Thromboembolism and Antithrombotic Therapy

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Thrombosis: disease state, abnormal blood clots present in body
Thromboembolism: thrombi have broken free from the site at which they formed → embolize downstream location

Thrombosis

Virchow’s Triad: composed of the following 3 factors. Any one (or multiple) can predispose an individual to thrombosis
- Endothelial injury
  - Surgery
  - Trauma
  - Thermal injury
- Circulatory stasis
  - Polycythemia
  - Intracardiac distension
  - Low cardiac output
- Altered coagulability
  - DIC
  - Depletion of antithrombotic factors

Mechanisms of Thrombosis
- Platelet Adhesion: typically, in area of damaged arterial endothelium or on artificial surface (i.e. implants, prosthetics)
- Platelet aggregation: due to rise in platelet intracellular calcium as a response to collagen exposure, vascular injury, thrombin, serotonin, thromboxane A2
  - Can initiate thromboxane synthesis and platelet activation through arachidonic acid release
- Activation of clotting mechanisms → generation of thrombin after activation of platelet membrane
  - Thrombin enhances activation of platelet membrane & plays a key role in coagulation
- Platelet and vascular contraction: during activation, serotonin (and other vasoactive agents) are released from platelets, promoting formation of a hemostatic plug
  - If endothelium is intact – serotonin will promote vasodilation
  - If endothelium is damaged – serotonin will promote vasoconstriction
  - Other vasoconstrictors include inflammatory mediators (i.e. leukotrienes released from white cells, tissue macrophages) → vascular stasis
- **Fibrinolysis**: breakdown of fibrin (via plasminogen → plasmin) is initiated at the same time as clotting mechanisms are activated
  - Plasmin = enzyme responsible for hydrolysis of fibrin

**Systemic Thrombosis/Thromboembolism**

**Feline arterial (systemic) thrombosis/thromboembolism**

- **Associations**
  - Feline aortic thromboembolism (ATE/FATE): common, devastating sequelae to feline cardiomyopathy
  - Intracardiac thrombosis with subsequent embolization – major cause
  - Neoplasia (esp. pulmonary carcinoma) – maybe 5% of cases

- **Pathophysiology**
  - Intracardiac thrombi formation may relate to pathologic changes → exposure of thrombogenic surfaces
  - Chamber dilation, valvular regurgitation, partial outflow obstruction in cases of extreme hypertrophy → alterations in blood flow
  - DIC and other coagulopathies are reported in cats with ATE
  - Feline platelets = more reactive than other species
  - Interrupted blood flow past the distal aorta → ischemic myopathy & neuropathy
  - Humoral agents released from the blood clot (thromboxane, endothelin, serotonin, etc.) play an important role in the pathophysiology

- **Clinical presentation**
  - Distal aortic thromboembolism (aka “Saddle Thrombus”) occurs in >90% of cases. Common, especially in cats with known myocardial disease
    - **Clinical signs**
      - Posterior paresis/paralysis
      - Loss of femoral pulses
      - Cool posterior extremities
      - Cyanotic/pale rear-limb paw pads
      - Cyanotic nail beds that do not bleed
      - Firm, painful gastrocnemius muscles
      - Vocalization (presumably due to pain)
    - **Simultaneous onset of acute CHF is common**
      - Weakness
      - Dyspnea
      - Pulmonary edema
    - **Sudden death due to coronary thromboembolism/thrombus occluding LVOT is possible**
    - **Diagnosis**
      - Can be first presenting evidence of cardiovascular disease (heart disease was previously undetected)
• Usually clinical signs are clear enough to make a diagnosis

• Differentials
  - IVDD
  - FCE
  - Spinal lymphoma
  - Trauma!!

• Cardiomyopathy signs may be present
  - Jugular distension
  - Murmur or arrhythmia
  - Gallop sounds

• CHF signs may be present
  - Dyspnea
  - Tachypnea
  - Weakness
  - Pulmonary crackles
  - Cyanosis

• Further workup
  - Thoracic radiographs
  - ECG
  - NT-proBNP
  - Echo

• Nonspecific angiography of aorta is also diagnostic – can localize thrombus and evaluate collateral circulation (is usually NOT necessary/indicated though)

• Ancillary testing may indicate -
  - Muscle injury → enzyme release: Increased CPK, ALT, AST, LDH
  - Stress: leukogram, hypoglycemia
  - DIC
  - Hypoxemia

### Therapy

• Goals: supportive treatment of acute syndrome, relief of CHF, attempt to remove thrombi, establish collateral circulation

• If CHF present
  - Oxygen
  - Diuretics
  - +/- ACE inhibitors or pimobendan
  - AVOID propranolol and probably other beta-blocker (low cardiac output altered vasomotor tone may reduce blood flow to tissues at risk)

• Analgesics (i.e. fentanyl, buprenorphine, or other narcotics)

• Anticoagulation with heparin to prevent additional thrombosis
- Heparin can also activate plasminogen \(\rightarrow\) enhanced thrombolysis (unproven but suggested)
- Antiplatelet drugs in **acute** management

- Surgical embolectomy = high mortality rate. Reperfusion injury and decompensated condition of the patient at time of surgery. If done should likely be done early, within the first few hours of ATE

- Vasodilators (i.e. acepromazine or hydralazine) to induce collateral circulation
  - MAP = a KEY determinant of collateral flow!
  - These drugs can drop BP, and might reduce blood flow or limit opening up of collateral vessels
  - Efficacy not established

- Thrombolytic therapy (streptokinase, urokinase, or tissue plasminogen activator)
  - Common consequences of clot lysis include reperfusion injury (hyperkalemia and metabolic acidosis) and bleeding consequences can also happen with thrombolytics
  - Goal: early return of blood flow to tissues with compromised perfusion that are NOT yet necrotic
  - If thrombolytics are used – should be started within 12 hours, ideally within 1 hour of onset of clinical signs

- **Prevention**
  - Optimal therapy = cure underlying disease (i.e. DCM due to taurine deficiency)
  - Aspirin, heparin, LMWH, clopidogrel, Coumadin (warfarin)

- **Prognosis**
  - Devastating complication of feline myocardial disease
  - Median survival time = 61 d. – 11 mo. (if cat is not euthanized at time of presentation)
  - Repeated thrombosis is possible
  - Most common cause of subsequent death in treated cats = CHF

- Other clinical syndromes due to occlusion of –
  - Mesenteric artery
  - Renal artery
  - Hepatic artery
  - Splenic artery
  - Ovarian artery
  - Forelimb arteries (right forelimb may be more common than left forelimb; these often get better and cats usually will walk again)
Canine systemic thrombosis/thromboembolism

- Much less common in dogs
- Many cases are NOT of cardiogenic origin (rather due to systemic disease, develop in situ)
- Associations
  - Vascular disease
    - Arteriosclerosis
    - Vasculitis
    - Trauma
    - IV injection of an irritating/hypertonic substance
    - Neoplastic invasion
    - Bacterial endocarditis
  - Vascular stasis
    - Hypovolemia
    - Shock
    - Cardiac failure
    - Vascular compression
  - Hypercoagulability
    - Antithrombin III deficiency
    - Platelet disorders
    - Dehydration
    - Hyperviscosity
    - IMHA
    - Being a greyhound
  - Thrombotic events from sources in the veins (if ASD), cardiac valves/chambers
  - Introduction of foreign substances by trauma or iatrogenically
- Clinical presentation
  - Signs dependent on site of thrombosis, degree/duration of occlusion, and composition of thrombus
  - Some thrombi will NOT → clinical disease
  - In the dog – saddle thrombus can → posterior weakness/lameness ONLY (especially if partial or intermittent obstruction occurs; common when the thrombus develops in situ in the distal aorta)
  - Femoral pulses = weak to absent, hind limbs may be cool
  - Front limb thrombosis = LESS dramatic, unilateral
  - Endocarditis may → septic embolization of 1+ organ beds (kidneys, gut, liver, spleen, heart, spinal cord, brain)
    - Clinical signs are dependent upon which site is affected
- Diagnosis
  - Radiographs of thorax/abdomen may suggest underlying disease
    - Dirofilariasis
    - Neoplasia
    - Cardiomegaly
Radiopaque foreign object
- Laboratory tests may suggest systemic disease
  - Elevated hepatic/pancreatic enzymes
  - Azotemia
  - Proteinuria
  - Hematuria
  - Leukocytosis
  - Hypoproteinemia
  - Microfilaremia
- Echo or abdominal ultrasound may be useful, based upon clinical signs
  - i.e. visible thrombus in abdominal aorta or iliac arteries
- Angiography or CT of selected area could reveal lesions
- Treatment: newer anticoagulants and Coumadin MAY be most effective!
  - Correct underlying abnormality
  - Supportive therapy
    - Rehydration
    - Analgesics
  - Prevent thrombus enlargement
    - Heparin
    - Antiplatelet drugs
    - Coumadin or newer drugs like direct acting Factor anti-Xa inhibitors like rivaroxaban or apixaban may be the best approach!!
  - Thrombolytic therapy
  - Surgical embolectomy
- Prognosis is dependent upon underlying disease (usually guarded). Thrombosis recurrence is common

Pulmonary Thrombosis/Thromboembolism

- Associations
  - Dirofilariasis: heartworm is a well-documented cause of PTE
  - Nephrotic syndrome: proteinuria → loss of antithrombin
  - Autoimmune hemolytic anemia: many patients will succumb to PTE
  - Other causes of antithrombin deficiency
    - Hyperadrenocorticism
    - Hypothyroidism
    - Pancreatitis
    - DIC
    - Etc.
  - Deep vein thrombosis (esp. in people): thrombi embolize to the pulmonary circulation
- Clinical Presentation
  - Signs are nonspecific, mimic other cardiorespiratory diseases
Acute onset of dyspnea common***

- Diagnosis = difficult at best
  - Acutely ill patient, could succumb from diagnostic testing alone
  - Suggestive findings
    - Arterial hypoxemia (PaO2 < 80 mmHg)
    - Thoracic radiographs are NOT always suggestive of cardiorespiratory disease
      - Sometimes normal
      - Changes that MAY be seen include –
        - Pulmonary vessel size change
        - Lobar lucency
        - Small vessels in area that is affected by thrombus
        - RVE
        - Pulmonary infiltrates
        - Pleural effusion
  - Pulmonary angiography: injection of contrast may demonstrate filling defect in pulmonary artery OR a complete interruption of blood flow
    - Negative study = significant disease is NOT present
  - CT scan of thorax with contrast: currently the best diagnostic test for PTE. Can see the thrombus in the PA.

- Prevention: prophylactic therapy may be initiated if patient is predisposed to PTE (sepsis, neoplasia, prolonged recumbency, IMHA). Treat underlying disease/condition

- Treatment
  - Support with oxygen
  - Fluid support to maintain circulation
  - Heparin or LMWH
  - Antiplatelet drugs
  - Coumadin
  - +/- Newer anticoagulants like direct acting Factor anti-Xa inhibitors (rivaroxaban or apixaban), Thrombolytics in acute setting

- Prognosis: poor – guarded in severely ill patients requiring oxygen supplementation

**Therapeutic Modalities for Thrombotic Diseases**

*Antiplatelet therapy:* reduces platelet aggregation → altered thrombus formation. Prevention of vasoconstriction due to platelet release of substances (i.e. serotonin, PDGF)

- Aspirin (acetylsalicylic acid): blocks PG synthesis by irreversibly acetylating & inactivating COX.
  - The production of thromboxane is blocked
  - Prostacyclin synthesis (a vasodilator) is blocked simultaneously → potential consequences of vasoconstriction & vascular stasis
BUT – endothelial cells are able to produce prostacyclin within hours, so the antithrombotic effects predominate. Platelet inhibition = low doses
  - Used in cats with significant myocardial disease to prevent thromboembolic events
  - Side effects
    - GI distress
    - Potential for gastric ulceration/bleeding
  - Clopidogrel (Plavix): good antiplatelet therapy in most animals, less SE than aspirin

Anticoagulation therapy: prevent thrombus formation
  - Heparin (IV or SC): enhances the activity of antithrombin
    - Antithrombin = protease inhibitor found in normal plasma
    - Heparin-antithrombin complex will neutralize proteases formed during coagulation – i.e. thrombin (IIa)
    - Increases plasminogen activator → activation of fibrinolysis
    - Must give parenteral via IV CRI or frequent SC injections
    - Can use prior to starting a long-term therapy (i.e. warfarin) to initiate anticoagulation
    - Therapeutic dosage monitored via PTT levels
      - PTT increase 1.5X baseline or normal indicates the drug is working
    - Bleeding is a significant complication
    - Protamine sulfate = antidote
      - High side effect potential in dogs
  - Low-Molecular weight heparin: prevent thrombus formation
    - i.e. enoxaparin (Lovenox) and dalteparin (Fragmin)
    - Require SC injection of small volumes
    - Longer half-life than unfractioned heparin – only give 1-3X daily
    - Much more expensive than unfractioned heparin
    - Used for more chronic use (mo. – yr.)
    - Low MW fragments have a HIGH affinity for antithrombin III, inhibit factor X strongly, do NOT inhibit thrombin, and do NOT have a strong tendency to cause hemorrhage
  - Coumadin (Warfarin derivative): vitamin K-dependent anticoagulant
    - Prothrombin = coagulation factor dependent on vitamin K for synthesis
    - Can give orally, long-term prevention of thromboembolism
    - Inhibit the synthesis of coagulation factors – are NOT immediately active in vivo
    - Also decreases levels of protein C (antithrombotic agent) – so give with heparin for immediate therapy and to avoid an initial hypercoagulable state
    - PT is suggestive of drug efficacy – 2X increase from baseline. Monitor every 3-5 d. for 4-6 wk., then every few weeks while administering this drug
  - Newer anticoagulants: i.e. Rivaroxaban or apixaban – these drugs will likely replace Coumadin in the future
Thrombolytic therapy: treatment of acute thrombosis and arterial occlusion

- Dependent on presence of circulating plasminogen
- Plasmin = protease which cleaves circulating proteins, including fibrinogen, plasminogen, and also plasmin.
  - Fibrinogen degradation → fibrin degradation products (FDPs), which are anticoagulants
  - Excess concentration of plasmin due to generalized fibrinolysis activation (systemic fibrinolytic state) can → accumulation of plasmin, excessive fibrinolysis, bleeding
- Streptokinase: produced by Beta-hemolytic Streptococcus
  - Must be given in animals with plasminogen or plasmin BEFORE it can activate plasmin
  - Currently unavailable
- Urokinase: enzyme produced by human kidney cells, cleaves plasminogen
  - Theoretical advantages: preferential affinity for tissue plasminogen
  - Administered systemically or locally (intra-arterially)
  - Currently unavailable
- Tissue plasminogen activator (t-PA): an intrinsic (nonantigenic) protein of all mammals
  - Low affinity for circulating plasminogen – BIG advantage because it may allow systemic administration without induction of a systemic fibrinolytic state (will ONLY act on clots theoretically, but bleeding side effects are still possible)
  - Complications in cats with ATE
    - “Reperfusion syndrome” with hyperkalemia and metabolic acidosis
    - Bleeding complications
    - Neurologic signs
- Surgery (embolectomy): not common in vet med
  - Is not stated to improve clinical outcome
  - One recent case report