





DVT/PE

Opposing Factors

- 75 % of patients who present with suspected DVT/PE DO NOT have these conditions
 - Untreated (UNDIAGNOSED) DVT/PE can have a FATAL OUTCOME
- 




Diagnosis of DVT

- History and physical examination are often NOT suggestive of DVT
 - Phlebitis was present in only 32 % of 327 patients with documented PE in the UPET phase I and II trials
 - Homan's sign is neither sensitive nor specific for the diagnosis of DVT.
- 



Venous Thromboembolic Disease

CAVEAT

- ALWAYS CONSIDER THE DIAGNOSIS !
 - High index of suspicion
 - Low threshold for diagnostic evaluation
- 

Risk Factors for Venous Thromboembolism

ACQUIRED

- **Virchow's Triad
(stasis, venous injury, hypercoagulable)**
- **Prior history of thromboembolic disease**
- **Prior surgical history or trauma**
- **Immobilization/paralysis**
- **Cancer**
- **Estrogen Therapy**
- **Pregnancy/Postpartum**
- **Antiphospholipid antibody syndrome**

Venous Thromboembolism

- **Interesting Factoids on Cancer and VTE**
 - Occult cancer in 0.5 – 5% of VTE pts
 - 3x more likely to get cancer in next 3 yrs if idiopathic VTE
 - 19% of cancer pts have a VTE
 - Chemo increases risk of VTE because it increases tissue factor and expression of E-selectin, thereby increasing thrombus potential



Hypercoagulable states associated with BOTH Arterial and Venous Thrombosis

Cancer

Myeloproliferative syndromes

Antiphospholipid antibodies
(APA)

Hyperhomocysteinemia

Heparin-induced
thrombocytopenia.



Table 2:

Established or Potential Hypercoagulable States

- **Activated protein C resistance**
- **Alpha-macroglobulin deficiency**
- **Anticardiolipin antibodies**
- **Antithrombin deficiency**
- **Dysfibrinogenemia**
- **Factor V Leiden**
- **Factor V deficiency/excess**
- **Factor VII excess**
- **Factor VIII excess**
- **Factor XI excess**
- **Heparin cofactor II deficiency**
- **Hyperhomocysteinemia**
- **Hyperfibrinogenemia**
- **Lupus anticoagulants**
- **PAI-1 excess**
- **Plasminogen deficiency**
- **Protein C deficiency**
- **Protein S deficiency**
- **Prothrombin G20210A**
- **tPA deficiency**
- **TFPI deficiency**
- **Thrombomodulin deficiency**

PAI-1=plasminogen activator inhibitor-1; TFPI=tissue factor pathway inhibitor; tPA=tissue plasminogen activator

Table 1:


Prevalence of Major Hypercoagulable States in Different Patient Populations			
Hypercoagulable State	General Population (%)	Patients with Single VTE (%)	Thrombophilic Families (%)
Factor V Leiden	3-7	20	50
Prothrombin G20210A	1-3	6	18
Antithrombin deficiency	0.02	1	4-8
Protein C deficiency	0.2-0.4	3	6-8
Protein S deficiency	N/A	1-2	3-13
Hyperhomocysteinemia	5-10	10-25	N/A
Antiphospholipid antibodies	0-7	5-15	N/A

N/A=not readily available or unknown.



Heparin-Induced Thrombocytopenia & Thrombosis Syndrome (up to 30%)

Site	Venous, occasional arterial
Mech	Heparin-dependent IgG has and Fc receptor that causes platelets to aggregate together -starts 3-14 days after initiation of heparin
Dx	-suspect if plts ↓ by 50% or if Plts<100K -suspect if thrombosis in unusual area -ELISA usually used, but SRA more accurate
Tx	-stop all heparin, including flushes -coumadin only if initially used w/ other anticoagulant due to initial prothrombotic state -cannot use LMW heparin (92% cross-reactivity) -Hirudin or argatroban or abciximab




Diagnostic studies for DVT

1. Impedance plethysmography (IPG)
 2. Doppler Ultrasound (DUS)
 3. Contrast venography
 4. I-125 Fibrinogen scan
-
-
-



D-Dimer


for diagnosis of DVT/PE

- **D-dimer is generated from degradation of circulating, crosslinked fibrin**
 - **The test is elevated in patients with acute venous thrombosis**
- 



D-Dimer


for diagnosis of DVT/PE

- Several assays are available to determine D-dimer levels
 - Most common assays are ELISA and Latex Agglutination
- 



D-Dimer Assay Characteristics


<i>ELISA</i>	<i>LATEX</i>
Quantitative	Semi Quant
Slow (hours)	Rapid (minutes)
Detects low levels	Needs higher levels





D-Dimer Assay Characteristics


<i>ELISA</i>	<i>LATEX</i>
Sensitivity 97%	Sensitivity 79%
Specificity 38% (high FP)	Specificity 71%






D-Dimers

Valuable screening test

- High sensitivity; low specificity
 - » Helpful only if *Negative*
 - » *Strong Negative Predictive Value-- Rules out PE when low probability*
 - Safe, noninvasive
 - Rapid, inexpensive
- 



Treatment of DVT

- Intravenous Heparin
 - SQ Low-molecular-weight heparin
 - ? Thrombolytic Therapy
 - Prevent post-phlebitic syndrome
 - Perhaps for proximal obstructive DVT
 - Oral Coumadin
- 

Comparison of Fractionated and LMW Heparin

Unfractionated

- heterogeneous mixture of polysaccharide chains
- 3,000 to 30,000 MW


LMW Heparin

- Fragments of unfractionated heparin
- chemical or enzymatic degradation
- Multiple fragments
- (5,000 MW)

Commercially Available **LMWH**


<u>Generic</u>	<u>Trade</u>	<u>MW</u>	<u>anti Xa/IIa</u>
Dalteparin	Fragmin	5000	4
Exoxaparin	Lovenox	3800	3
Nadroparin	Fraxiparin	4500	2
Reviparin	Clivarin	4000	4
Tinzaparin	Innohep	4900	2
Certoparin	Sandoparin	7600	2
Parvoparin	Fluxum	5000	3





Low Molecular Weight Heparin

ADVANTAGES

- **Longer half life**
 - **Predictable dose response**
 - **No lab monitoring**
 - **Fixed dosing**
 - **Less thrombocytopenia**
- 

Monitoring Requirements of Anticoagulants

<i>Indication</i>	<i>Monitoring Requirement</i>		
	<i>Regular Heparin</i>	<i>LMW Heparin</i>	<i>Coumadin</i>
<i>Prophylaxis</i>	<i>None</i>	<i>None</i>	<i>INR</i>
<i>Treatment</i>	<i>APTT</i>	<i>None</i>	<i>INR</i>

Check antiXa level in renal insufficiency , wt < 50 or > 80 kg



*Low M. Wt. Heparin
for out patient TX of DVT*

Two large randomized trials of
selected patients with proximal
DVT

Levine NEJM 1996; 334:677-81

Koopman NEJM 1996; 334:682-7


Showed that outpatient treatment
with LMWH was as safe and
effective as inpatient UH IV





*Results of a Randomized Trial Comparing
Out patient LMWH to Inpatient UH
for DVT (LEVINE et al)*


<i>EVENT</i>	<i>LMWH (N=247)</i>	<i>UH (N=253)</i>
<i>Recurrent Thromboembolism</i>	<i>5.3 %</i>	<i>6.7 %</i>
<i>Major Bleeding</i>	<i>0.5 %</i>	<i>2.0 %</i>
<i>Death</i>	<i>6.9 %</i>	<i>8.0 %</i>





*Results of a Randomized Trial Comparing
Out patient LMWH to Inpatient UH
for DVT (KOOPMAN et al)*


<i>EVENT</i>	<i>LMWH (N=202)</i>	<i>UH (N=198)</i>
<i>Recurrent Thromboembolism</i>	<i>6.9 %</i>	<i>8.5 %</i>
<i>Major Bleeding</i>	<i>2.0 %</i>	<i>1.2 %</i>
<i>Death</i>	<i>4.0 %</i>	<i>6.3 %</i>





COUMADIN

Clinical Points (1)

- Use INR (2.0 to 3.0)
 - When starting coumadin, you must continue heparin for at least FOUR DAYS.
 - Reason: Coumadin reduces protein c and Factor VII levels more quickly than the other Vit K factors - hypercoagulable
- 



Duration of Coumadin Therapy

Calf Vein

3 to 6 months

**DVT with
transient risk**

**4 to 6 weeks or
until risk resolves**

DVT with cancer

3 to 6 months plus


Recurrent DVT

Indefinite (life)





Prothrombin Time and the INR (International Normalized Ratio)

- *Thromboplastins from different animals or manufactures have significant effects on the PT obtained in different laboratories.*
 - *The INR has been adopted as a method for standardizing the PT results from different laboratories*
- 

Method for Calculating INR


$$INR = \left(\frac{PT \text{ (patient)}}{PT \text{ (group normals)}} \right)^{ISI}$$

*ISI = International Sensitivity Index
Adjustment for the sensitivity
of each type of thromboplastin*



Recommendations for Use of INR

Clinical State	Recommended INR
DVT/PE	2.0 to 3.0
Prosthetic Valve	2.5 to 3.5



Natural History of PE

- Studies suggest that nearly every patient with thrombus in the upper leg or thigh will have a PE if a sensitive enough test is done to look for it
- Current techniques allow us to demonstrate PE in 60-80% of these patients, even though about half have no clinical symptoms to suggest PE.

Emedicine: PE Feied C: June 2006





Sources of Pulmonary Emboli

DVT

Propagation from calf vein thrombi

Pelvic vein thrombi

Caval Thrombi

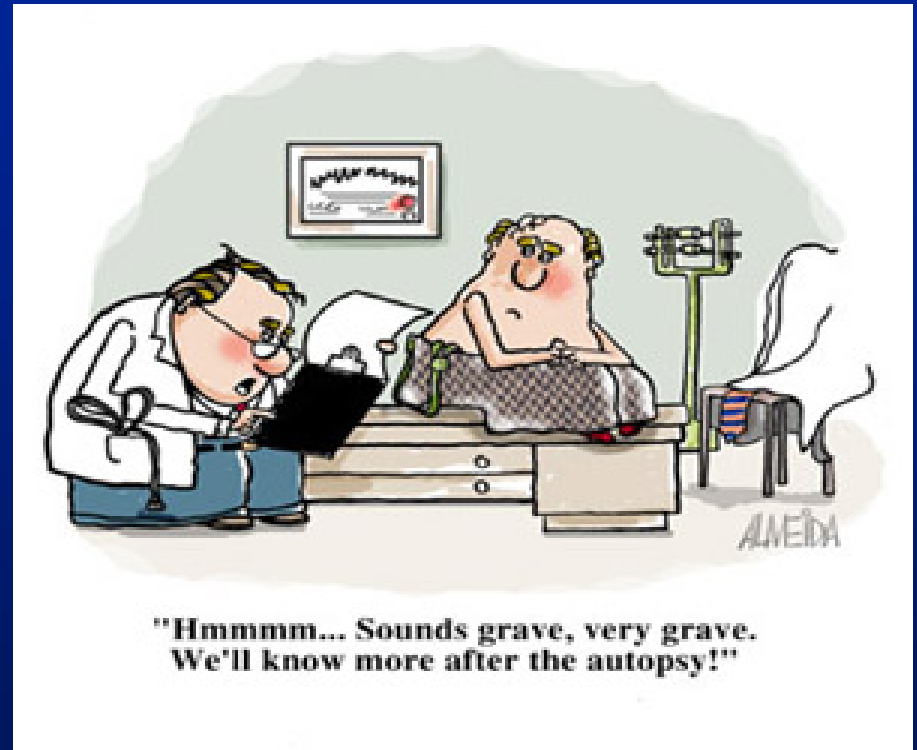
Renal vein thrombi

Right heart thrombi

Upper extremity thrombi




Autopsy Specimens of Venous Thrombi



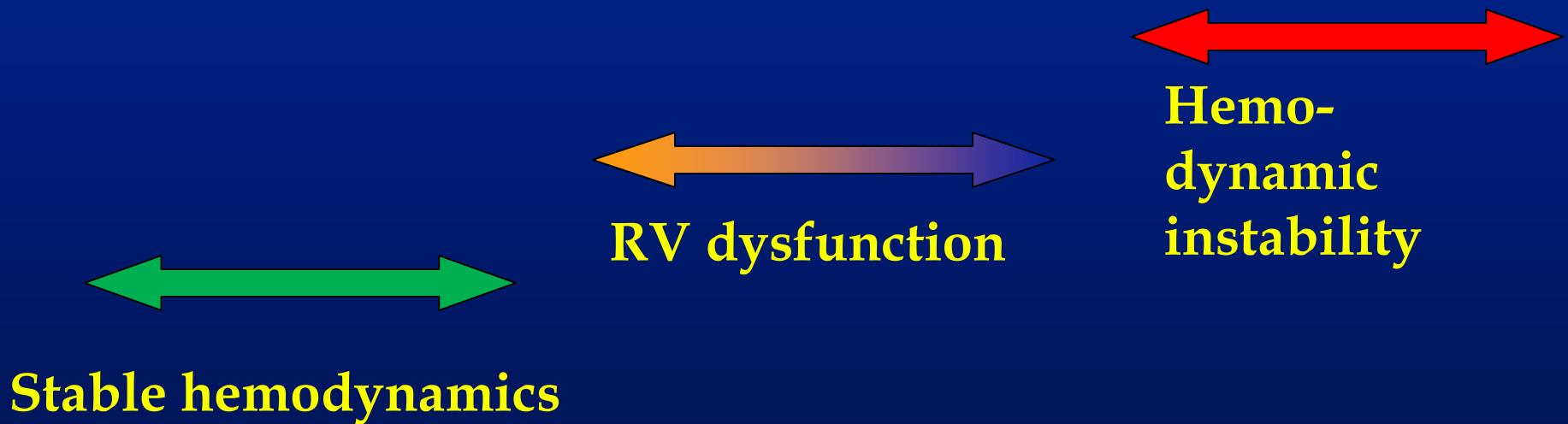
**"Hmmm... Sounds grave, very grave.
We'll know more after the autopsy!"**



Clinical Syndromes

- Pts with massive PE present with systemic arterial hypotension and evidence of peripheral thrombosis
 - Pts with moderate PE will have right ventricular hypokinesis on echocardiogram but normal systemic arterial pressure
 - Pts with small to moderate PE have both normal right heart function and normal systemic arterial pressure
- 

THE SPECTRUM OF PULMONARY EMBOLISM





Clinical Signs and Symptoms of Pulmonary Embolism

Dyspnea
Hemoptysis
Chest pain
Tachypnea
Tachycardia

Syncope

Hypotension



Table 2

Wells' Criteria for Assessment of Pretest Probability

The Wells Criteria for assessing pretest probability is important for diagnosing DVT and PE. Below describes the criteria and scoring system:

Criteria	Points		
Suspected DVT	3.0		
An alternative diagnosis is less likely than PE	3.0		
Heart rate > 100 beats per minute	1.5		
Immobilization or surgery in the previous four weeks	1.5		
Previous DVT or PE	1.5		
Hemoptysis	1.0		
Malignancy (on treatment, treated in the past six months or palliative)	1.0		
Score range	Mean probability of PE	% with this score	Interpretation of risk
<2 points	3.6%	40	Low
2 to 6 points	20.5%	53	Moderate
>6 points	66.7%	7	High

Source: Adapted with permission from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: Increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost.* 2000;83:416-420.

Table 1. Modified Wells Criteria for PE

Criteria	Points
Clinical signs of DVT	3.0
An alternate diagnosis is less likely than PE	3.0
Heart rate >100 beats per minute	1.5
Immobilization or surgery in past 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy (being treated, treated in past 6 months, or palliative)	1.0
Traditional Clinical Probability Assessment	
0-1 points	Low probability of PE
2-6 points	Moderate probability
>6 points	High probability
Simplified Clinical Probability	
PE likely	>4 points
PE unlikely	≤4 points



BioMarkers in Pulmonary Embolism

BNP

- Normal BNP: Benign Prognosis
- Elevated BNP associated with adverse outcome
- Other causes of elevated BNP in RV pressure overload:
 - Primary pulmonary hypertension
 - Chronic thromboembolic pulmonary hypertension
 - Chronic lung disease



BioMarkers in Pulmonary Embolism

Troponin

- In acute pulmonary embolism elevated troponin levels have been shown to predict an adverse outcome.
- Serum troponin levels should help stratify patients with submassive acute pulmonary embolism into a group in which aggressive medical or surgical intervention would be considered



Techniques for diagnosis of PE

EKG

Chest Radiographs

Echocardiogram

V/Q Scans


Helical CT

MRI





EKG Findings of Pulmonary Embolism

- Tachycardia
 - T-wave changes
 - ST-segment changes
 - Right axis deviation
 - S1-Q3-T3
 - RBBB
 - p-pulmonale
- 

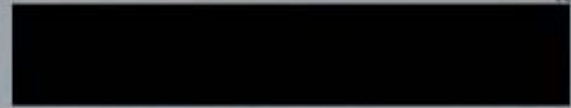
RY:
Dx:

Room:
Oper:

Rate 119
PR 112
QRSD 89
QT 31
QTc 43
36
RS 57
-7

Sinus tachycardia, rate 119.....Normal P axis, rate >= 100
High QRS voltage.....R in aVL >= 1.2 mV
Inferior infarct, age indeterminate.....O's & neg T's II, III, aVF
Anterior infarct.....2 Q waves in V2-V4

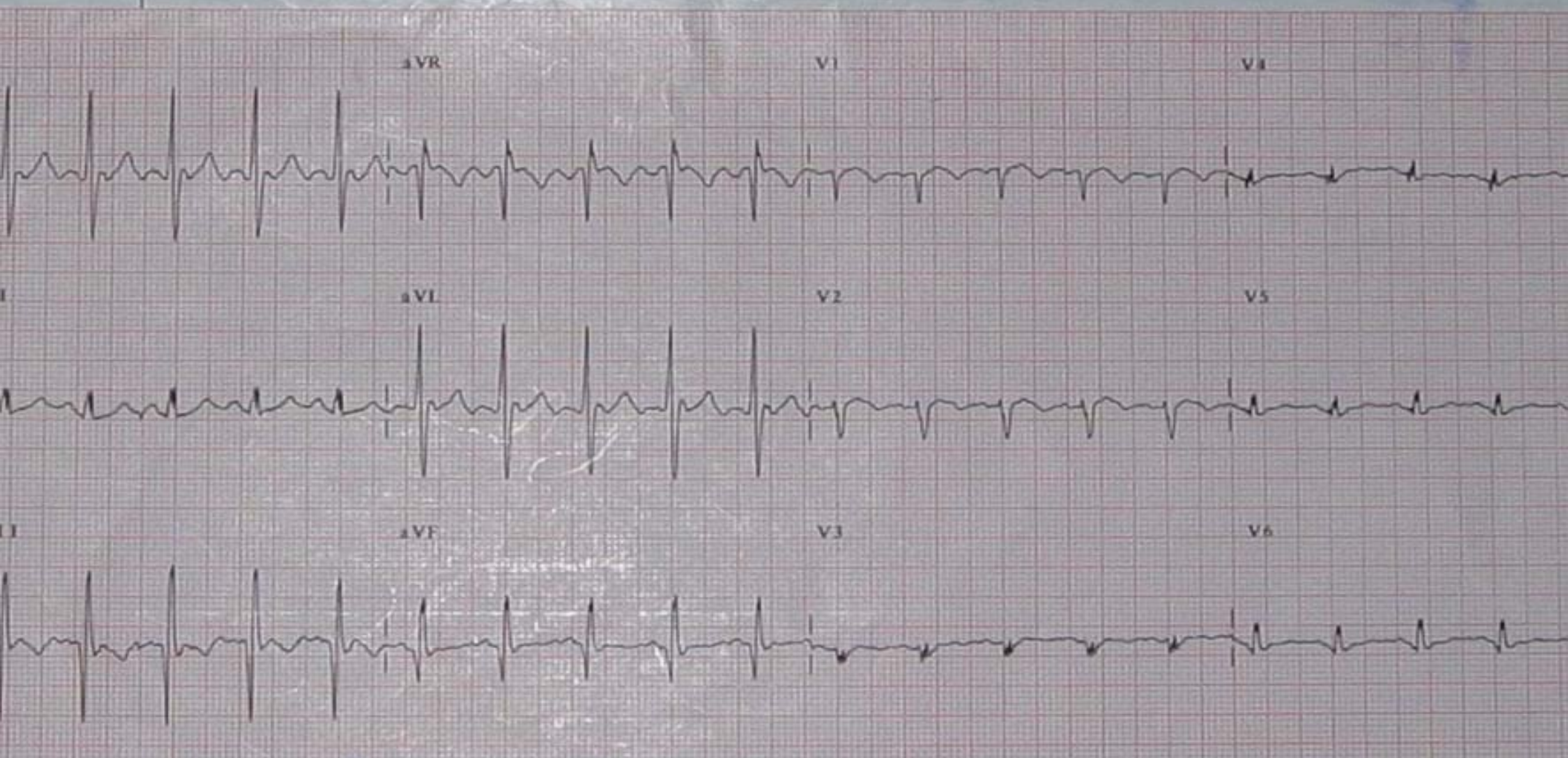
S1Q3T3



Requested by:

- ABNORMAL ECG -

PRELIMINARY-MD MUST REVIEW




Echocardiogram

- Useful for rapid triage of pts
- Assess right and left ventricular function
- Diagnostic of PE if hemodynamics by echo are consistent with clinical hx




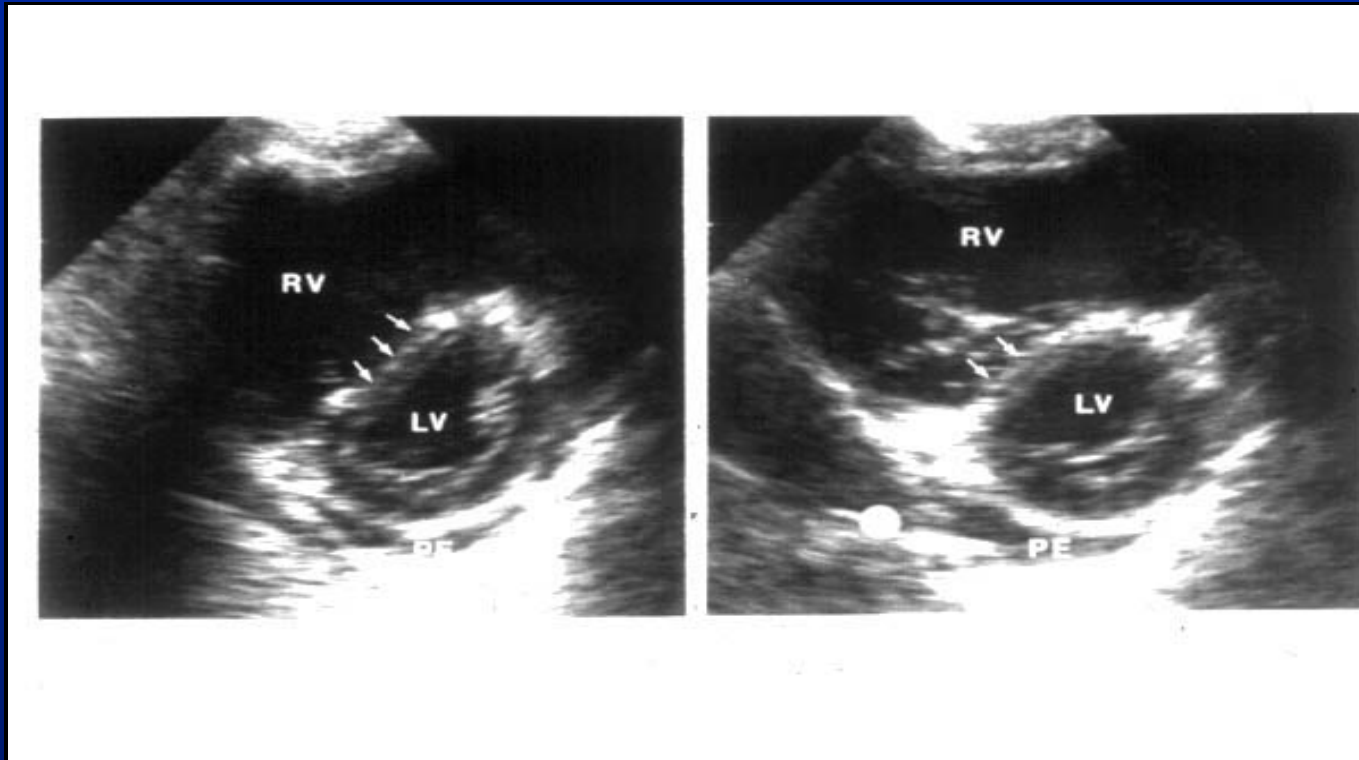
Echocardiogram

- TEE more sensitive than TTE
 - Demonstrate intracardiac clot or signs of right ventricular failure
 - Emboli observed = 42-50% mortality rate
 - Indirect evidence
 - right ventricular dilation
 - dilated pulmonary artery
 - abnl right ventricular wall motion
 - dilated vena cava
- 



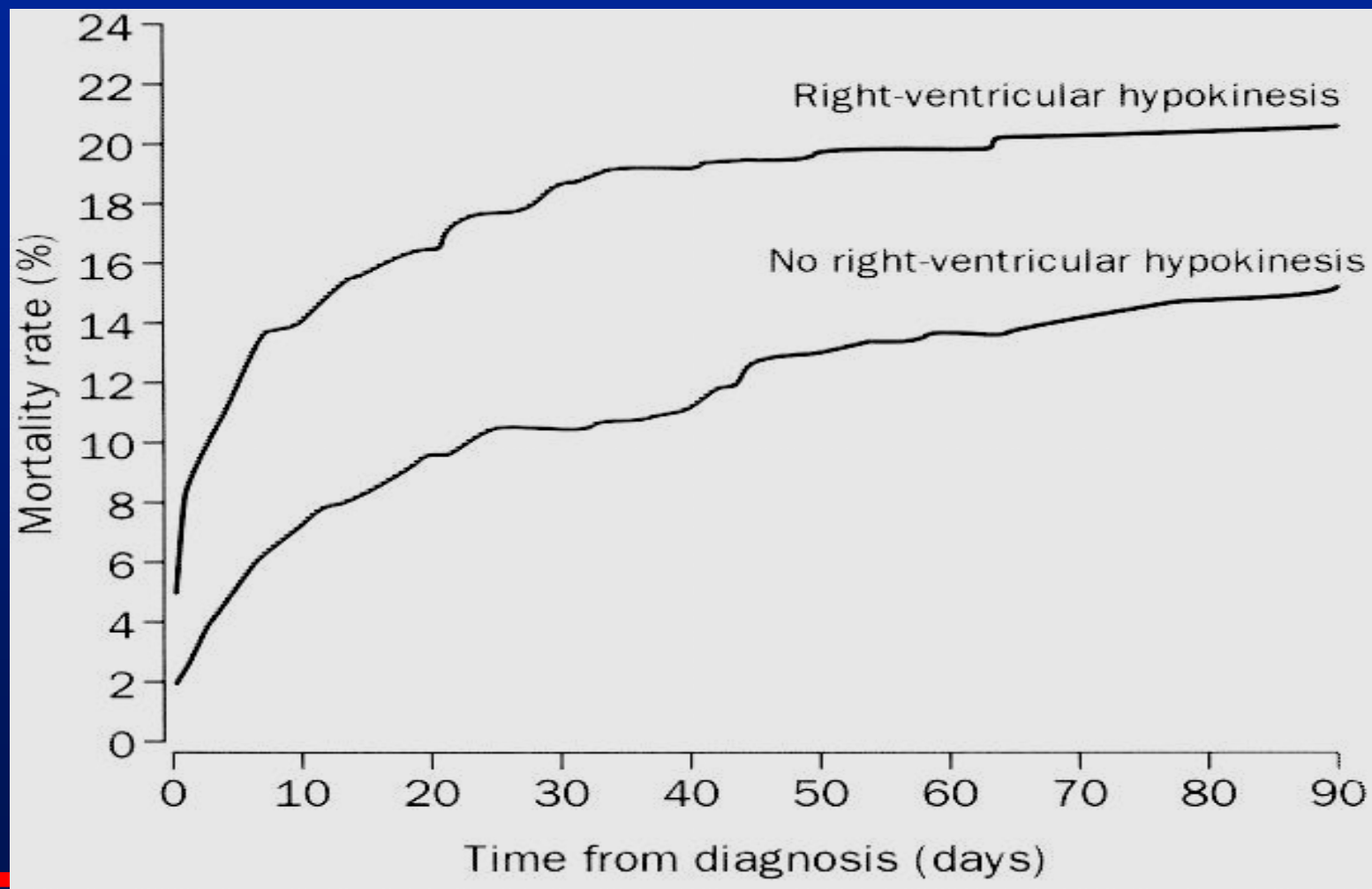
Right Ventricular Dysfunction

- Progressive right heart failure is the usual immediate cause of death from PE
 - As pulmonary vascular resistance increases, right ventricular wall tension rises and perpetuates further right ventricle dilation and dysfunction
 - Interventricular septum bulges into and compresses the normal left ventricle
- 



**Echocardiogram suggesting a PE.
Diastole on the left, systole on the
right**

MORTALITY *with RV* DYSFUNCTION



Goldhaber, et al. *Lancet*. 353: 1386-89;24 April 1999



Chest X-Ray Findings of Pulmonary Embolism

NORMAL

Atelectasis

Pleural Effusion

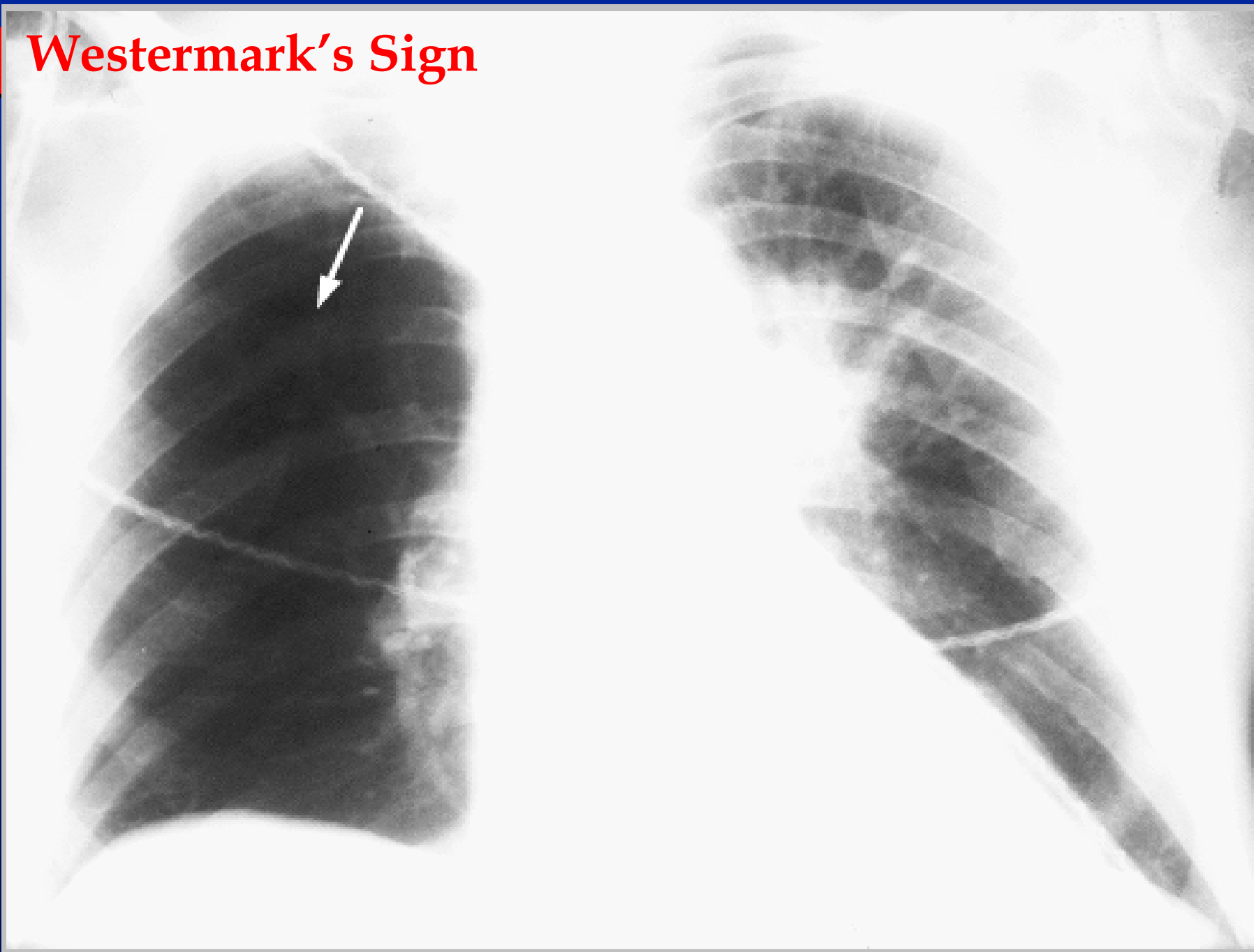
Infiltrate

Elevated diaphragm

Hampton's hump
Westermark's sign



Westermarck's Sign



*Hamptons
Hump*



Pulmonary Infarction

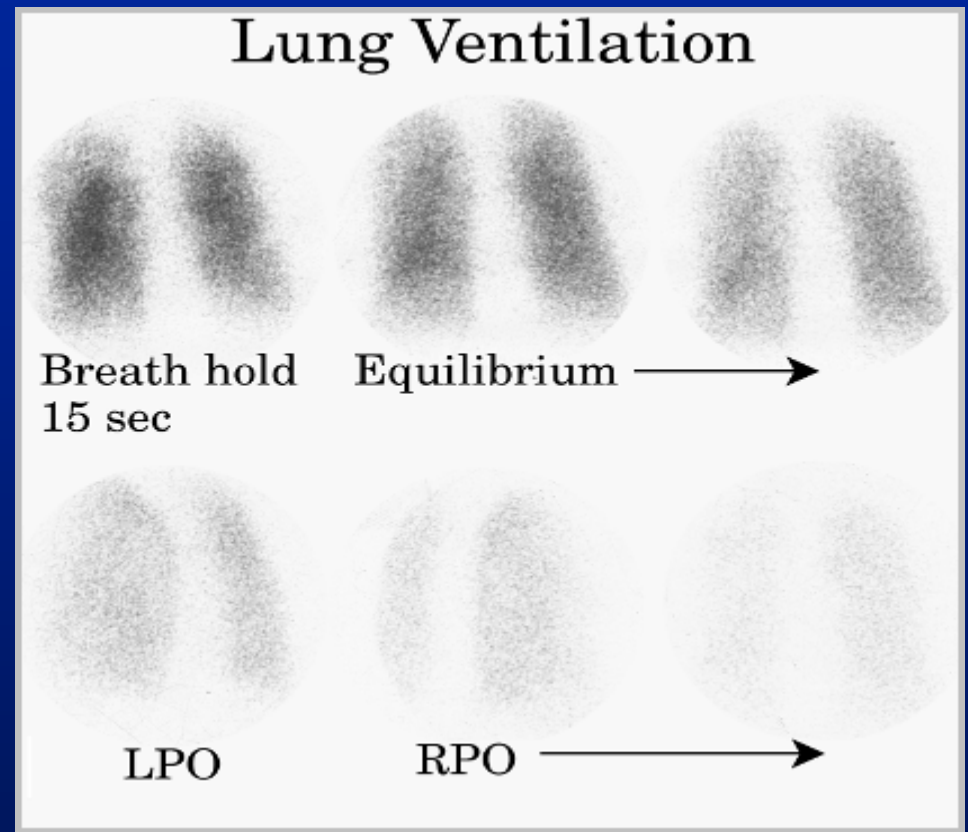
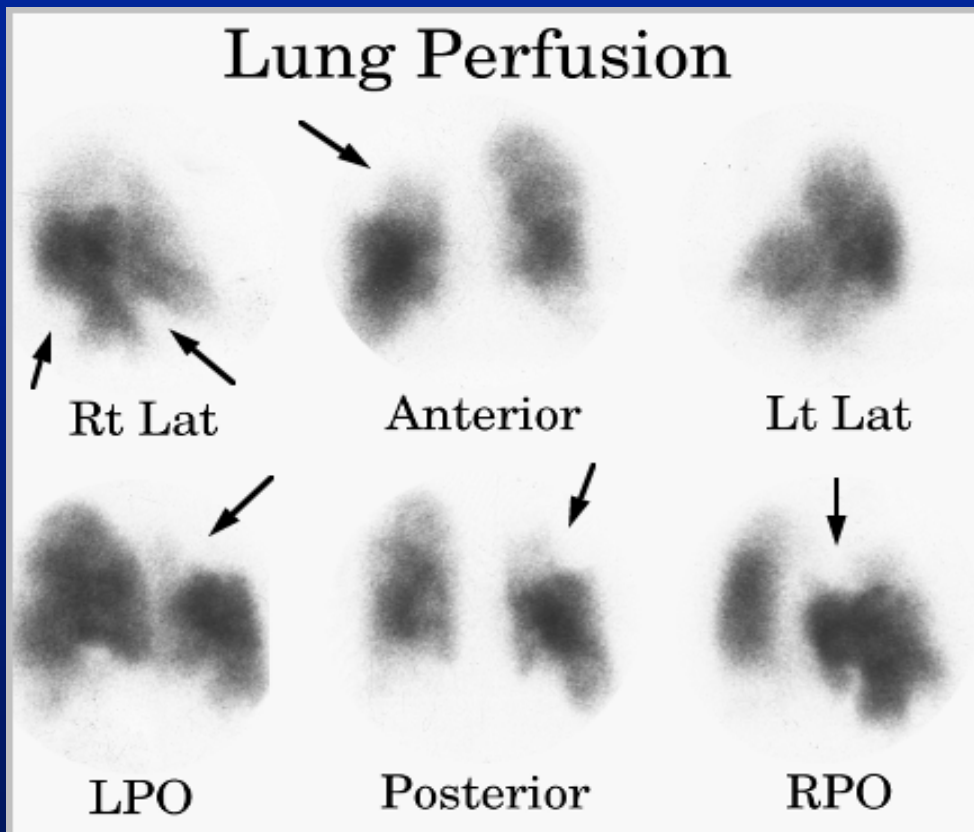
Hampton's Hump



V/Q Scan

- **Historically, the principal imaging test for the diagnosis of PE**
 - A perfusion defect indicates absent or decreased blood flow
 - Ventilation scan obtained with radiolabeled gases
 - A high probability scan is defined as two or more segmental perfusion defects in presence of normal ventilation scan

High Probability V/Q Scan



V/Q Scan

- Useful if the results are normal or near normal, or if there is a high probability for PE
 - As many as 40% of pts with high clinical suspicion for PE and low probability scans have a PE on angiogram



V/Q Lung Scan

- Normal V/Q Sensitivity 99%
 - Rules *out* PE
 - High Prob V/Q Specificity 96%
 - Rules *in* PE
 - But, >60% nondiagnostic
 - Takes >2 hr to perform
 - Not available at all times
-
-

Results from PIOPED V/Q (n=755)

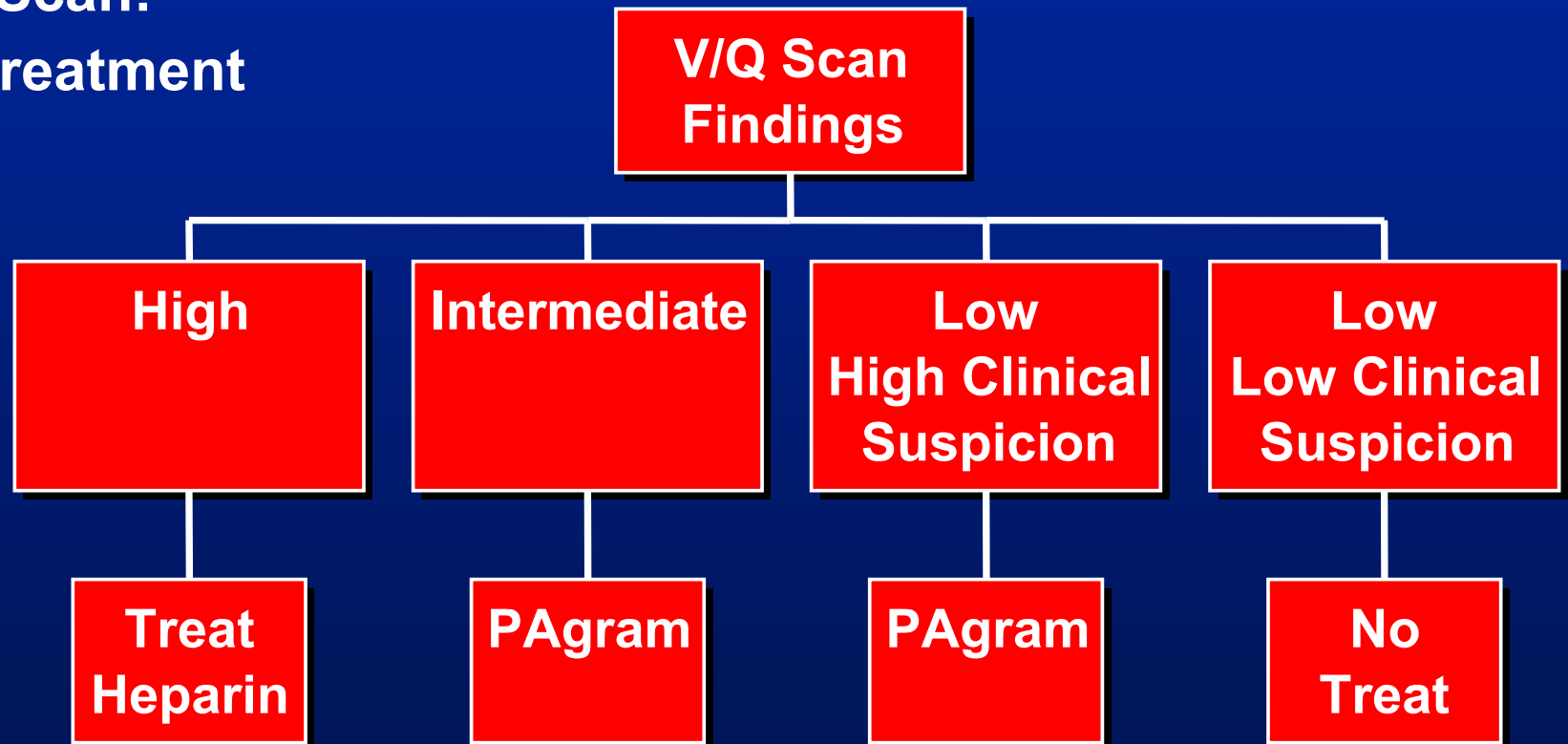
255/755 (31%) had PE at Angiogram)

SCAN	INCIDENCE	+Predictive Value
HIGH	13 %	88 %
INTERMEDIATE	39 %	33 %
LOW	34 %	16 %
VERY LOW	14 %	9 %

Treatment Algorithm

based on PIOPED Results

Normal Scan:
No Treatment





CT Pulmonary Angiogram


- Identifies proximal PE (which are the ones usually hemodynamically important)
- Not as accurate with peripheral PE





CT Angiogram

TESTS	Accuracy	False Negative
Helical CT alone	70%	30%
CT plus Negative US	87%	21%
CT plus Neg US plus V/Q	94%	5%

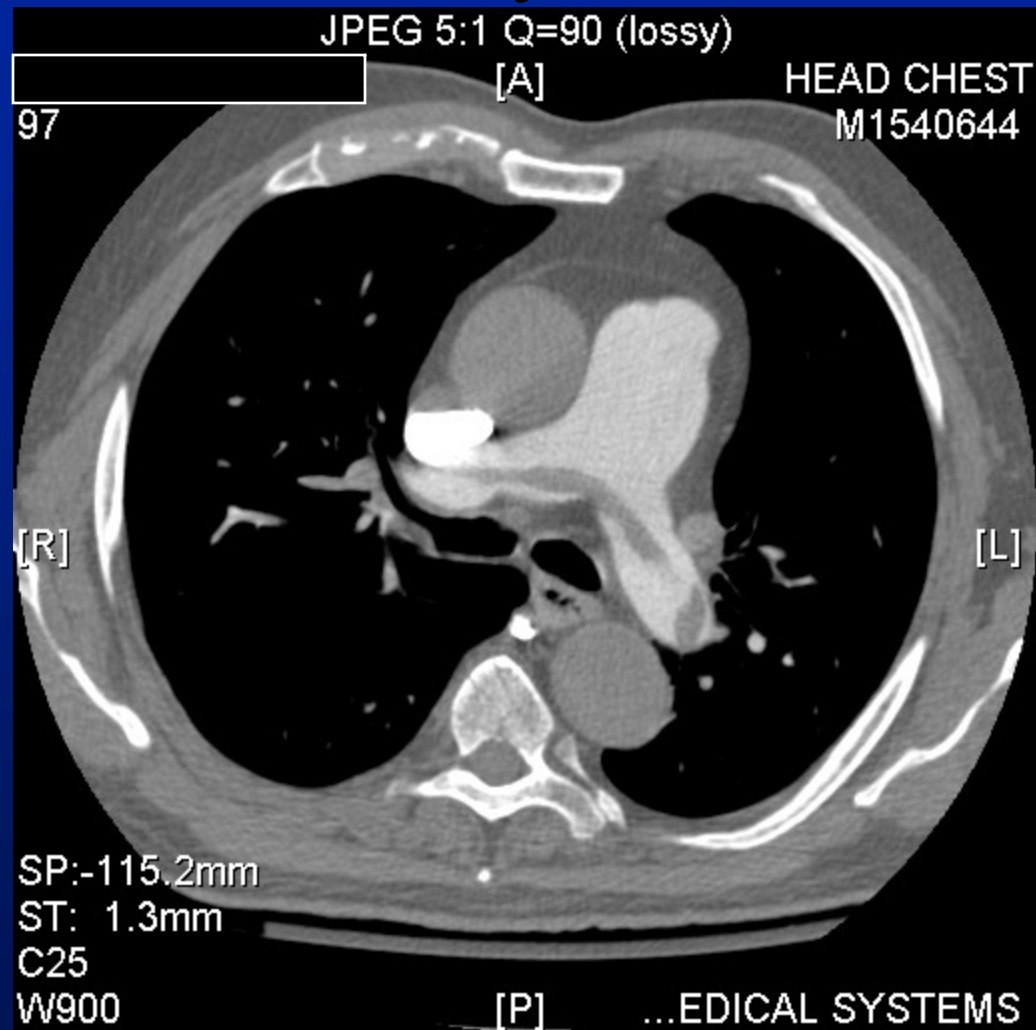


CT Angiogram

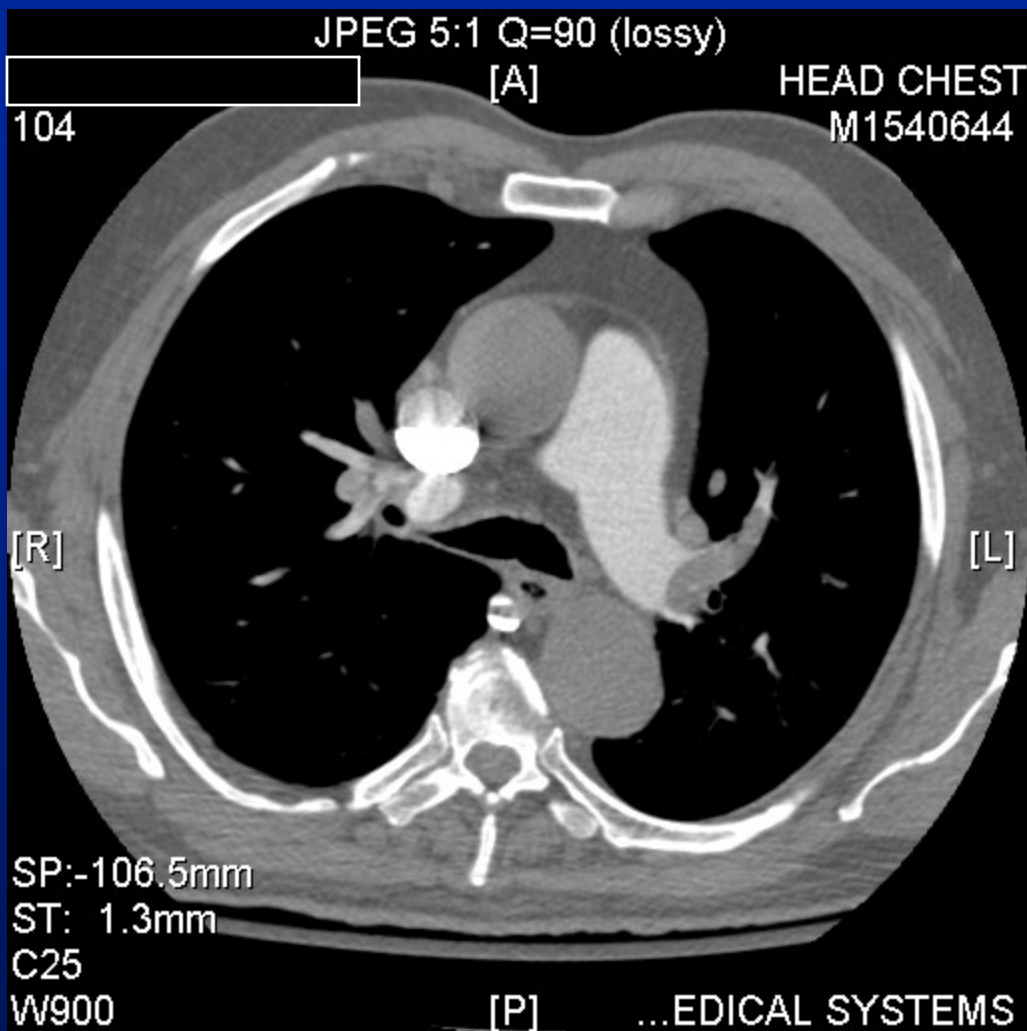
- Prospective study of consecutive, nonselected patients in a Geneva ER included 299 with suspected PE
- 39% had confirmed PE
 - High prob V/Q, +US, or +Angio
- **CT Sensitivity 70%**
- **CT Specificity 91%**

Perrier et al. *Ann Intern Med.* 2001; 135:88-97

Spiral CT for Dx PE




*Spiral
CT for
Dx
PE*





Spiral CT for PE

<i>Author</i>	<i>#pt / #PE</i>	<i>Sensitivity</i>	<i>Specificity</i>
Remy-Jardin 1992	42 / 18	100	96
Remy-Jardin 1996	72 / 39	91	78
Van Rossum 1996	77 / 39	95	97
Sostman 1996	28 / 21	73	97
Goodman1996	20 / 11	86	92
Mayo 1995	139 / 46	87	95
Drucker 1998	47 / 15	60	81




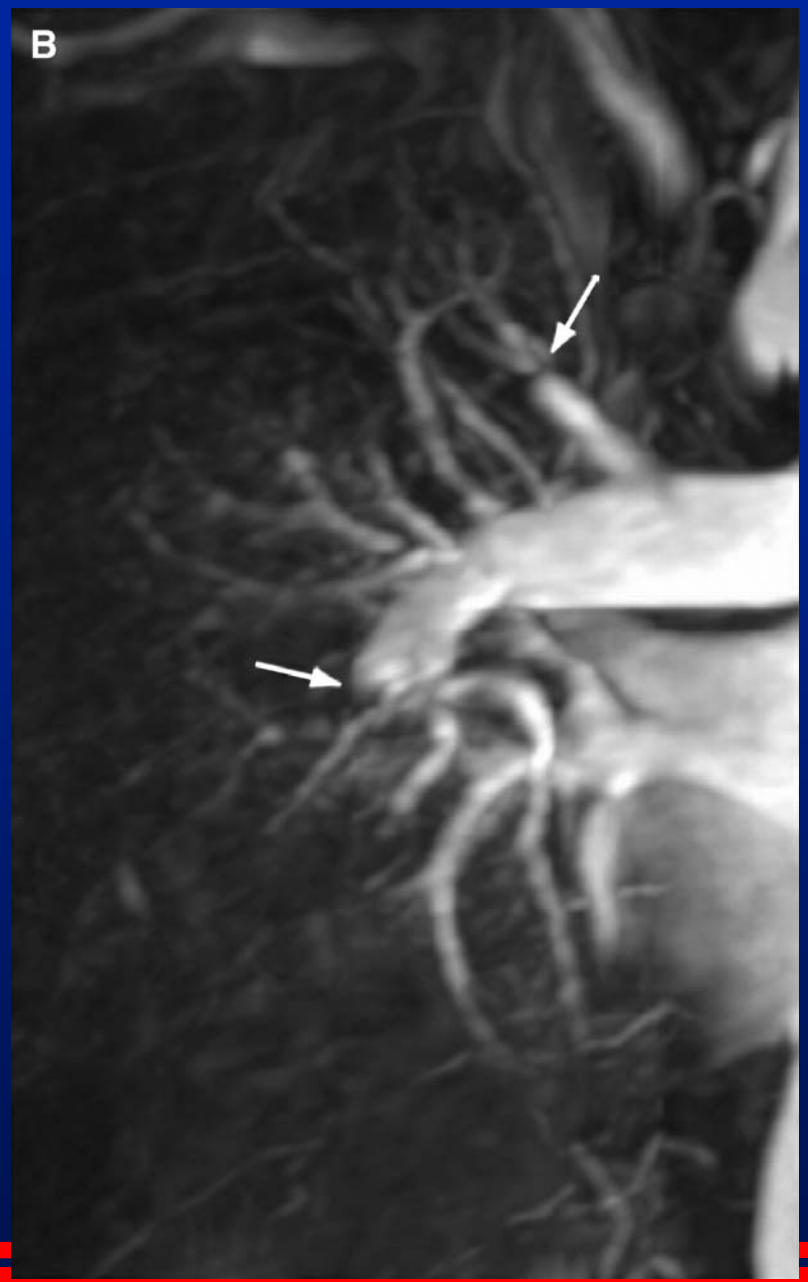
Pulmonary Embolism by CT






MRI/MRA

- No radiation or contrast exposure
 - Expensive
 - Not uniformly available
 - Limited data
 - Role not established
- 



Pulmonary Angiogram

- Most specific test available for diagnosis of PE
 - Can detect emboli as small as 1-2 mm
 - Most useful when the clinical likelihood of PE differs substantially from the lung scan or CTPA results
- 



Pulmonary Angiography

Diagnostic Findings

Well tolerated

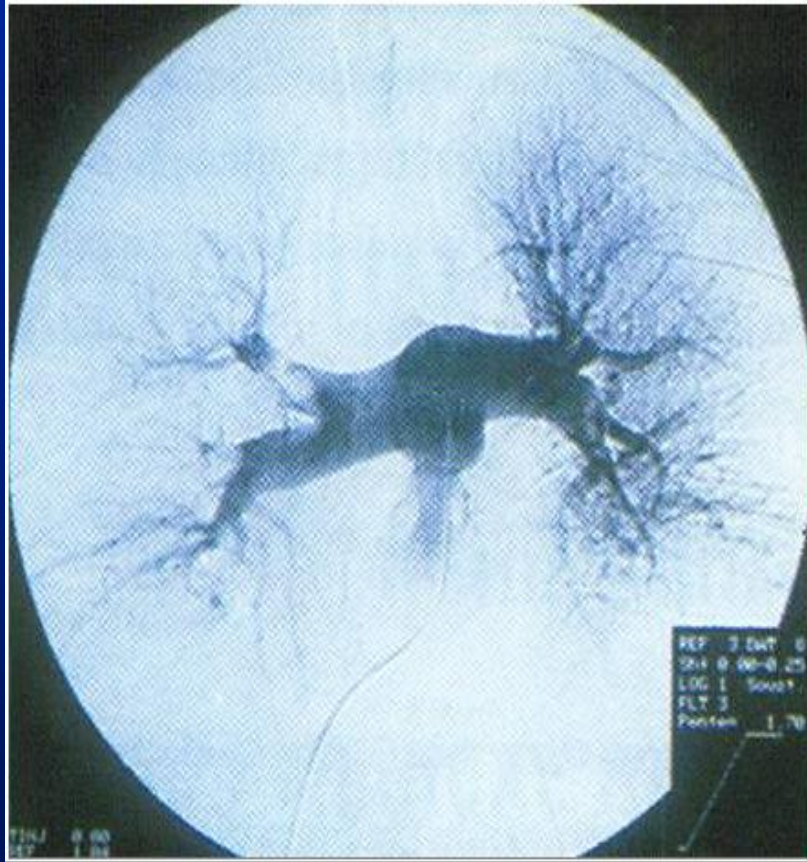
0.5 % Mortality

1 % Major Morbidity

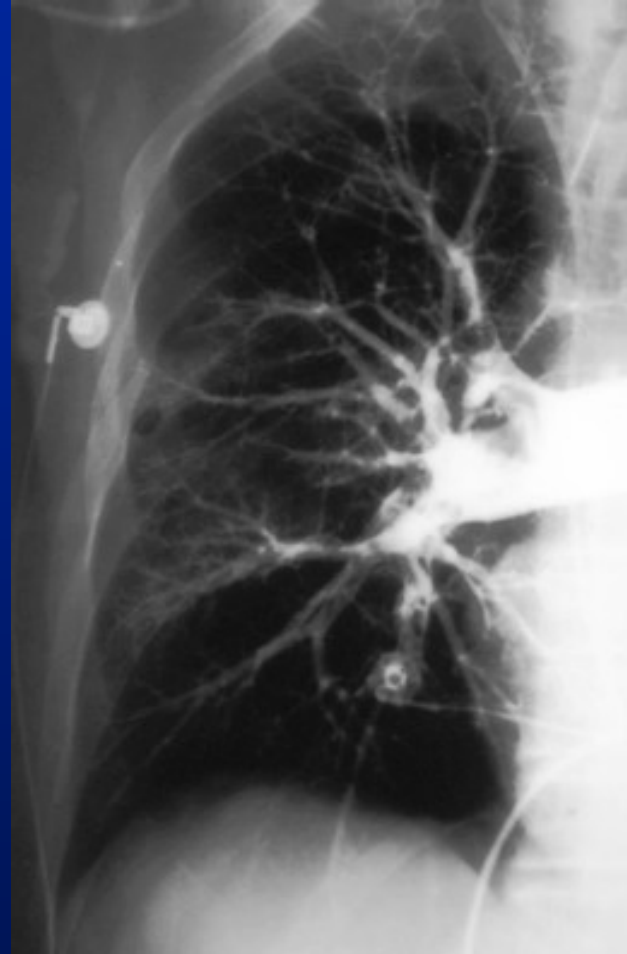
Diagnostic Findings	
	Intraluminal filling defects
	Vascular Cutoffs

In general, PIOPED has made PAgram MORE NECESSARY


Pulmonary angiogram



Pulmonary angiogram




Treatment of Pulmonary Embolism

- Intravenous Heparin
(most common treatment)
 - SQ Low-molecular-weight heparin
 - Thrombolytic Therapy
(for massive PE with shock)
 - Caval Interruption
- 



Low Molecular Weight Heparin Preparations


PREPARATION	MW	AntiXa/ IIa Ratio
Ardeparin (Normiflo)	6000	1.9
Dalteparin (Fragmin)	6000	2.7
Enoxaparin (Lovenox)	4200	3.8
Naroparin (Fraxiparin)	4500	3.6
Reviparin (Clivarine)	4000	3.5
Tinzaparin (Innohep)	4500	1.9




Plasma Half-life of LMW Heparin

- Plasma half-life of LMW heparin is 2 to 4 times that of unfractionated heparin
 - **Intravenous** - 2 to 4 hours
 - **Subcutaneous** - 3 to 6 hours
-
-


LMWH in the Treatment of Venous Thromboembolism

- The Columbus Investigators NEJM 1997; 337:657-62
 - 1,021 patients randomly - about 1/3 had PE
 - Fixed dose, LMWH (reviparin) or Adjusted dose, UH, IV
 - Followed for 12 weeks
- 



Results of a Randomized Trial Comparing LMWH to UH for DVT /PE The Columbus Investigators

<i>EVENT</i>	<i>LMWH (N=510)</i>	<i>UH (N=511)</i>
<i>Recurrent Thromboembolism</i>	<i>5.3 %</i>	<i>4.9 %</i>
<i>Major Bleeding</i>	<i>3.1 %</i>	<i>2.3 %</i>
<i>Death</i>	<i>7.1 %</i>	<i>7.6 %</i>



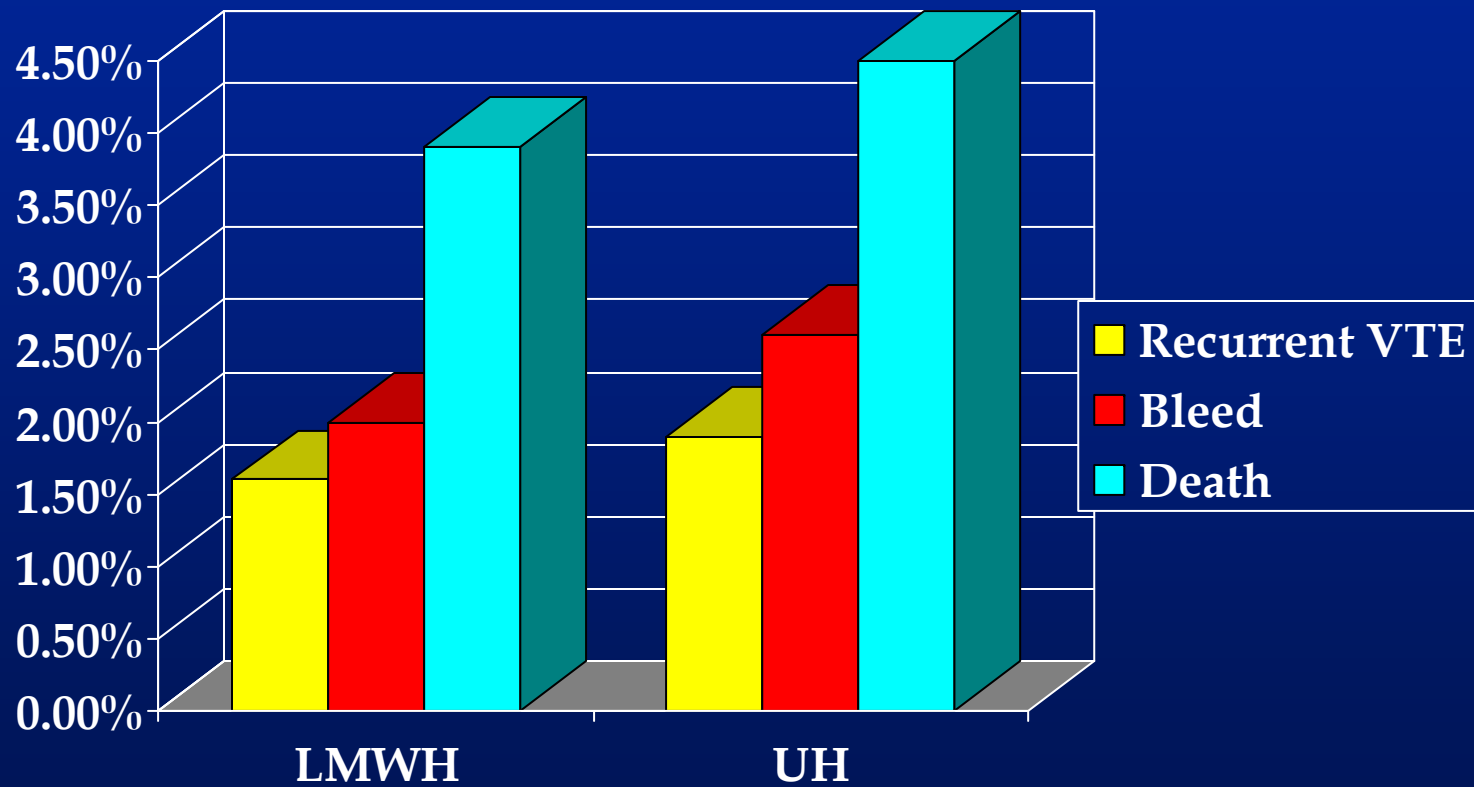
LMWH vs UH for Acute Pulmonary Embolism

Simonneau et al. NEJM 1997; 337:663-9

612 pts with acute PE

- 304 pts SQ LMWH (tinzaparin)
175 U/kg/day - once
 - 308 pts IV UH - adjusted
 - coumadin - 3 month follow-up
-
-


LMWH vs UH for PE ***(Simonneau et al)***





Lytic Therapy for PE

When and Who

- Higher risk of bleed and higher cost than heparin
 - When lytic Tx and heparin were compared, the mortality and degree of clot lysis were about the same by day 5.
 - When rapid clot lysis is essential (i.e. hemodynamic instability) lytic therapy is warranted.
- 

Approved Thrombolytic Regimens for Pulmonary Embolism

AGENT	Dosage Regimen
STREPTOKINASE	250,000 U IV loading dose over 30 min then 100,000 U/Hr for 24 hrs
UROKINASE	2,000 U/lb IV loading dose over 10 min then 2,000 U/lb/Hr for 12 to 24 Hr
TISSUE PLASMINOGEN ACTIVATOR	100 mg IV over 2 Hr




Contraindications to Systemic Thrombolytic Therapy

ABSOLUTE

- Previous hemorrhagic CVA
- Intracranial Neoplasm
- Head Trauma or neurosurgery
- Active/recent internal bleeding


RELATIVE

- Bleeding diathesis
- Uncontrolled severe hypertension
- CPR
- Pregnancy
- Nonhemorrhagic CVA





Indications for Vena Caval Interruption

1. Contraindication to anticoagulation
 2. Recurrent emboli on adequate Tx
 3. Serious bleeding on anticoagulation
 4. Massive pulmonary embolism
 5. Psychosocial reasons
- 



Embolectomy in Acute PE

METHODS

1. Surgical Embolectomy

Requires Bypass

High morbidity and mortality emergently

? In-house

Reserved for refractory patients

2. Catheter Embolectomy (fragmentation)

No Bypass

Can be done in-house

Less technical expertise



