, **thrombolytic** therapy may be utilized with ***streptokinase*** at 90,000 IU over 20 minutes followed by 45000 IU CRI for 2-24hrs. Streptokinase generates the proteolytic enzyme plasmin to drain the rent money by the minute ($125 per 250 000IU vial), and is only associated with a 33% survival. The 401K can be tapped with ***Tissue Plasminogen Activator (t-PA)*** catalyzing plasminogen to plasmin through recombinant technology. Suggested dose by **Smith** et al. at U of Minn. is 1mg/kg IV q1hr for 10 doses in the **dog**. **Pion** et al. suggest 0.25-1.0mg/kg/hr/iv (total dose 1-10mg/kg) for the **cat**. **Bliss& Harvey** recommend (in the **dog**) ***0.2-0.4 mg/kg slow bolus over 1 minute every 60 minutes until thrombus dissolves (monitored by ultrasound) up to 4 treatments***. Hemorrhage at catheter sites or elsewhere is the dose limiting phenomenon. The advantage of tPA over streptokinase is quicker action, less anaphylaxis, less hemorrhage, a %50 survival rate (addressed in one published study to date), and $1100 (per vial) less for Jimmy's college fund. Studies are underway regarding calcium channel blockers, phosphodiesterase inhibitors, ADP binding inhibitors, and GP IIa/IIIb receptor blockers as anti-platelet medications. There is some promising research using the drugs deltaparin (Fragmin) and clopidogrel (Plavix), however it has not been established whether these drugs will decrease the frequency of recurrence or severity of ATE in cats. ***Don't use this patient to teach phlebotomy techniques to your fledgling technician!*** **Studies repeatedly demonstrate little advantage to the utilization of t-PA and streptokinase as opposed to unfractionated heparin and general support.**

Prognosis for survival is fair, and improves under the following conditions: 1. Single limb affected with retained motor function, 2. rectal temperature above 98.9 and normal heart rate, 3. normal serum phosphorus concentrations. A recent study (Hogan et al acvim 2006) reports a survival rate of 68-93% in single limb infarctions vs. 15-36% survival in bilateral pelvic involvement. Reperfusion injury tends to be more severe when bilateral limbs

are involved **Recurrence needs to be expected**, and average time to recurrence may be 6 months however this varies widely. The Hogan study reports a 1-year recurrence rate of 25050% if an antithrombotic drug is utilized. However, it is more common that patients succumb to progressive heart disease. Prognosis is ***favorable*** if arrhythmias are controlled, lack of cardiac smoke or clots, positive appetite, stabilized or decreasing renal values and electrolytes, normalization of coagulation parameters, return of organ function and viability, positive femoral pulses, pink nails, and lack of financial disease. Prognosis is ***poor*** if the opposites are true and supported by persistent hypothermia, respiratory distress, and organ failure. Happy sleepless nights and say a prayer for our painful friends!

This text was compiled from, but not limited to, ACVIM 2001, 2002, 2003, 2006, 2008 VIN, Vet. Clin. Sm. Anim. And Compendium.

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