# Pulmonary Thromboembolism: Pathophysiology and Diagnosis

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# Outline

- Pathophysiology
- Predisposing Factors
  - Associated Disease Processes
- Presentation
  - Clinical Signs
  - Physical Examination
- Diagnostics
  - Minimum Database
  - Diagnostic Imaging
  - Ancillary Tests
- Human Scoring Systems
- Summary

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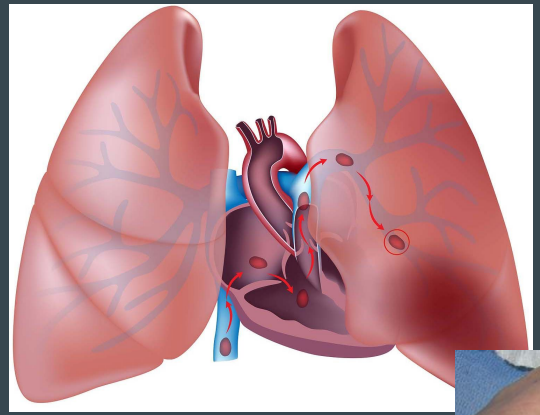
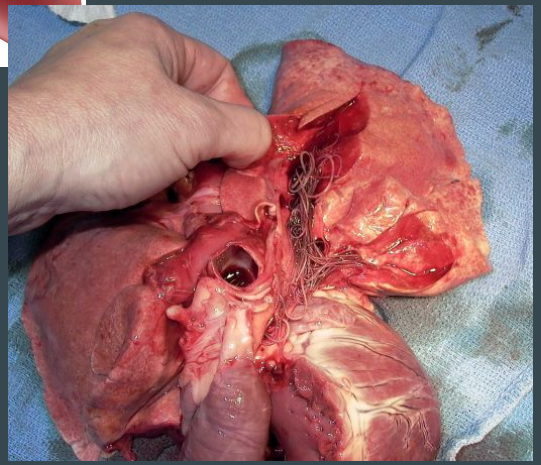
# Pathophysiology of Pulmonary Thromboembolism

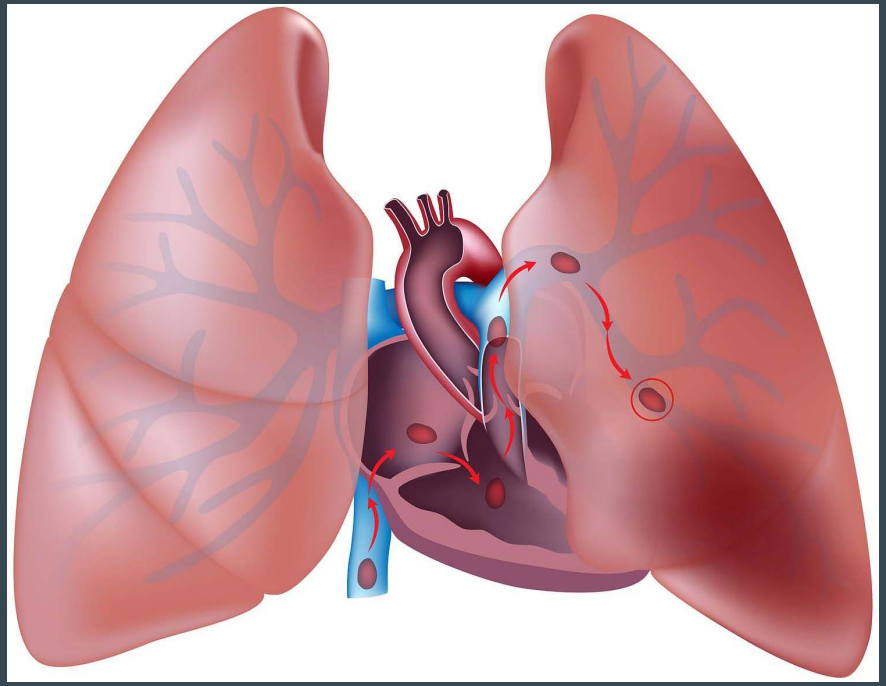
- Pulmonary thromboembolism (PTE) or pulmonary embolism (PE) is an obstruction of pulmonary arteries due to:
  - Thrombus
    - Pulmonary embolism
    - Can be due to any material
    - Most often thought of as blood clot
  - Local formation of clot in pulmonary vasculature
    - Primary pulmonary thrombosis





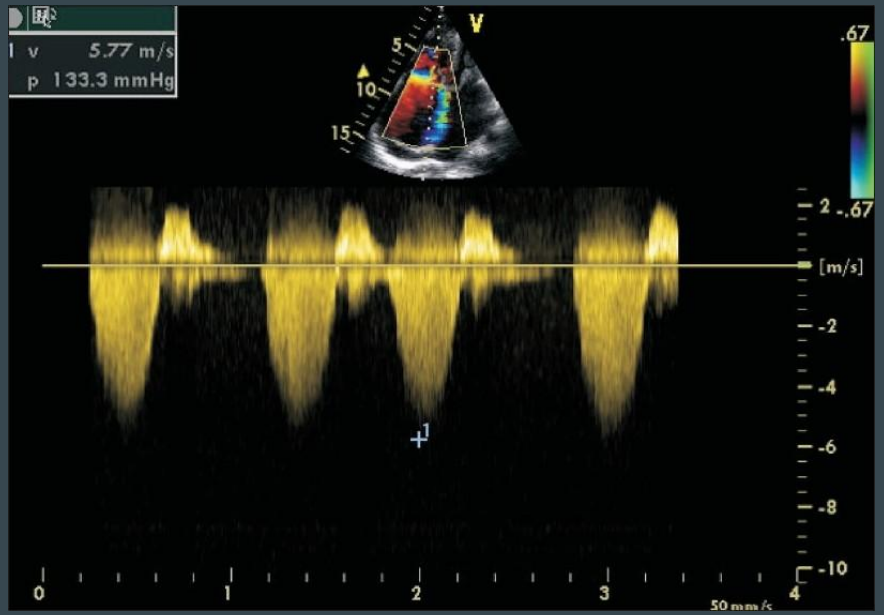
# Pathophysiology of Pulmonary Thromboembolism

- Multiple factors involved in pathophysiology of PTE
  - Two Major body systems involved are the pulmonary system and cardiovascular system
- Degree of Severity highly depends on cardiac and pulmonary reserve
  - Smaller obstructions can cause big problems in patients with previously compromised heart or lungs



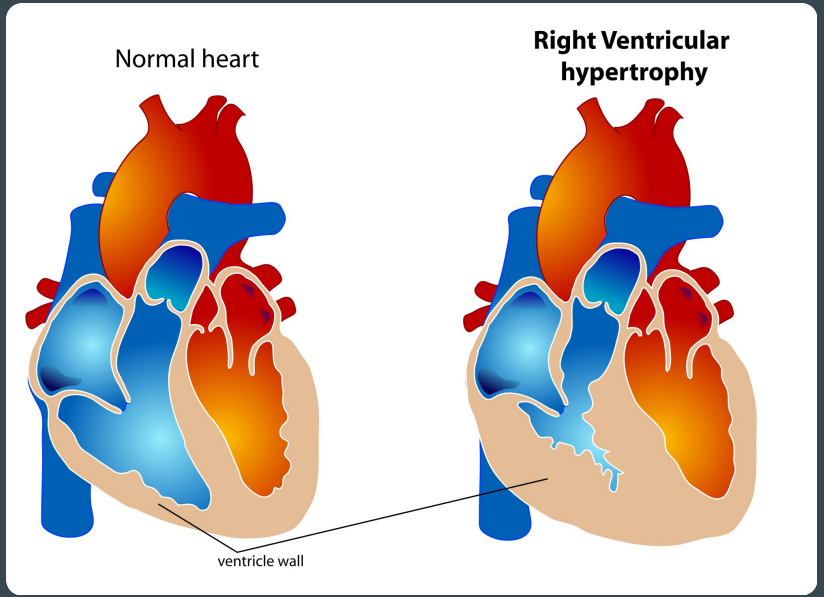
# Pathophysiology of Pulmonary Thromboembolism

- Cardiac effects of PTE
  - Increase in pulmonary vascular resistance and pulmonary hypertension leads to increased right ventricular afterload
  - RV becomes dilated/enlarged
    - Can occur acutely
  - Can overwhelm compensatory mechanisms leading to PEA and sudden death



# Pathophysiology of Pulmonary Thromboembolism

- Cardiac effects of PTE
  - Decrease in right sided output leads to decreased left sided filling and decreased cardiac output
  - Acute right sided heart changes also impedes left ventricular function
    - ventricular interdependence
  - Left sided functional deficits result in
    - Syncope
    - Systemic hypotension
    - Cardiogenic shock

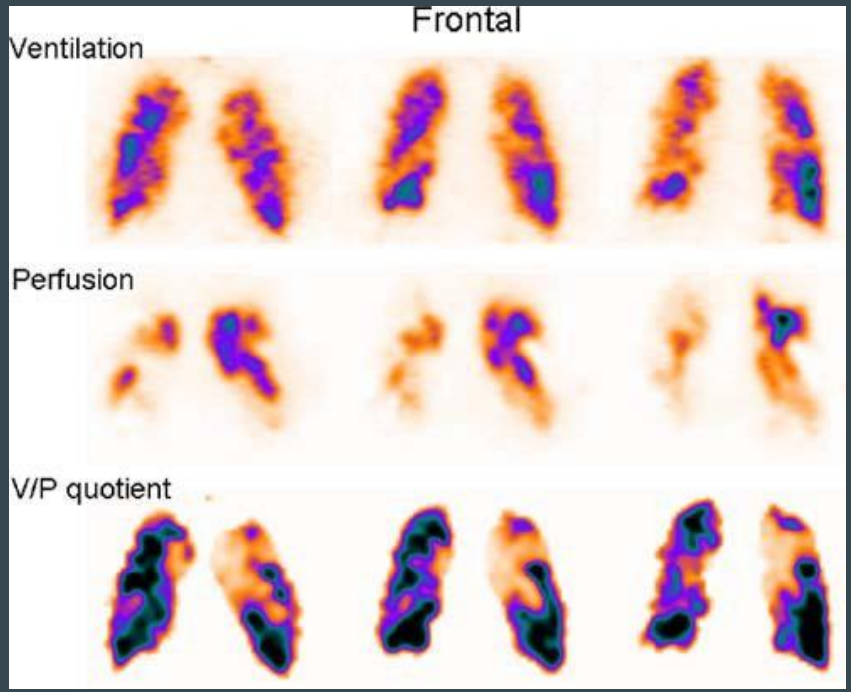


# Pathophysiology of Pulmonary Thromboembolism

- Cardiac effects of PTE
  - Right ventricular overload can decrease right coronary perfusion pressures
    - Right coronary artery is less resistant to right ventricular changes than left CA
  - Leads to subendocardial ischemia or infarction and further right sided dysfunction

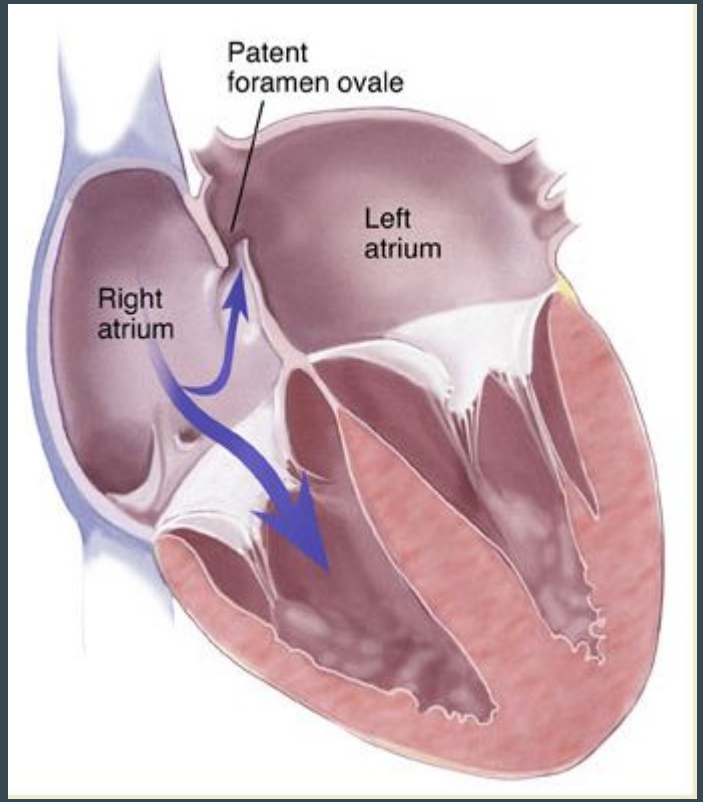
# Pathophysiology of Pulmonary Thromboembolism

- Pulmonary effects of PTE
  - Occlusion of pulmonary arterial vasculature will result in decreased perfusion of lung tissue
  - If ventilation remains constant, then V/Q mismatch (high V low Q mismatch) occurs with subsequent hypoxemia
  - Reflex and humoral vasoconstriction may occur
    - Some human papers suggest this is



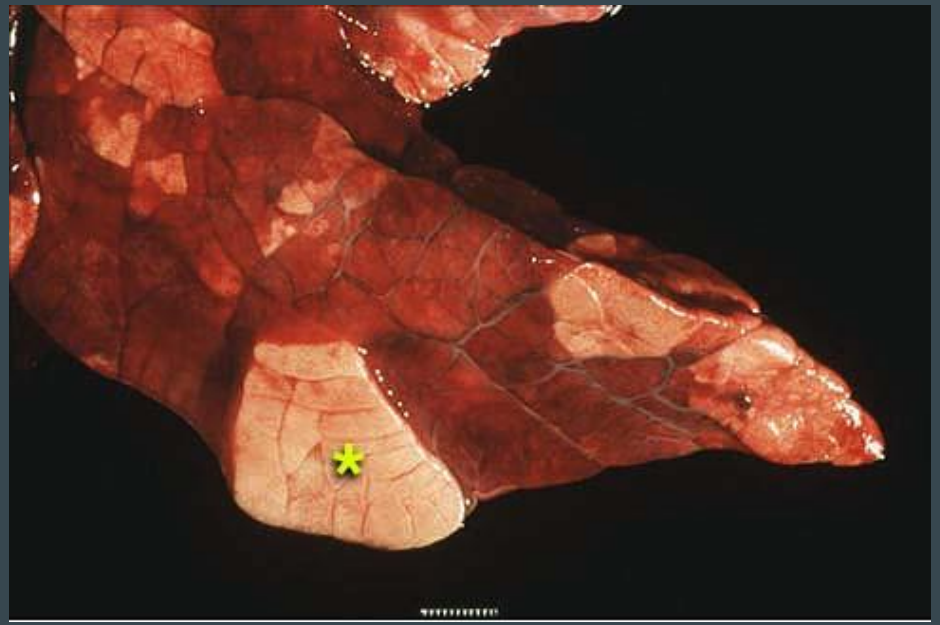
# Pathophysiology of Pulmonary Thromboembolism

- Pulmonary effects of PTE
  - Increases in right ventricular and right atrial pressures can open foramen ovale and cause increased right to left shunting and even paradoxical thromboemboli into the arterial circuit
  - Hypercapnia is rare except in the most severe cases
    - Compensatory mechanisms allow for sufficient ventilation



# Pathophysiology of Pulmonary Thromboembolism

- Pulmonary effects of PTE
  - Congestive atelectasis
    - Pulmonary edema due to decreased type II pneumocyte surfactant production
    - Possibly only an experimental phenomena



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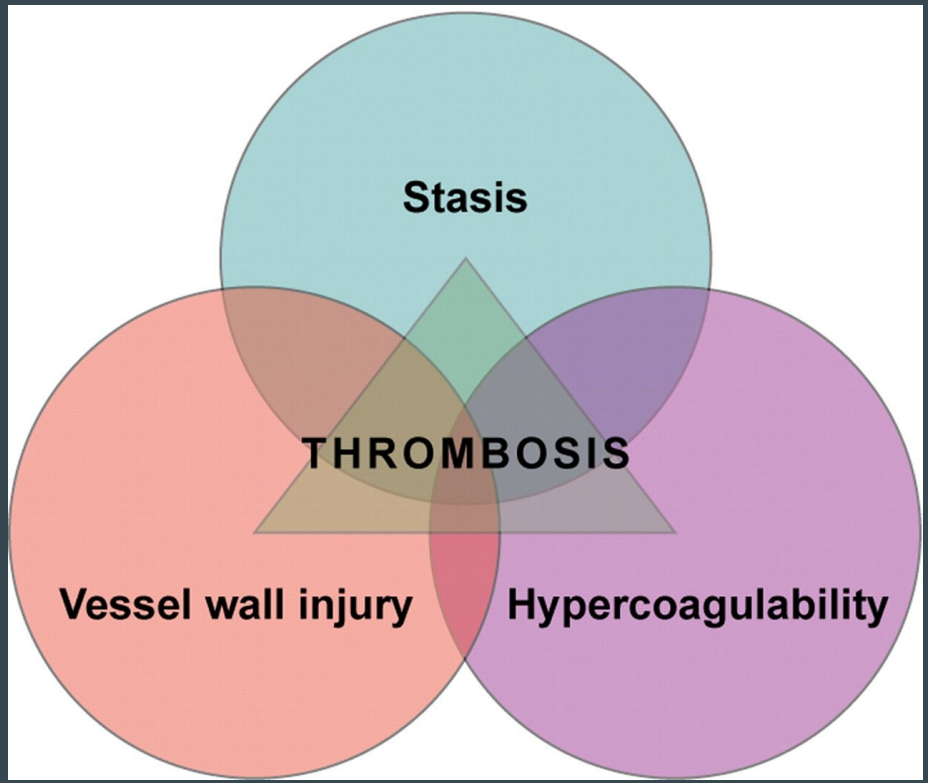
# Predisposing Factors

- Any abnormalities in Virchow's triad can lead to thrombosis and PTE
    - Stasis and deep vein thrombosis is #1 predisposing factor in humans
- Multiple diseases in veterinary patients cause hypercoagulability



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- Multiple diseases in veterinary patients cause hypercoagulability

**Table 1:** Recognized risk factors for pulmonary thromboembolism (PTE) and disease processes with a known association with thromboembolic disease in the dog with proposed mechanisms.

| Disease process/ risk factor | Hyper-coagulable state | Vascular flow abnormalities/ stasis | Endothelial injury/ dysfunction |
|---|---|---|---|
| Corticosteroid administration*[4,8,9] | √ | | |
| Diabetes mellitus[10] | √ | | |
| Dirofilariasis[11,12] | √ | | √ |
| DIC*[3,4,12] (secondary to other disease) | √ | | |
| Endocarditis[3] (tricuspid/ pulmonic) | √ | | √ |
| Feline infectious peritonitis*[5] | √ | | √ |
| Hyperadrenocorticism[3,12–14] | √ | | |
| Hypothyroidism[10] | √ | | |
| IMHA*[3,4,15,16] | √ | | ? |
| Indwelling venous catheters*[3,4,12] | | √ | √ |
| Myocardial disease[3,5,8] | √ | √ | √ |
| Neoplasia*[3–5,8,9] | √ | √ | |
| Pancreatitis*[4,5,9] | √ | | √ |
| Protein-losing enteropathy*[4] | √ | | |
| Renal amyloidosis/ PLN*[3,4,10,14,17–19] | √ | | |
| Sepsis*[3,4,8,9] | √ | | √ |
| Surgery[20] | √ | √ | √ |
| Trauma*[21] | | √ | √ |

*Those conditions also associated with an increased risk in the cat are marked. Question mark signifies the role of this mechanism in the associated disease process is uncertain.

Goggs et al, JVECC, 2009

# Predisposing Factors

**Table 2.** Primary clinical diagnoses in 29 dogs with pulmonary thromboembolism.

| Primary Disease | No. with PTE | Total No. Dogs with Postmortem Examination[a] | Relative % of Primary Disease with PTE[b] |
|---|---|---|---|
| IMHA | 5 | 53 | 10.6 |
| Neoplasia | 12 | | |
| Lymphosarcoma/leukemia | 5 | 283 | 1.8 |
| Brain tumor | 3 | | |
| Osteosarcoma | 1 | | |
| Splenic histocytoma | 1 | | |
| Transitional cell carcinoma (bladder) | 1 | | |
| Carcinoma (shoulder) | 1 | | |
| Systemic bacterial disease | 6 | | |
| Sepsis | 4 | 46 | 8.7 |
| Pneumonia and/or pyothorax | 1 | 110 | 0.9 |
| Bacterial endocarditis | 1 | | |
| Hyperadrenocorticism | 2 | 91 | 2.7 |
| Amyloidosis | 2 | 27 | 7.4 |
| Dilated cardiomyopathy | 1 | 63 | 1.6 |
| Megaesophagus | 1 | | |

PTE, pulmonary thromboembolism; IMHA, immune-mediated hemolytic anemia.

[a] Total number of cases with this postmortem diagnosis in the same time period. Data only available for those diseases for which numbers are listed.

[b] Number of cases with PTE divided by the total number of cases with this postmortem diagnosis.

Johnson et al
JVIM 1999

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# Clinical Signs

- In humans, most common signs are
  - Coughing
  - Hemoptysis
  - Chest Pain
  - Dyspnea
- Veterinary patients less frequently have the first three.  Instead, our patients have
  - Dyspnea
  - Tachypnea
  - Lethargy
- Less commonly
  - Cough, hemoptysis, cyanosis, syncope

# Clinical Signs

- Auscultation findings include
  - Pulmonary crackles
  - Harsh lung sounds
  - Or dull lung sounds
    - Pleural effusion possible
  - Or even normal lung sounds...

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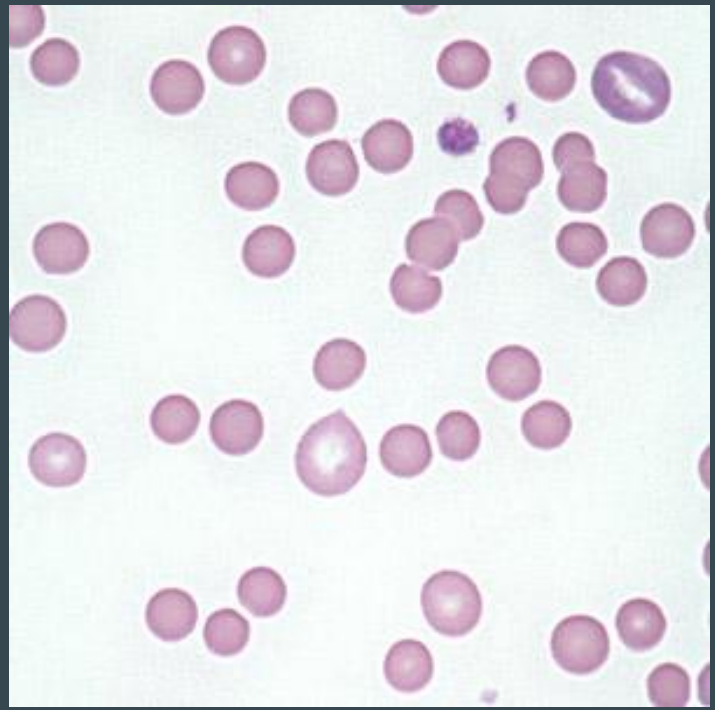
# Minimum Database

- Complete Blood Count
  - No specific findings in CBC will help in directly diagnosing PTE
  - Helpful for looking for predisposing factors
    - IMHA
  - Primary (essential) thrombocytosis may predispose to thromboembolic disease
    - Secondary thrombocytosis does not
  - Markers of DIC should increased index of suspicion for PTE
    - Thrombocytopenia
    - Schistocytosis
- Serum Biochemistry
  - Same as CBC - no specific changes for PTE, but helps look for underlying causes



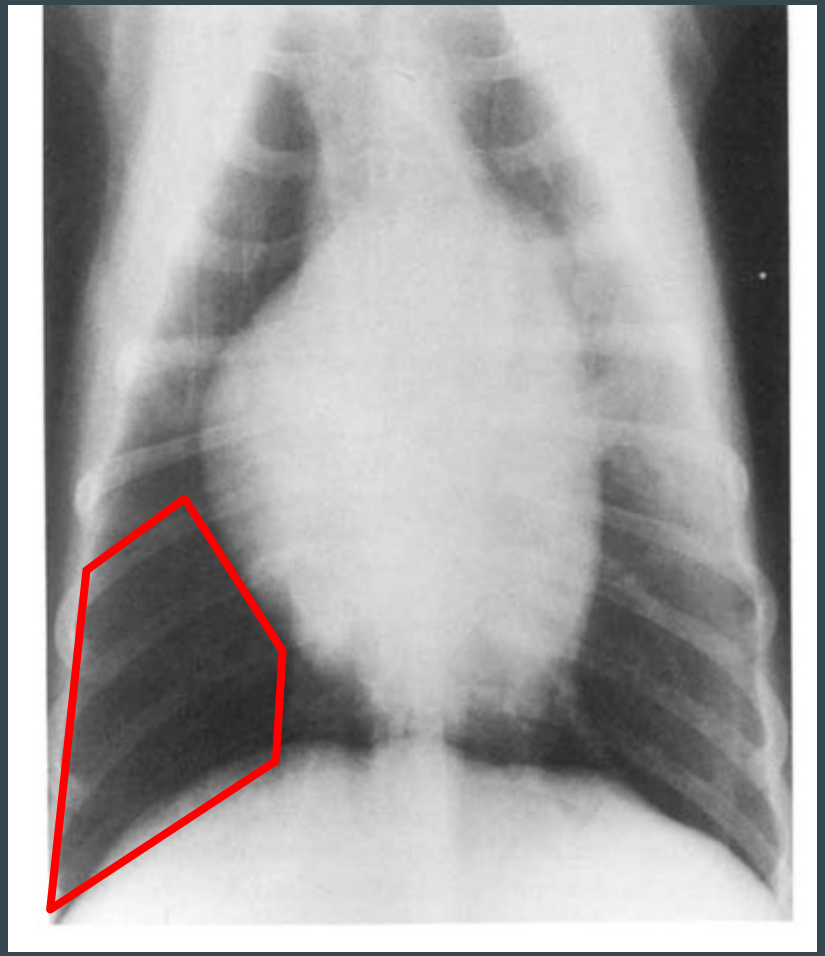
# Diagnostic Imaging

- Chest Radiographs
  - Most common two patterns are
    - Alveolar pattern
    - Regional hypovascular lung pattern

TABLE 1. Radiographic Findings in 21 Dogs with Pulmonary Thrombosis or Embolism

| | No. of Dogs |
|---|---|
| Normal | 2 |
| Abnormal | 19 |
| Pulmonary pattern | |
| Alveolar | 10 |
| Hyperlucent | 6 |
| Combined alveolar and hyperlucent | 3 |
| Shape of alveolar opacity* | |
| Fluffy, indistinct margins | 11 |
| Lobar consolidation, distinct margins | 5 |
| Triangular, base towards heart | 3 |
| Pulmonary vascular changes | 14 |
| Primary or loss of lobar artery | 11 |
| Loss of lobar vein | 14 |
| Lung volume loss | 6 |
| Pleural effusion | 14 |
| Cardiomegaly | 10 |
| Generalized (3 primary heart failure) | 4 |
| Right heart enlargement (1 primary heart failure) | 6 |
| Main pulmonary artery enlargement | 4 |

* 9 dogs had more than one alveolar opacity.



Flückiger and Gomez, Vet Radiology, 1984

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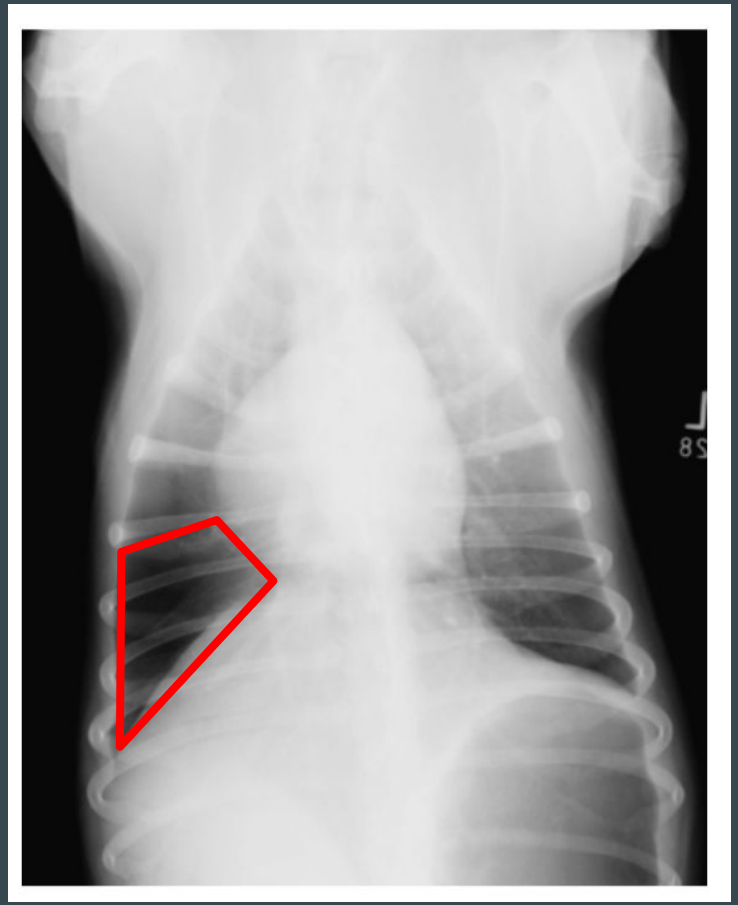

Goggs et al, JVECC, 2009

# Diagnostic Imaging

- Chest Radiographs
  - Up to 27%  can have normal radiographs

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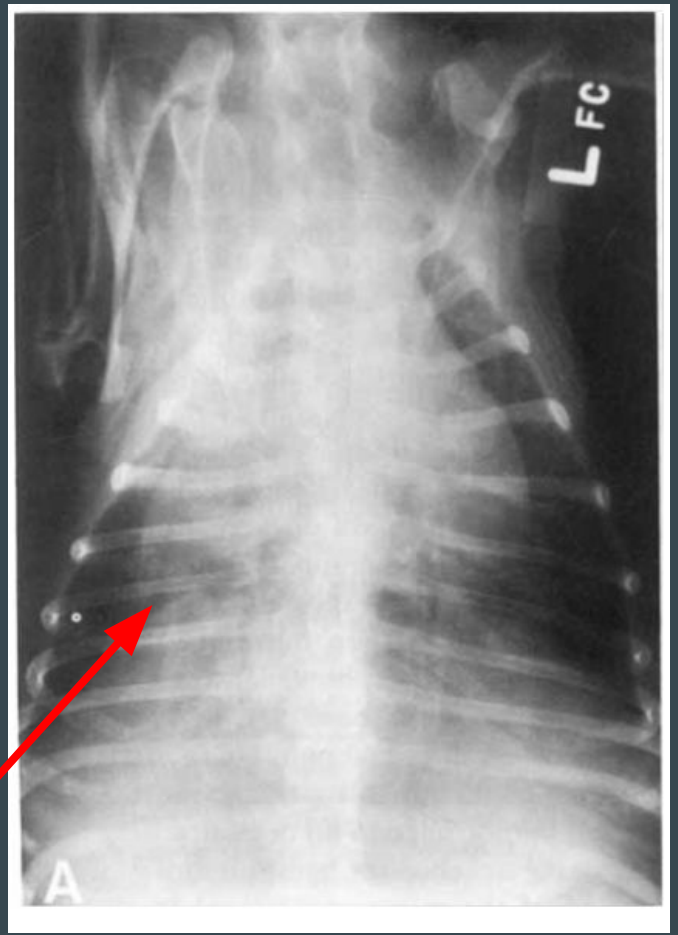
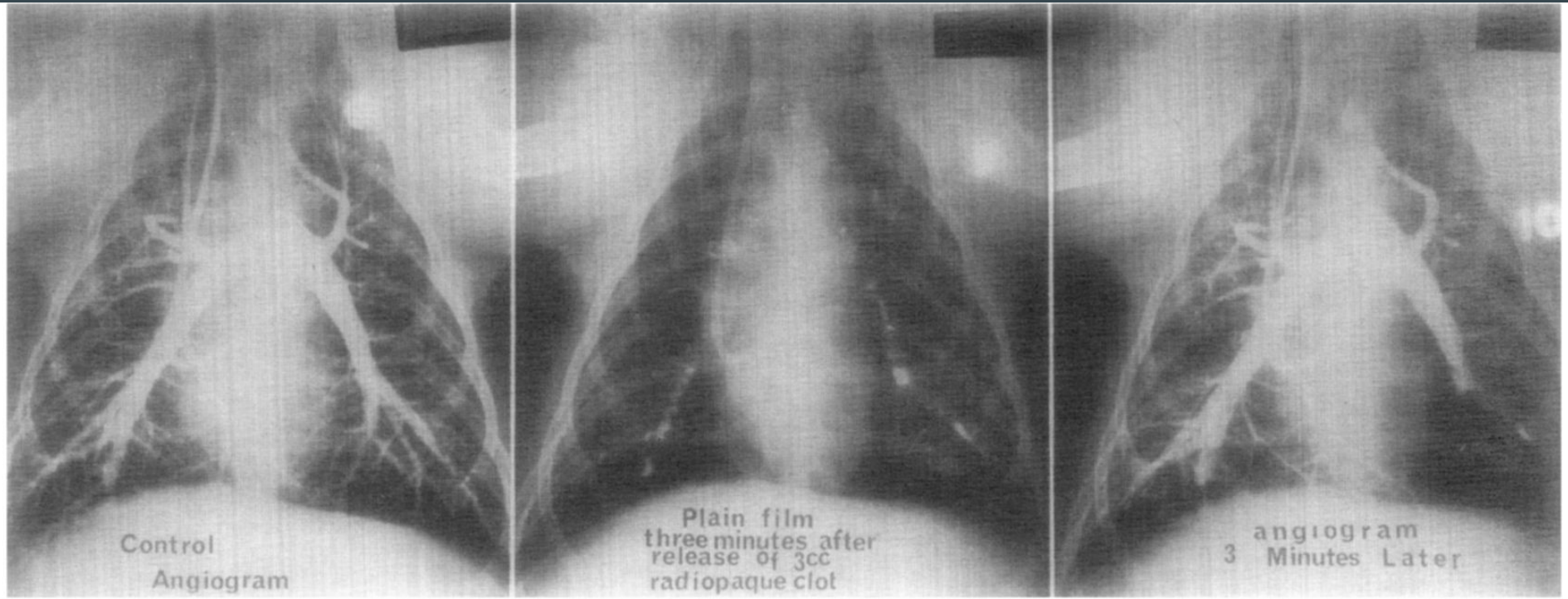



Flückiger and Gomez, Vet Radiology, 1984

# Diagnostic Imaging

- Pulmonary Angiography
  - Selective
    - Requires pulmonary artery catheter
    - Bolus of contrast into PA
    - Highlights pulmonary arterial tree
    - Diagnostic
      - Intraluminal filling defects
      - Abrupt pulmonary arterial termination
      - absence of arterial branches
    - Suggestive
      - Loss of vascularity
      - asymmetry
      - Tortuous PA
      - Premature vessel tapering
    - Requires anesthesia for PA catheter
  - Non-selective
    - Jugular catheter
    - Much more difficult to interpret due to large amount of vascular highlighting from contrast

# Diagnostic Imaging

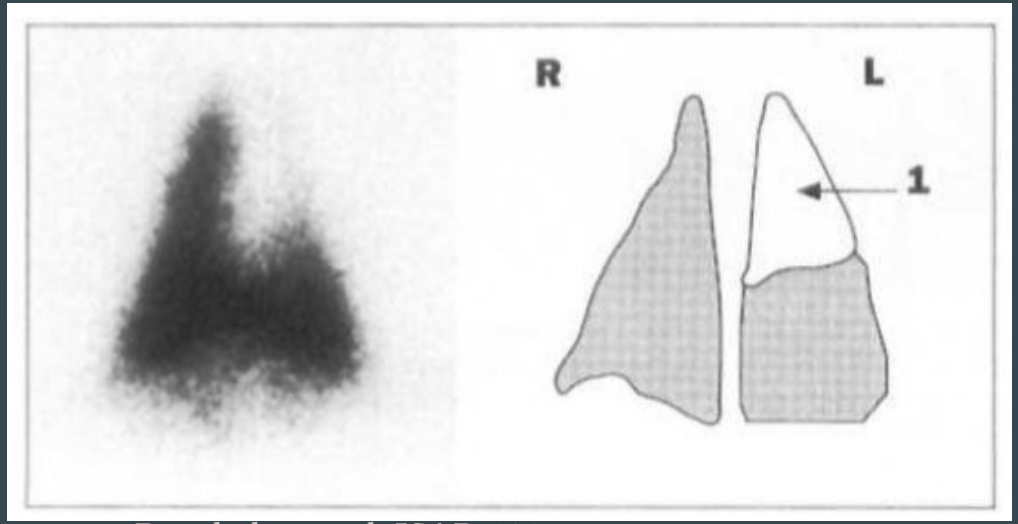



Dalen et al, American Heart Journal , 1966

# Diagnostic Imaging

- Scintigraphy
  - Ventilation/perfusion (V/Q) scan
  - May require anesthesia depending on patient
  - Requires radioactive medium and specialized equipment
  - Two separate studies
    - Ventilation study using radionuclide labeled gas for inspiration
    - Perfusion study requiring technetium-labeled IV infusion
  - Well ventilated, but poorly perfused areas of lungs suggestive of PTE
  - Can do with just perfusion scan compared to thoracic radiographs

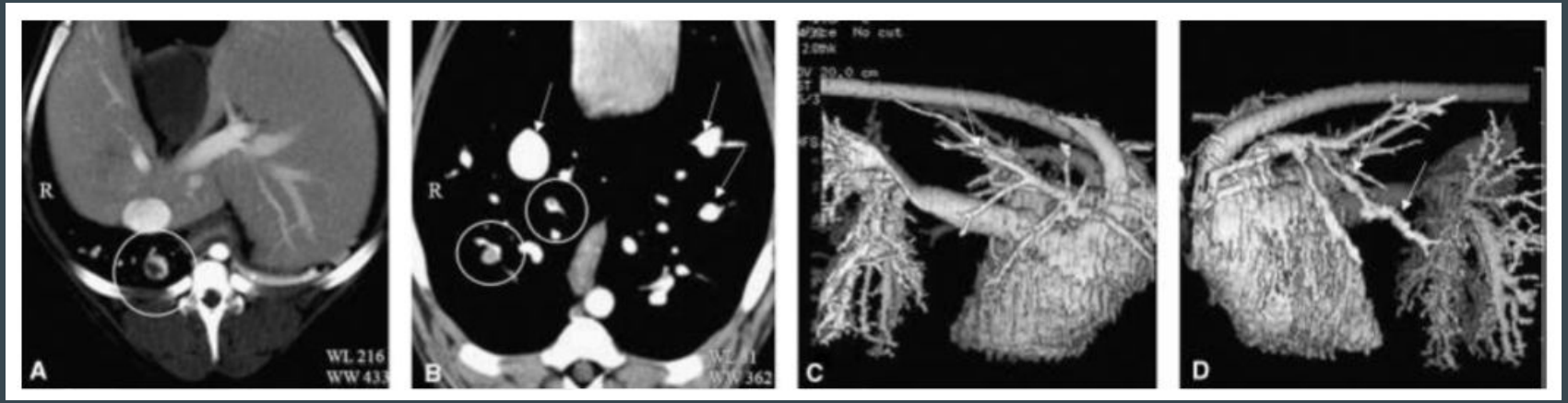
Scintigraphy scan in cat with PTE




Pouchelon et al, JSAP, 1997

# Diagnostic Imaging

- Computed Tomography with Pulmonary Angiography (CTPA)
  - Newest additional to the diagnostic imaging of PTE
  - Similar to radiographic pulmonary angiography, but with CT
  - Heavy sedation or anesthesia may be required for contrast comparison
  - Studies in dogs have been done with experimentally induced PTE, so unknown sensitivity or specificity



# Diagnostic Imaging

- Computed tomography with pulmonary angiography (CTPA) combined with venous phase imaging (CTA-CTV) in humans
    - Positive predictive values and negative predictive values are very highly dependant on the clinical probability of PTE based on scoring system developed for humans

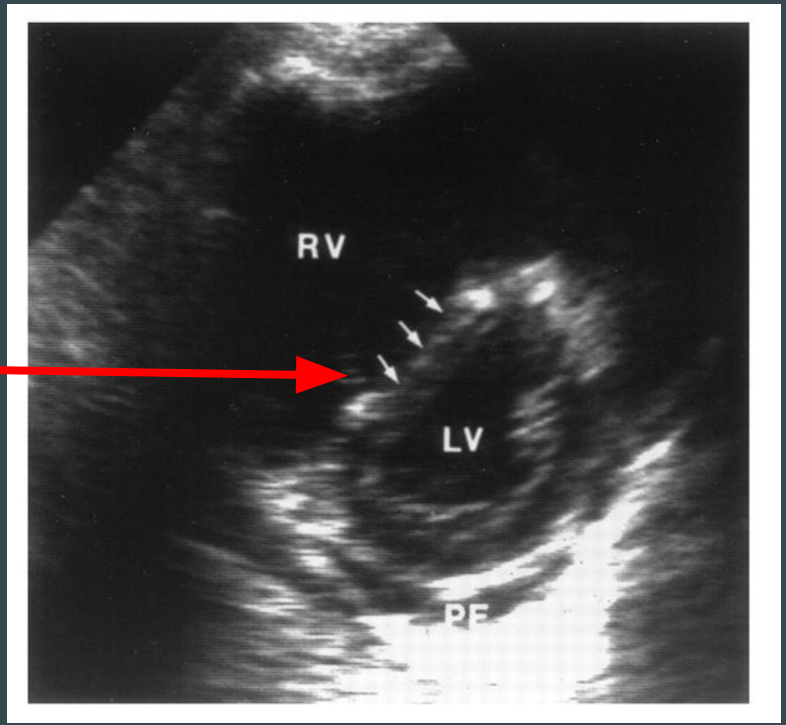
**Table 5. Positive and Negative Predictive Values of CTA, as Compared with Previous Clinical Assessment.***

| Variable | High Clinical Probability | | Intermediate Clinical Probability | | Low Clinical Probability | |
|---|---|---|---|---|---|---|
| | No./Total No. | Value (95% CI) | No./Total No. | Value (95% CI) | No./Total No. | Value (95% CI) |
| Positive predictive value of CTA | 22/23 | 96 (78–99) | 93/101 | 92 (84–96) | 22/38 | 58 (40–73) |
| Positive predictive value of CTA or CTV | 27/28 | 96 (81–99) | 100/111 | 90 (82–94) | 24/42 | 57 (40–72) |
| Negative predictive value of CTA | 9/15 | 60 (32–83) | 121/136 | 89 (82–93) | 158/164† | 96 (92–98) |
| Negative predictive value of both CTA and CTV | 9/11 | 82 (48–97) | 114/124 | 92 (85–96) | 146/151† | 97 (92–98) |

Stein et al, NEJM, 2006

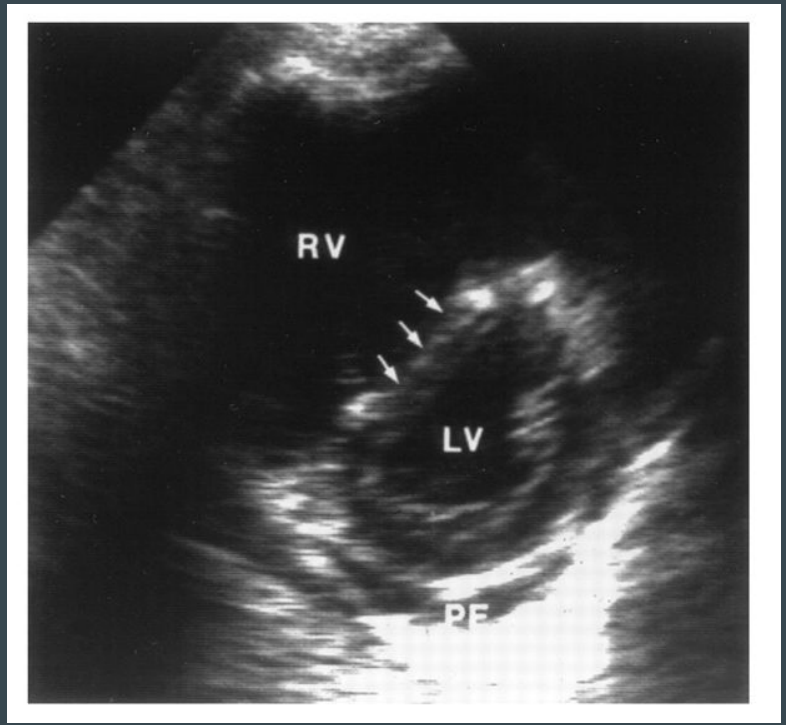
# Diagnostic Imaging

- Echocardiography
  - Since cardiovascular effects of PTE are often more significant than pulmonary effects, echocardiogram is very important diagnostic
  - Right heart enlargement
    - even in acute PTE
  - Pulmonary hypertension
  - Flattening of interventricular septum
  - Sometimes able to visualize PTE in proximal pulmonary artery/trunk



# Diagnostic Imaging

- Echocardiography
  - Conflicting evidence of usefulness in human medicine
  - Given severe cardiovascular abnormalities seen with PTE, can be helpful for ruling out other cardiac disease



# Ancillary Tests

- Arterial blood gas analysis
  - Allows for determination of oxygenation ability, as well as for A-a gradient
  - Study of 29 dogs with PTE, 15 had arterial blood gas
    - 100% had increased A-a gradient
    - 80% had hypoxemia
    - 47% had hypocapnia

# Ancillary Tests

- Arterial blood gas analysis
  - Calculation of A-a gradient
  - $P_AO2$ =
  - $P_AO2$ =
  - $P_AO2$ - $P_aO2$ should be

# Ancillary Tests

- Coagulation Testing
  - PT and aPTT are often normal
    - depending on underlying disease
  - Antithrombin levels
    - May be reduced in a number of diseases and states that predispose to PTE
    - May be helpful in determining the risk of thrombosis

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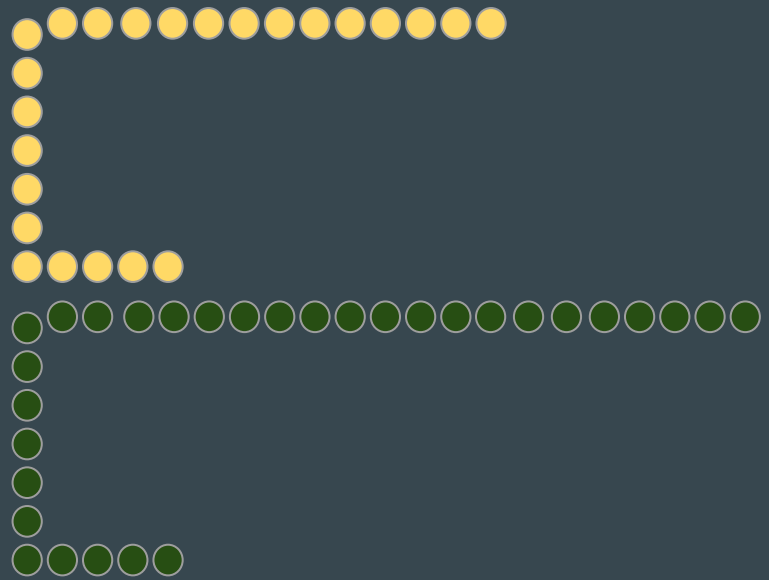

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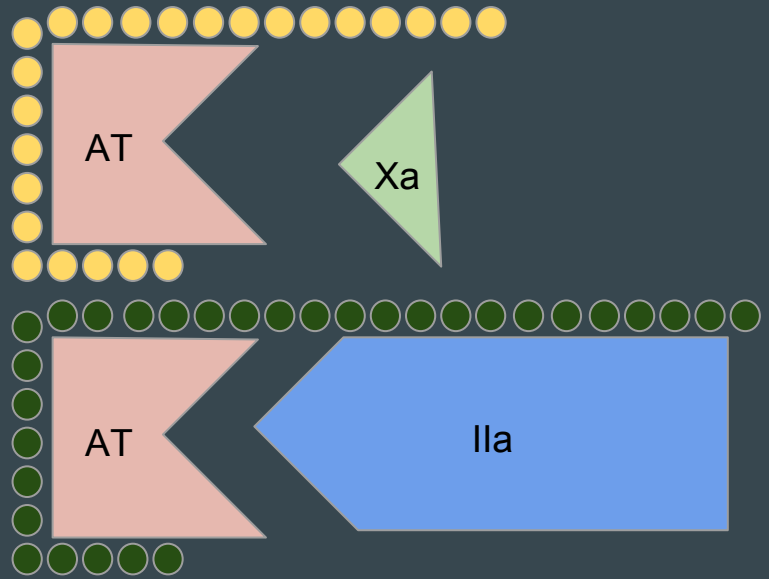

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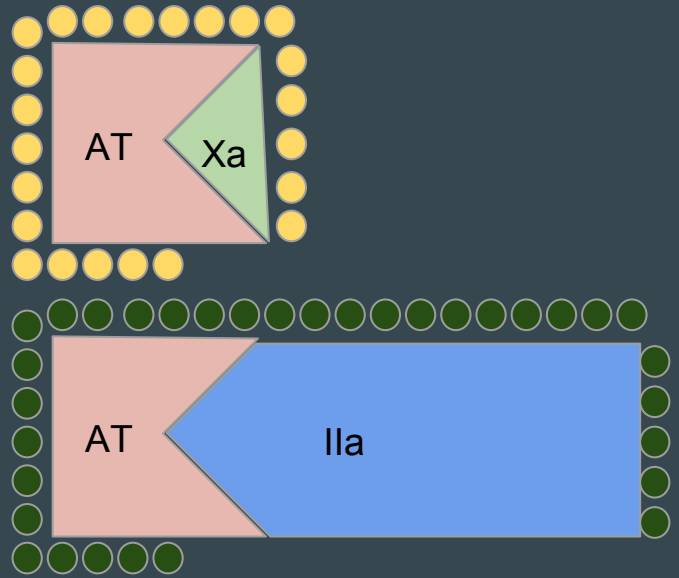
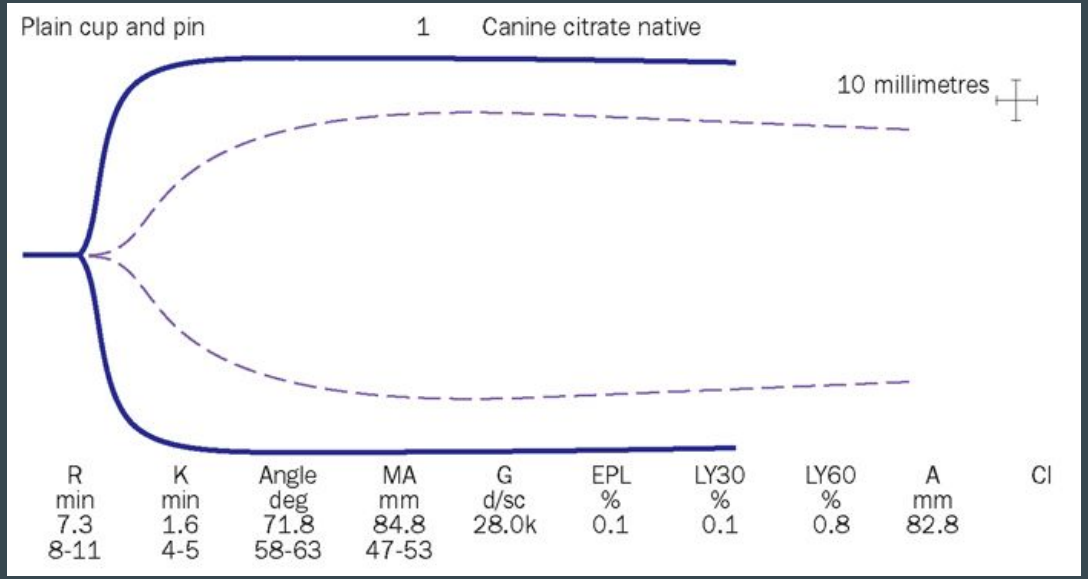


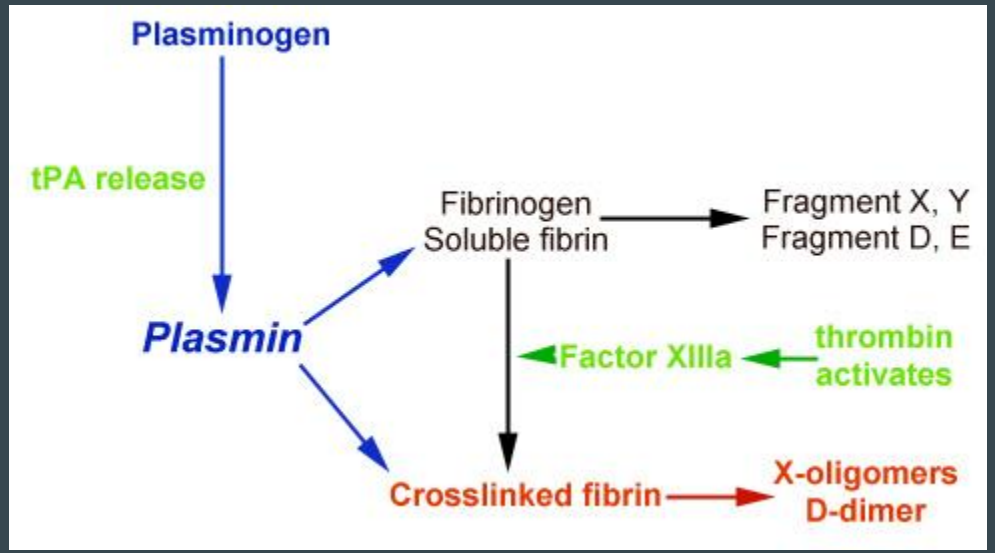
# Ancillary Tests

- Thromboelastography
  - Risks based on TEG have been establish in human studies
    - Increased overall thromboembolic disease risk in post-surgical people with increased MA
    - Thromboembolic disease includes PTE, myocardial infarction or stroke



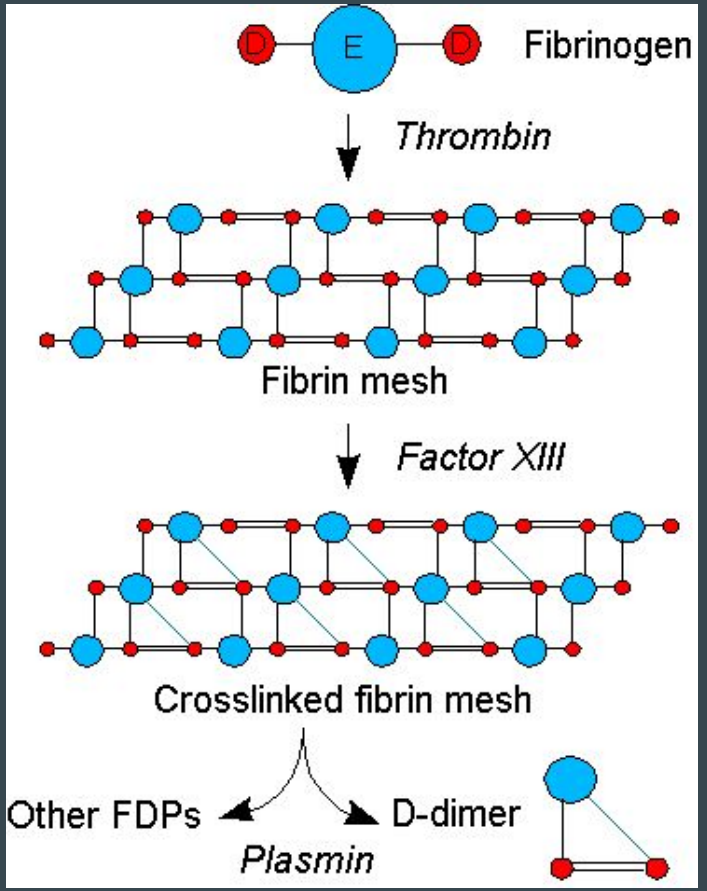
# Ancillary Tests

- D-Dimers and FDPs
  - Difference between FDPs and D-dimers is crosslinking of fibrin by factor XIIIa
  - FDPs more specific to actual clot formation



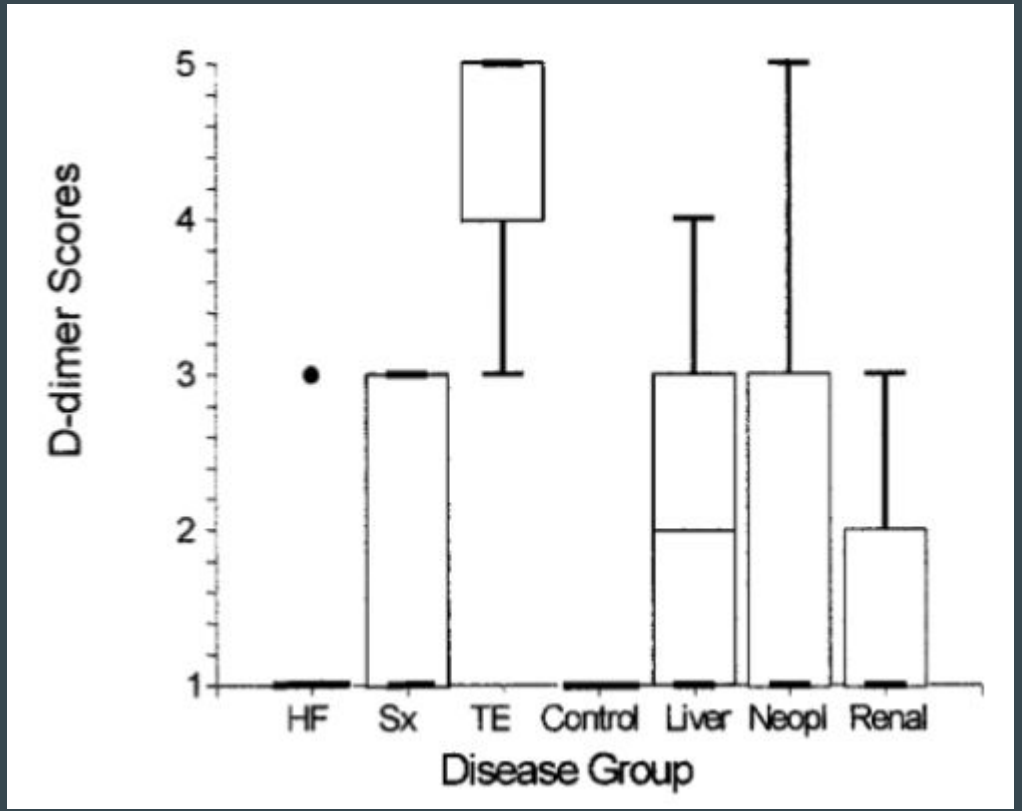
# Ancillary Tests

- D-Dimers and FDPs
  - Major screening test (high sensitivity) in human medicine for PTE or other thrombotic disease
    - In patients that do not have high probability calculations
  - Usually not run in patients in high probability groups due to low specificity



# Ancillary Tests

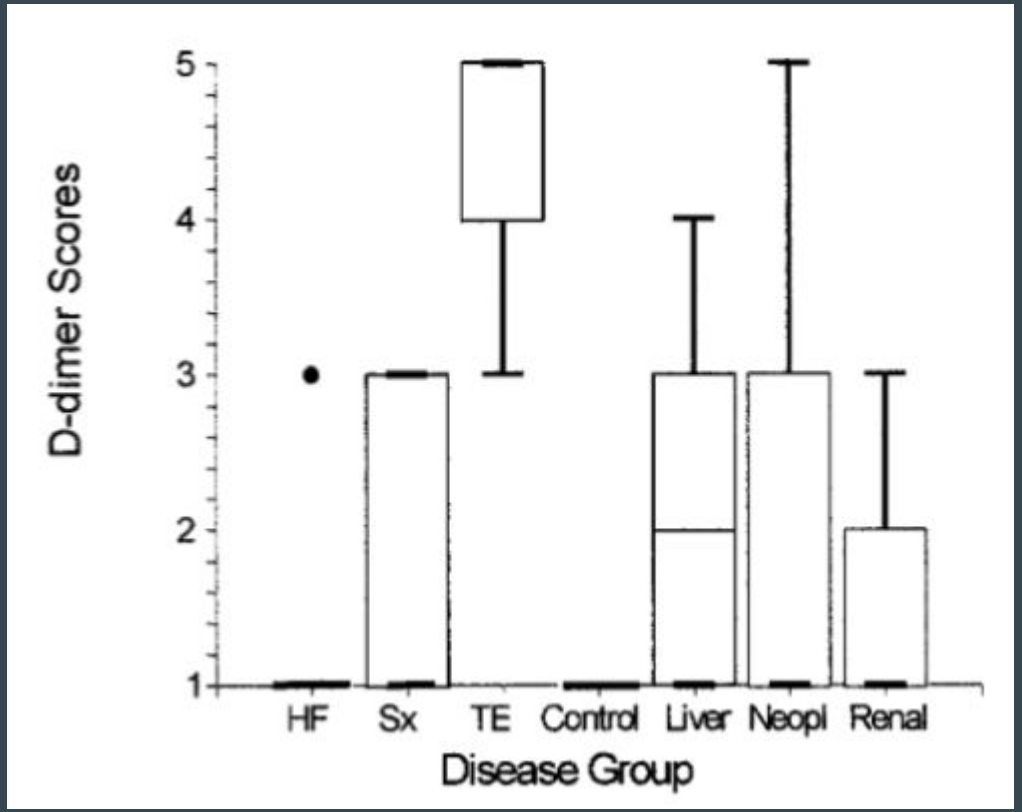
- D-Dimers and FDPs
  - Sensitivity and specificity in dogs is dependant on cutoff values
    - Using 500 ng/mL is very sensitive (100%, but there is overlap with other disease processes (Sp 70%)
    - Using 2000 ng/mL is very specific (98.5%) for TE disease but lacks sensitivity (36%)




Nelson and Andreasen, JVIM, 2003

# Ancillary Tests

- D-Dimers and FDPs
  - TE group was 20 dogs with TE (almost all confirmed with necropsy or direct visualization with echo/ultrasound)
  - 19/20 TE was PTE
    - One multi-organ thrombosis
  - Most common cause of PTE in this study was PLN (5)
    - Followed by IMHA (3)




Nelson and Andreasen, JVIM, 2003

# Outline

- Pathophysiology
- Predisposing Factors
  - Associated Disease Processes
- Presentation
  - Clinical Signs
  - Physical Examination
- Diagnostics
  - Minimum Database
  - Diagnostic Imaging
  - Ancillary Tests
- Human Scoring Systems
- Summary

# Human Scoring Systems

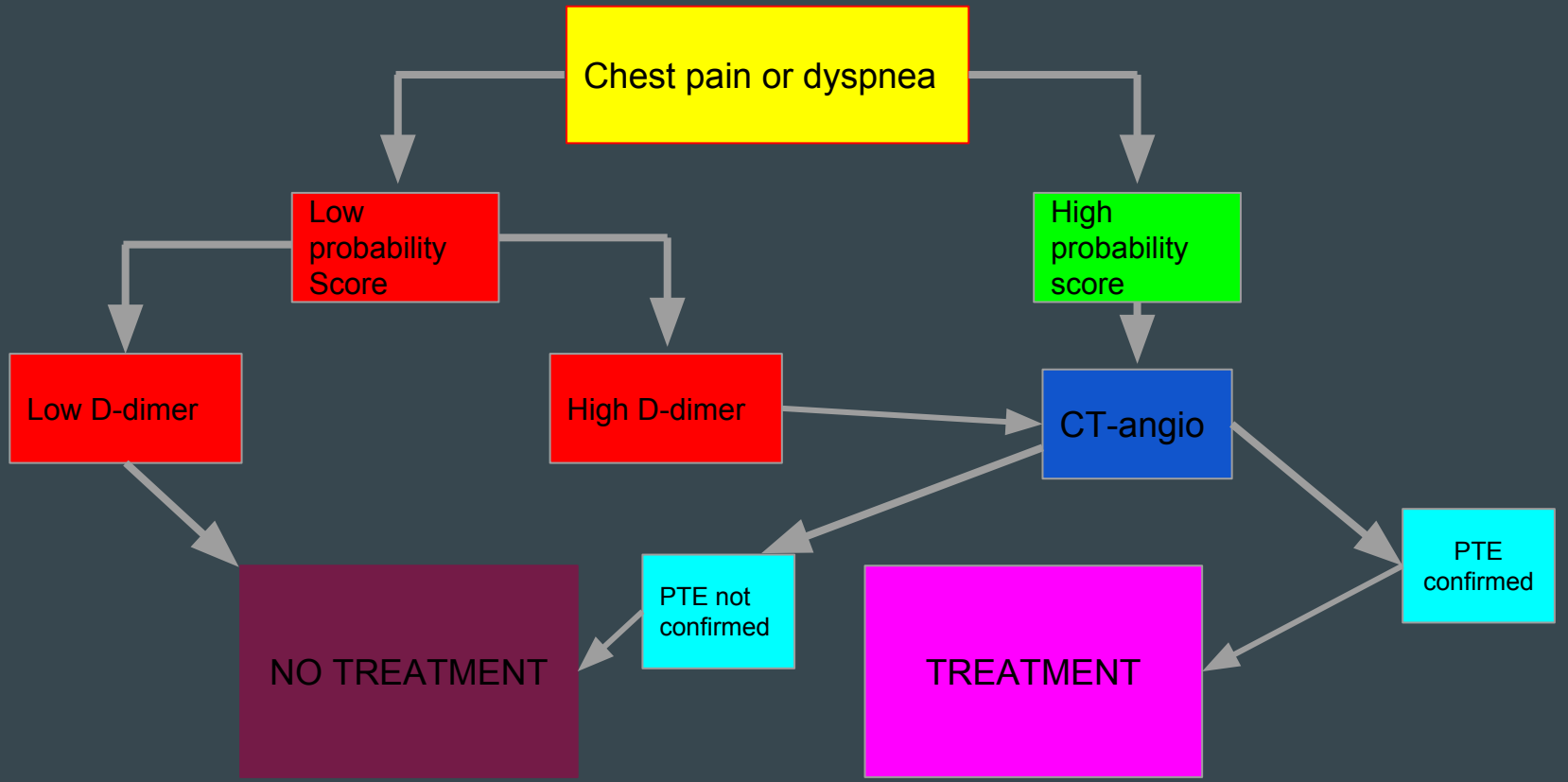
- Scoring systems in human medicine the cornerstone of diagnostic work-up of PTE
  - First line defence
  - Algorithms based on clinical probability dictate further testing
    - D-Dimers for low probability groups
    - Imaging for high probability groups

**Table 7** Clinical prediction rules for PE: the Wells score and the revised Geneva score

| Revised Geneva score[64] | |
|---|---|
| **Variable** | **Points** |
| Predisposing factors | |
| Age >65 years | +1 |
| Previous DVT or PE | +3 |
| Surgery or fracture within 1 month | +2 |
| Active malignancy | +2 |
| Symptoms | |
| Unilateral lower limb pain | +3 |
| Haemoptysis | +2 |
| Clinical signs | |
| Heart rate | |
| 75–94 beats/min | +3 |
| ≥95 beats/min | +5 |
| Pain on lower limb deep vein at palpation and unilateral oedema | +4 |
| **Clinical probability** | **Total** |
| Low | 0–3 |
| Intermediate | 4–10 |
| High | ≥11 |

| Wells score[65] | |
|---|---|
| **Variable** | **Points** |
| Predisposing factors | |
| Previous DVT or PE | +1.5 |
| Recent surgery or immobilization | +1.5 |
| Cancer | +1 |
| Symptoms | |
| Haemoptysis | +1 |
| Clinical signs | |
| Heart rate | |
| >100 beats/min | +1.5 |
| Clinical signs of DVT | +3 |
| Clinical judgement | |
| Alternative diagnosis less likely than PE | +3 |
| **Clinical probability (3 levels)** | **Total** |
| Low | 0–1 |
| Intermediate | 2–6 |
| High | ≥7 |
| **Clinical probability (2 levels)** | |
| PE unlikely | 0–4 |
| PE likely | >4 |

# Human Scoring Systems



# Outline

- Pathophysiology
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# Conclusions

- PTE is a very difficult diagnosis with many possible clinical presentations and predisposing disease processes
- Clinical suspicion should be heavily weighted
- Do not forget to think about possibility of PTE
- D-dimers is the most helpful test for ruling out PTE
- CT-Angio may be helpful in more stable animals
- Less stable animals may benefit most from echocardiogram, DIC panel, and chest x-rays