# 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

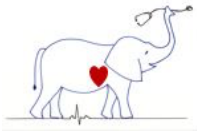
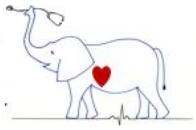
**Thrombosis**

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 <u>hemostatic plug</u>
    - 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

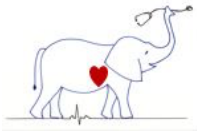
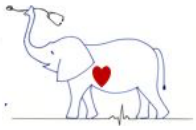



- Fibrinolysis: breakdown of fibrin (via plasminogen → plasmin) is initiated at the same time as clotting mechanisms are activated
    - Plasmin = enzyme responsible for hydrolysis of fibrin

**Systemic Thrombosis/Thromboembolism**

*Feline arterial (systemic) thrombosis/thromboembolism*

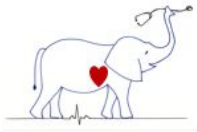
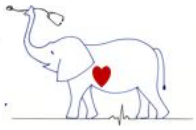
- Associations
    - Feline aortic thromboembolism (ATE/FATE): common, devastating sequelae to feline cardiomyopathy
    - Intracardiac thrombosis with subsequent embolization – major cause
    - Neoplasia (esp. pulmonary carcinoma) – maybe 5% of cases
- Pathophysiology
    - Intracardiac thrombi formation 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 = <u>more reactive</u> 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)

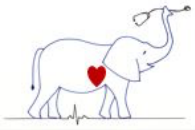
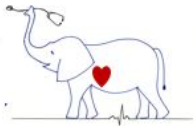
- Usually clinical signs are clear enough to make a diagnosis
- Differentials
    - IVDD
    - FCE
    - Spinal lymphoma
    - Trauma!!
- Cardiomyopathy signs may be present
    - Jugular distension
    - Murmur or arrhythmia
    - Gallop sounds
- CHF signs may be present
    - Dyspnea
    - Tachypnea
    - 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

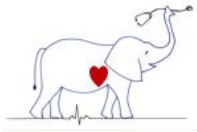
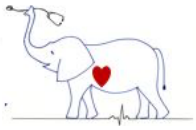



        - Heparin can also activate plasminogen → enhanced thrombolysis (unproven but suggested)
        - Antiplatelet drugs in <u>acute</u> management
    - Surgical embolectomy = high mortality rate. Reperfusion injury and decompensated condition of the patient at time of surgery. If done should likely be 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*

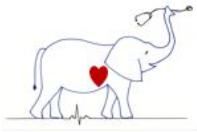
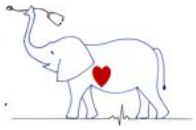
- Much less common in dogs
- Many cases are NOT of cardiogenic origin (rather due to systemic disease, develop in situ)
- Associations
    - Vascular disease
        - Arteriosclerosis
        - Vasculitis
        - Trauma
        - IV injection of an irritating/hypertonic substance
        - Neoplastic 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 <u>common</u>

**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

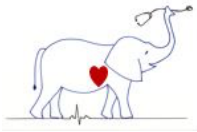
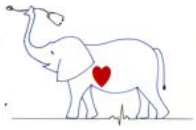



    - Acute onset of dyspnea common***
- Diagnosis = difficult at best
    - Acutely ill patient, could succumb from diagnostic testing alone
    - Suggestive findings
        - Arterial hypoxemia (PaO2 < 80 mmHg)
        - Thoracic radiographs are NOT always suggestive of cardiorespiratory disease
            - 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 <u>best diagnostic test for PTE.</u> 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**

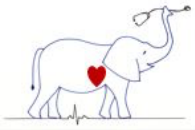
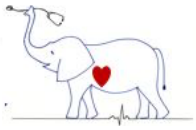
*Antiplatelet therapy:* reduces platelet aggregation → altered thrombus formation. Prevention of vasoconstriction due to platelet release of substances (i.e. serotonin, PDGF)

- 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 <u>prevent</u> 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. <u>thrombin</u> (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 <u>synthesis</u> 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 <u>avoid an initial hypercoagulable state</u>
    - 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