Feline Arterial Thromboembolism

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Background

Thromboembolism	Thrombosis
• Endothelial surfaces are normal. • Associated with blood stasis. • Common in veterinary patients.	• Damaged endothelial surfaces. • Associated with high shear flow within narrowed blood vessel. • Rare occurrence.

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Normal Hemostasis

- Primary Hemostasis
  - Exposure of subendothelial collagen with platelet adhesion
  - Platelet activiation & aggregation
    - Vasoconstrictive amines
    - Procoagulant factors
- Secondary Hemostasis
  - Activation of coagulation cascade

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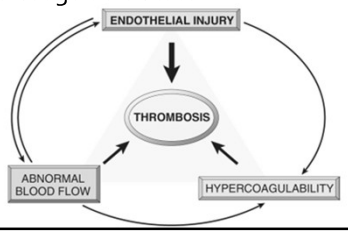
Virchow's Triad

- Endothelial Injury
- Blood Stasis
- Hypercoagulable State



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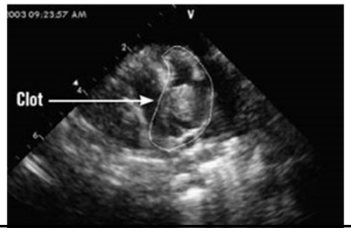
Endothelial Injury

- Dilated left atrium (cats with HCM)
- Damaged aortic valve (dog with SAS)
- Tumor invasion of arterial tree



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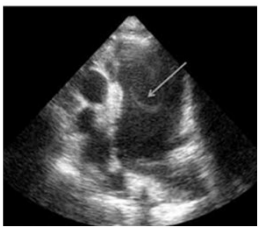
Blood Stasis

- Dilated cardiac chambers
- Restricted blood flow from tumor growth



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Procoagulable State

- Hard to define in veterinary medicine
- Known Human Conditions:
  - Inherited procoagulant disorders
    - IIa, Va, VIIIa
  - Inherited antithrombotic factor disorders
    - Antithrombin III (AT III), protein C, protein S deficiencies.
  - Platelet hypersensitivity, increased homocysteine, lipoprotein(a), plasminogen activator inhibitor (PAI-1), and thrombin-activatable fibronlysis inhibitor (TAFI)

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Veterinary Perspective

- Known risk factors/conditions:
  - Increased platelet hypersensitivity
  - Decreased AT III and protein C activity (including loss)
  - Increases in factors II, V, VII, VIII, IX, X, XII and fibronogen.
- Early thrombus is platelet rich, but becomes more fibrin-rich as thrombus grows.
- As thrombus grows, will become more lamellated.
  - Risk factor for fragmentation and multifocal clots.

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Clinical Signs

- Dependent on location of embolization.
  - Kidney
  - Cerebral
  - Mesentery
  - Spleen
  - Aortic Bifurcation

Sudden death is possible

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Aortic Thromboembolism

- Aortic trifucation ("saddle thrombus")
  - Loss of blood flow to pelvic limbs with ischemic neuromyopathy (INM).
  - Presentation
    - 70-75% Bilateral Pelvic
    - 10-15% Unilateral Pelvic
    - Rarely Unilateral Forelimb
      - Usually right forelimb

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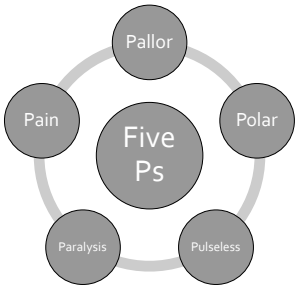
ER Diagnosis ('Five-P Rule')



Immediate Diagnostics/Confirmation
Low Glucose and/or High Lactate in affected limb

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Clinical Note

- Cardiomyopathy reported at etiology in 90% of FATE cases
  - Median Age at Diagnosis: 8-12 years old
  - Only 20% have known history of underlying cardiomyopathy
    - *Translation*:
      - *in 80% of FATE cases, the ATE event is the first manifestation*

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Clinical Signs

- Typically develop acutely and can worsen, but are usually stagnant.
- Typical improvement in days to weeks.
- Major factor for ischemic neuromyopathy:
  - Vasoactive substances (serotonin)
- Experimental Model of Aortic Ligation:
  - Flow maintained through vertebral and epaxial collateral circulation.

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Serotonin

- Released from activated platelets
- Research model:
  - Serotonin in isolated aortic segment results in loss of collateral network and signs of INM.
  - Pretreatment with steotonin antagonists prevent these changes.

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Associated Clinical Signs

- Dependent upon underlying diseases
  - **Sepsis**:
    - Fever, Depression, Dyspnea
  - **IMHA**:
    - Depression, Tachypnea, Pallor
  - **Nephrotic Syndrome**:
    - Depression, Ascites, Peripheral Edema
  - **Hyperadrenocorticism**:
    - Tachypnea, Weakness, PU/PD
  - **Cardiac Disease**:
    - *44-66% present with CHF.*

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Treatment

- Prevention is key!
- Reduce Thrombus Formation
- Improve Blood Flow (Thrombolytics)
- Improve Collateral Flow
- Pain Management
- Concurrent Disease Management

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Reduce Thrombus Formation

- **Unfractionated Heparin**
  - Pentasaccharide that binds to AT III
  - Inhibits IIa, Xa, IXa, XIIa.
  - Inhibits thrombin-catalyzed activation of factors V and VIII.
  - In humans, has been shown to exhibit antiplatelet effects by inhibiting thrombin-induced platelet aggregation and binding to von Willebfand factor.
- Doses: 250-375 IU/kg IV initially, then 150-250 IU/kg SQ q6-8h
- Must utilize baseline PT/PTT and monitor thereafter

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Reduce Thrombus Formation

- **Low Molecular Weight Heparin**
  - Daltaperin (Fragmin)
    - 100 IU/kg SQ q12-24h
  - Enoxaparin (Lovenox)
    - 1.0-1.5 mg/kg SQ q12-24h
  - Clinical trials in veterinary medicine lacking
  - More popular to use as prevention.

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Improve Blood Flow

- **Themobolytic Therapy**
  - Surgical extraction
  - Medical dissolution
    - Streptokinase
    - Urokinase
    - Tissue Plasminogen Activator (t-PA)

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Streptokinase

- Combines with plasminogen to form activator complex, converting plasminogen to plasmin (proteolytic compound)
- Plasmin degrades fibrin, fibrinogen, plasminogen, coagulation factors, and streptokinase.
- Streptokinase-plasminogen complex converts circulating and fibrin-bound plasminogen – considered nonspecific activator of plasmin.
- Produced by streptococci
  - Antigenic stimulation is possible

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Streptokinase Studies

- 8 Cats
  - All developed respiratory distress and sudden death during maintenance phase
- 46 Cats
  - Approximately 50% had return of femoral pulses within 24 hours of SK therapy.
  - Motor function returned in 30% (80% of those within 24 hours)
  - Adverse Effects
    - Spontaneous bleeding 24% (transfusions required in 27%), Reperfusion Injury 40%
    - Overall Survival Rate: 33%

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Urokinase

- Similar activity to streptokinase, but more fibrin specific.
- High-molecular-weight (HMW) and low-molecular-weight (LMW) available commercially
- LMW binds with greater affinitiy to lysine-plasminogen form of plasminogen, which is more concentrated in thrombi.
- 12 Cat Study
  - 56% regained motor function, 27% regained pulses
  - No bleeding reported, 25% developed reperfusion injury
  - Survival Rate: 42%
- Dogs – small study, 100% mortality rate

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Tissue Plasminogen Activator (t-PA)

- t-PA is primary activator of plasmin in vivo.
- Does not bind readily to circulating plasminogen and therefore does not induce a systemic proteolytic state.
- High affinity for fibrin – causing fibrin-specific conversion of plasminogen to plasmin.
- Feline Study (6 Cats):
  - Minor hemorrhage (50%), fever (33%), reperfusion injury (33%)
  - Acute Survival: 50% (death due to reperfusion and shock)

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Improve Collateral Flow

- Acepromazine unsuccessful
  - Common anectodal advice in VetMed – NOT advisable
- Serotonin and Thromboxane appear to be significant factors
  - Inhibitors of platelets or these compounds beneficial
- Current focus of ongoing research

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Flow Effects of Aspirin and Plavix

- Aspirin Study
  - Reduced thromboxane secretion from activated platelets, but dose was very high and salicylate levels in this study associated with toxicity
- Clopidogrel (Plavix) Study
  - Reduced serotonin from activated platelets in cats
  - Some studies suggest reduced thromboxane.

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Pain Management

- Narcotic analgesia usually required
  - Methadone
  - Fentnyl CRI
  - Buprenorphine
  - Gabapentin

Preferred Approach: Give injections cranial to diaphragm as perfusion is compromised!

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Survival Data

- Initial Cardiogenic Thromboembolism Survival:
  - Similar in conservative management (35-39%) or thrombolytic (33%)
  - Single-limb embolization cases do better (68-93%) than cat with bilateral pelivc limb infarction (15-36%).
- Nonsurvival associated with:
  - Hypothermia, Reduced Heart Rate, Absent Motor Function
- Median Survival Time: 51-345 days
  - FATCAT Study – Prolonged time with Plavix use.

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Prevention

- Cats with left atrial enlargement are at increased risk
  - Criteria:
    - LA Direct Measure: >17 mm
    - LA/Ao: >2.0
    - Spontaneous Echocardiographic Contrast ("smoke") in Left Atrium or Left Auricle

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CURATIVE Guidelines Available

Special Article

Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 2—Defining rational therapeutic usage

Robert Goggs BVSc, DACVECC, DECVECC, PhD ✉ Lenore Bacek DVM, MS, DACVECC

JOURNAL OF Veterinary Emergency AND Critical Care

JVECC Vol 29, Issue 1. 17 JAN 2019

While cardiac disease is discussed, this special edition covers antithrombotics globally

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Aspirin

- Irreversible acetylation of platelet cyclooxygenase, preventing formation of Thromboxane A_2.
  - Thromboxane A_2
    - Potent vasoconstrictive and proaggregating effects.
- Modest and indirect antiplatelet agent
  - Inhibits secondary platelet aggregation.
- Dose: 20.5 – 81 mg PO q72h
  - Lower doses show unchanged efficacy with less GI side effects.

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Clopidogrel (Plavix)

- Second-generation thienopyridine
- Induces specific and irreversible ADP_{2Y12} receptor antagonism
  - Direct antiplatelet drug – primary and secondary platelet aggregation is blocked against multiple agonists
  - More potent effects than Aspirin
- Glycoprotein IIb/IIIa complex inhibited, which reduces binding of fibronogen and vWF.

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Plavix

- Vasomodulating effects noted *in vivo* and *in vitro*.
- Gastrointestinal ulceration not reported.
- Maximal antiplatelet effects noted within 3 days, lost by 7 days when stopped.
- No reported veterinary cases of agranulocytosis or thrombotic thrombocytopenic purpura (TTP) as seen in some humans.
- Dose: 18.75 mg PO q24h.

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Anticoagulant Agents

- **Warfarin**
  - Vitamin K-dependent factor inhibition (II, VII, IX, X) and protein C and S
  - Significant medication interactions
  - Careful monitoring of coagulation factors required
- **Low-Molecular Weight Heparain**
  - Binds AT III, inhibiting factor Xa with greatly reduced inhibition of IIa
  - Reduced anti-IIa activity causes negligible effect on aPTT
  - To monitor, must measure anti-Xa through chromogenic assay

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Synthetic Xa Inhibitors

- Inhibits Xa through potentiation of AT III.
  - Exclusive binding to AT III
  - Excellent bioavailability with SQ administration
- No known effect on factor IIa or platelet function
  - No effects on routine coagulation tests
  - Can monitor through anti-Xa activity
- Available Drugs:
  - Fondaparinux
  - Idraparinux
  - Rivaroxaban
  - Apixaban

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Rivaroxaban

- Factor Xa inhibitor
  - Typical Feline Dosage: 2.5 mg/cat q24h
  - Often combined with Clopidogrel 18.75 mg PO q24h
- SUPER-CAT Study
  - Clopidogrel vs. Rivaroxaban (similar to FATCAT)
    - ACVIM Forum 2023
    - No statistical difference between recurrence rates

	Median Recurrence Rate	Median Time to Death
Clopidogrel	663 Days	335 Days
Rivaroxaban	513 Days	296 Days

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Questions?

OLYMPIC VETERINARY CARDIOLOGY

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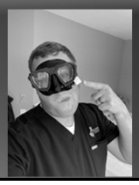

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