Pulmonary Embolism - 2023

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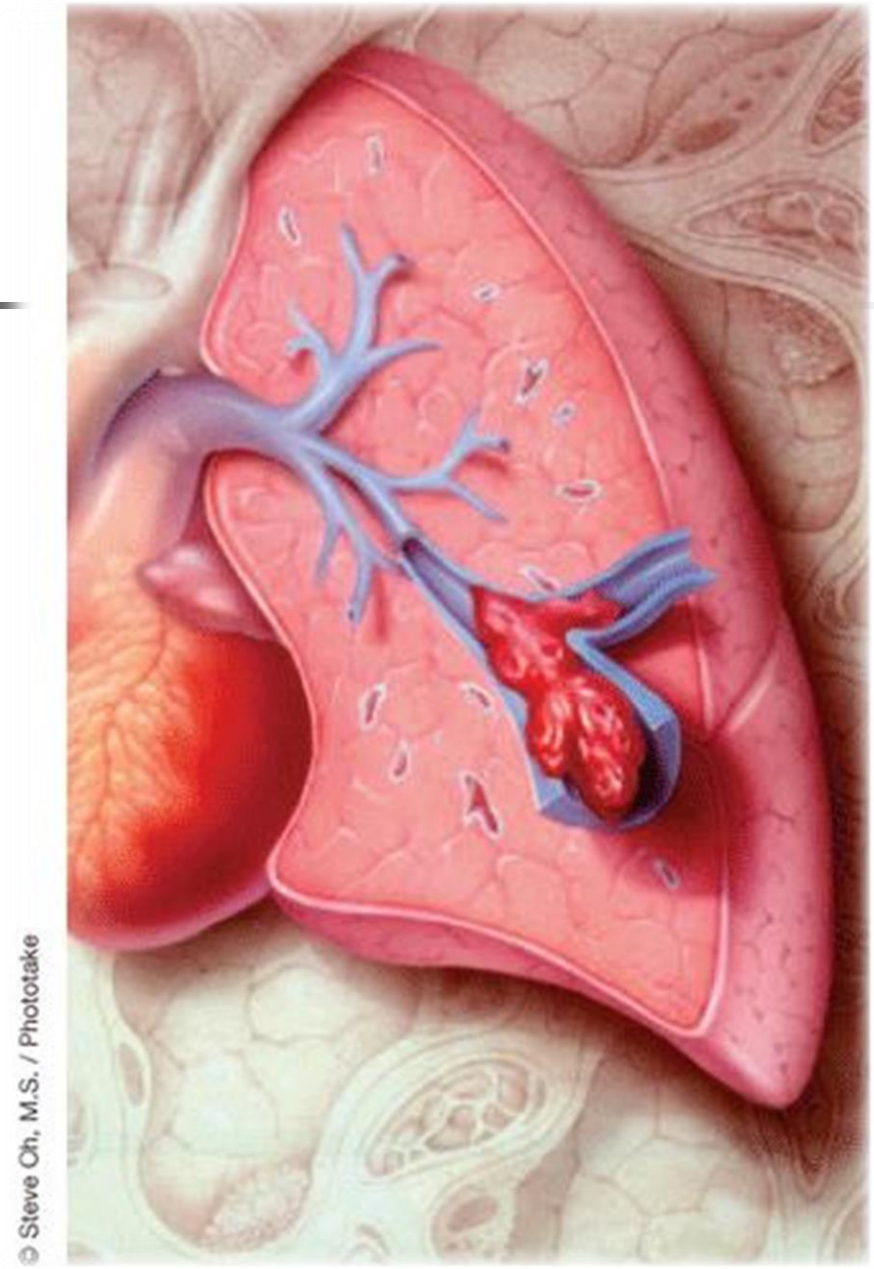
Pulmonary Embolism (PE)

Lecture Objectives:

To understand the followings:

- Prevalence of PE
- Risk factors
- Clinical features
- Pathophysiology
- Massive PE
- Diagnostic workup
- Treatment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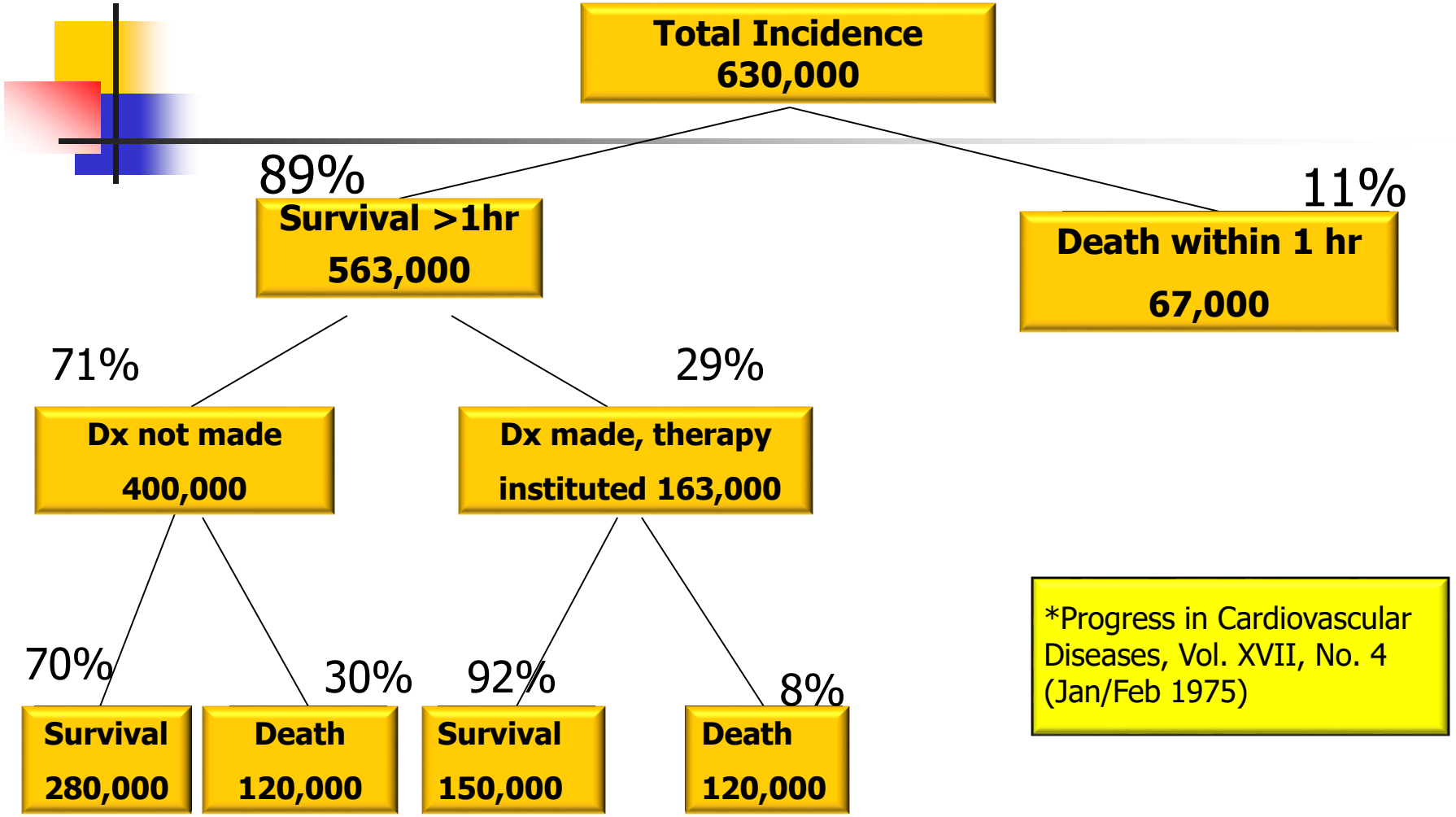
- 50,000 individuals die from PE each year in USA
- The incidence of PE in USA is 500,000 per year

Incidence of Pulmonary Embolism Per Year in the United States*



*Progress in Cardiovascular Diseases, Vol. XVII, No. 4 (Jan/Feb 1975)

Incidence

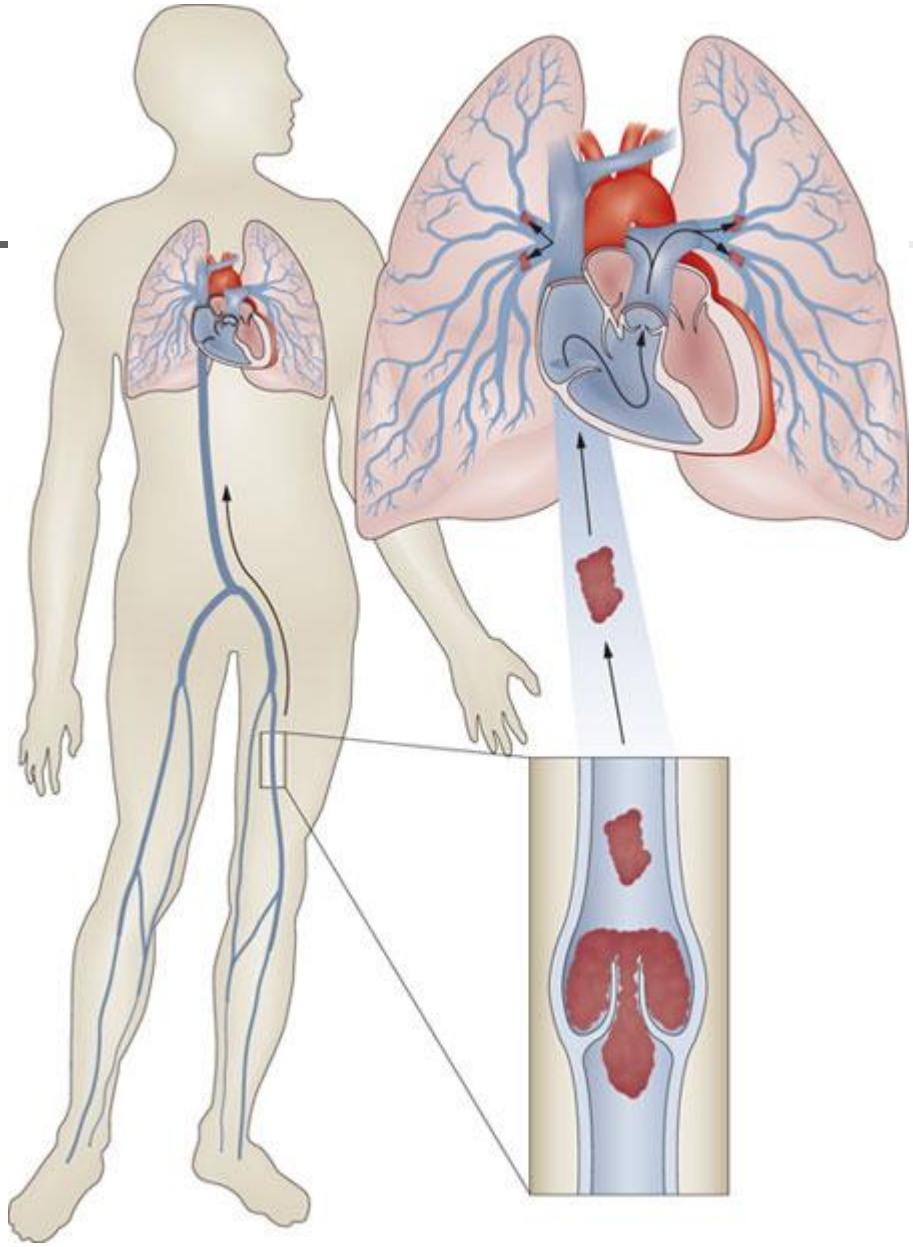
- The annual incidence of pulmonary embolism in the population is 1/1000 people,
- but this increases sharply with age,
  - 1.4 / 1000 people aged 40-49
  - 11.3 / 1000 aged 80 years or over

Risk factor for venous thrombosis

- Stasis
- Injury to venous intima
- Alterations in the coagulation-fibrinolytic system

Source of emboli

- Deep venous thrombosis (>95%)
- Other veins:
  - Renal
  - Uterine
  - Right cardiac chambers



Risk factors for DVT

- General anesthesia
- Lower limb or pelvic injury or surgery
- Congestive heart failure
- Prolonged immobility
- Pregnancy
- Postpartum
- Oral contraceptive pills
- Malignancy
- Obesity
- Advanced age
- Coagulation problems

Risk factors for DVT

Box 1: Transient risk factors for venous thrombosis[16]

Strong risk factor (odds ratio >10)
- Hip or leg fracture
- Hip or leg joint replacement
- Major general surgery
- Major trauma
- Spinal cord injury

Moderate risk factor (odds ratio 2-9)
- Arthroscopic knee surgery
- Central venous lines
- Congestive heart or respiratory failure
- Hormone replacement therapy
- Malignancy
- Oral contraceptive therapy
- Paralytic stroke
- Postpartum
- Previous venous thromboembolism
- Thrombophilia

Weak risk factor (odds ratio <2)
- Bed rest >3 days
- Immobility due to sitting (eg, prolonged road or air travel)
- Increasing age
- Laparoscopic surgery (eg, cholecystectomy)
- Obesity
- Pregnancy (antepartum)
- Varicose veins

BMJ 2020;370:m2177 | doi: 10.1136/bmj.m2177

Risk factors

- 50%of venous thromboembolism events are associated with a transient risk factor,
- 20% are associated with cancer,
- The remainder are associated with minor or no risk factors and are thus **classified as unprovoked**

Clinical features

- Sudden onset dyspnea
- Pleuritic chest pain
- Hemoptysis
- Clinical clues cannot make the diagnosis of PE; their main value lies in suggesting the diagnosis

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Pulmonary embolism	Dyspnea	73	77
	Tachypnea	70	70
	Chest pain	66	55
	Cough	37	—
	Tachycardia	30	43
	Cyanosis	1	18
	Hemoptysis	13	13
	Wheezing	9	—
	Hypotension	—	10

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Pulmonary Embolism	Syncope	—	10
	Elevated jugular venous pulse	—	8
	Temperature >38.5°C	7	—
	S-3 gallop	3	5
	Pleural friction rub	3	2

Signs or symptoms observed in patients with thromboembolism			
		Study	
		Stein et al., % (n= 117)	Anderson et al., % (n= 131)
Deep vein thrombosis	Swelling	28	88*
	Pain	26	56
	Tenderness	—	55
	Warmth	—	42
	Redness	—	34
	Homan's sign	4	13
	Palpable cord	—	6

Clinical probability scores

Modified Geneva rule*[33]	
Age ≥65 years	1
Previous DVT or PE	3
Surgery or fracture within 1 month	2
Active cancer	2
Unilateral lower limb pain	3
Pain on deep palpation of lower limb and unilateral edema	4
Hemoptysis	2
Heart rate 75-94 beats/min	3
Heart rate ≥95 beats/min	5
Simplified Geneva rule†[34]	
Age >65 years	1
Surgery or fracture within 1 month	1
Active cancer	1
Unilateral lower limb pain	1
Hemoptysis	1
Pain on deep vein palpation of lower limb and unilateral edema	1
Heart rate 75-94 beats/min	1
Heart rate >94 beats/min	2

Clinical probability scores

- Using modified score, <3 points indicates low probability, 4-10 points indicates intermediate probability, and>10 points indicates high probability.

- Using simplified score, ≤2 points indicates that PE is unlikely.

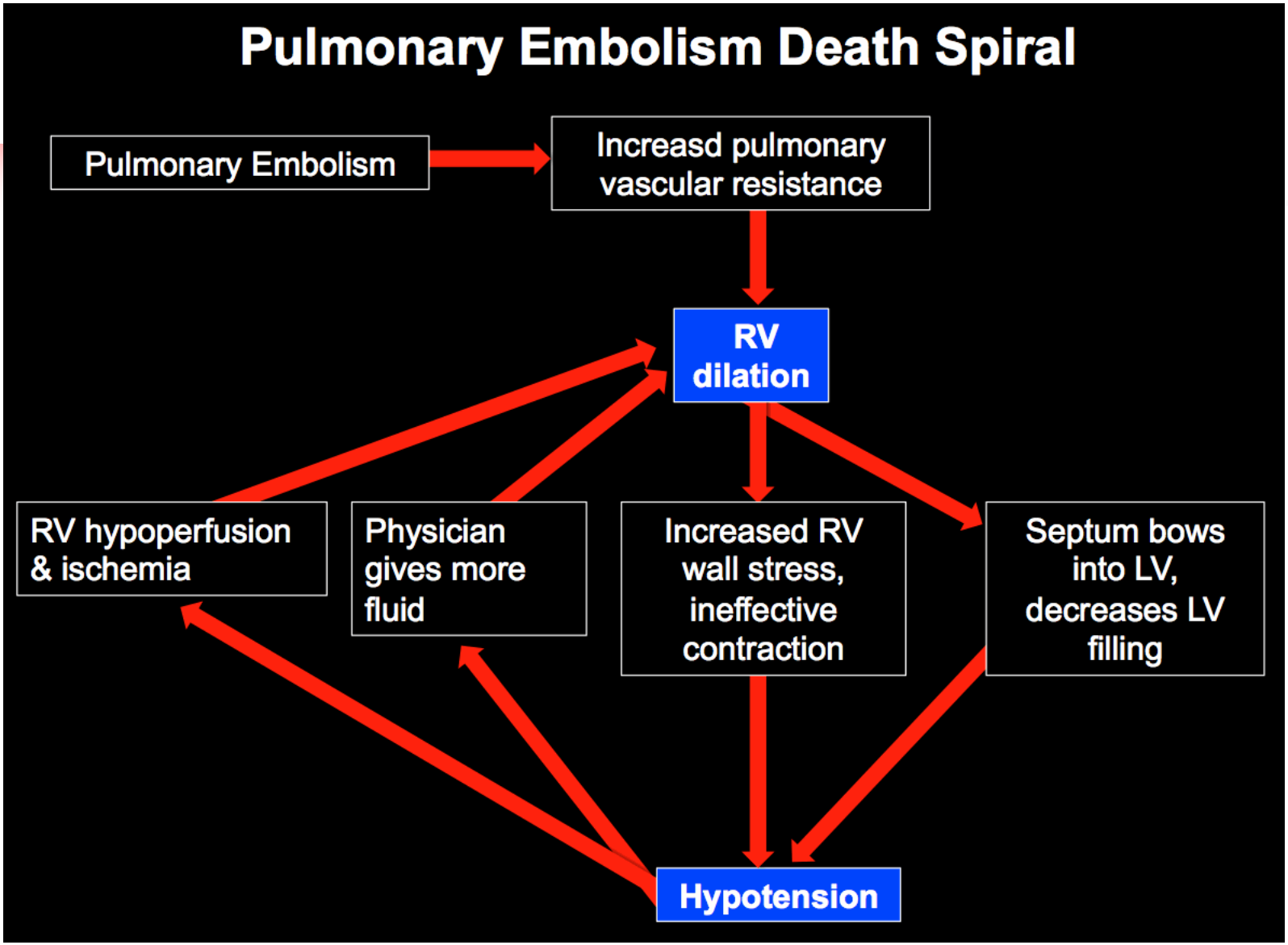
Clinical probability scores

Wells rule‡[35 36]	
Signs or symptoms of DVT	3
Alternative diagnosis is less likely than PE	3
Heart rate >100 beats/min	1.5
Immobilization/surgery in previous 4 weeks	1.5
History of DVT or PE	1.5
Hemoptysis	1
Active cancer	1

Using traditional score, >6.0 points indicates high probability, 2.0-6.0 points indicates moderate probability,
and <2.0 points indicates low probability of PE. Using simplified score, >4 points indicates that PE is likely and
≤4 points indicates that PE is unlikely.

Massive Pulmonary Embolism

- It is a catastrophic entity which often results in acute right ventricular failure and death
- Frequently undiscovered until autopsy
- Fatal PE typically leads to death within one to two hours of the event


Pulmonary Embolism Death Spiral
Pulmonary Embolism
Increasd pulmonary vascular resistance
RV dilation
RV hypoperfusion & ischemia
Physician gives more fluid
Increased RV wall stress, ineffective contraction
Septum bows into LV, decreases LV filling
Hypotension

Pathophysiology

- Massive PE causes an increase in PVR $\rightarrow$ right ventricular outflow obstruction $\rightarrow$ decrease left ventricular preload $\rightarrow$ Decrease CO

- In patients without cardiopulmonary disease, occlusion of 25-30 % of the vascular bed $\rightarrow$ increase in Pulmonary artery pressure (PAP)

- Hypoxemia ensues $\rightarrow$ stimulating vasoconstriction $\rightarrow$ increase in PAP

Pathophysiology

- More than 50% of the vascular bed has to be occluded before PAP becomes substantially elevated
- When obstruction approaches 75%, the RV must generate systolic pressure in excess of 50mmHg to preserve pulmonary circulation
- The normal RV is unable to accomplish this acutely and eventually fails

Original Article

Annals of Thoracic Medicine - Vol 4, Issue 1, January-March 2009

Outcome of patients with pulmonary embolism admitted to the intensive care unit

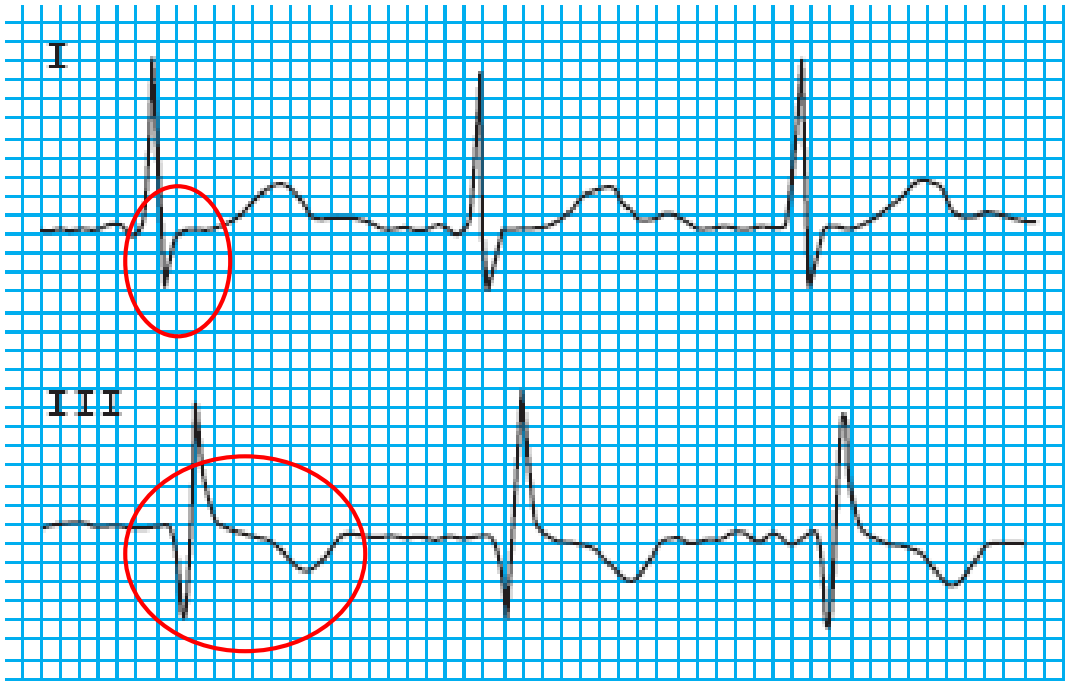
Hadeel Al Otair, Mohammed Chaudhry, Shaffi Shaikh, Ahmed BaHammam

- 56 patients with a mean age of patients was 40.6 ± 10.6 years.
- 12.5% had massive PE with hemodynamic instability, and 26.8% had sub-massive PE.
- Most common risk factors were recent
  - surgery (55.4%) and obesity (28.6%).
- One patient experienced fatal gastrointestinal bleeding post-thrombolysis.
- Two patients with massive PE and five with sub-massive PE died within 72 hours of ICU admission, resulting in an overall mortality rate of 14%.
- Non-survivors were older and had a higher prevalence of immobility and cerebrovascular diseases compared to survivors.
- **In conclusion,** the mortality rate of patients with PE admitted to the ICU in this study was comparable to other published studies. Older age, immobility, and coexistent cerebrovascular diseases were associated with worse outcomes

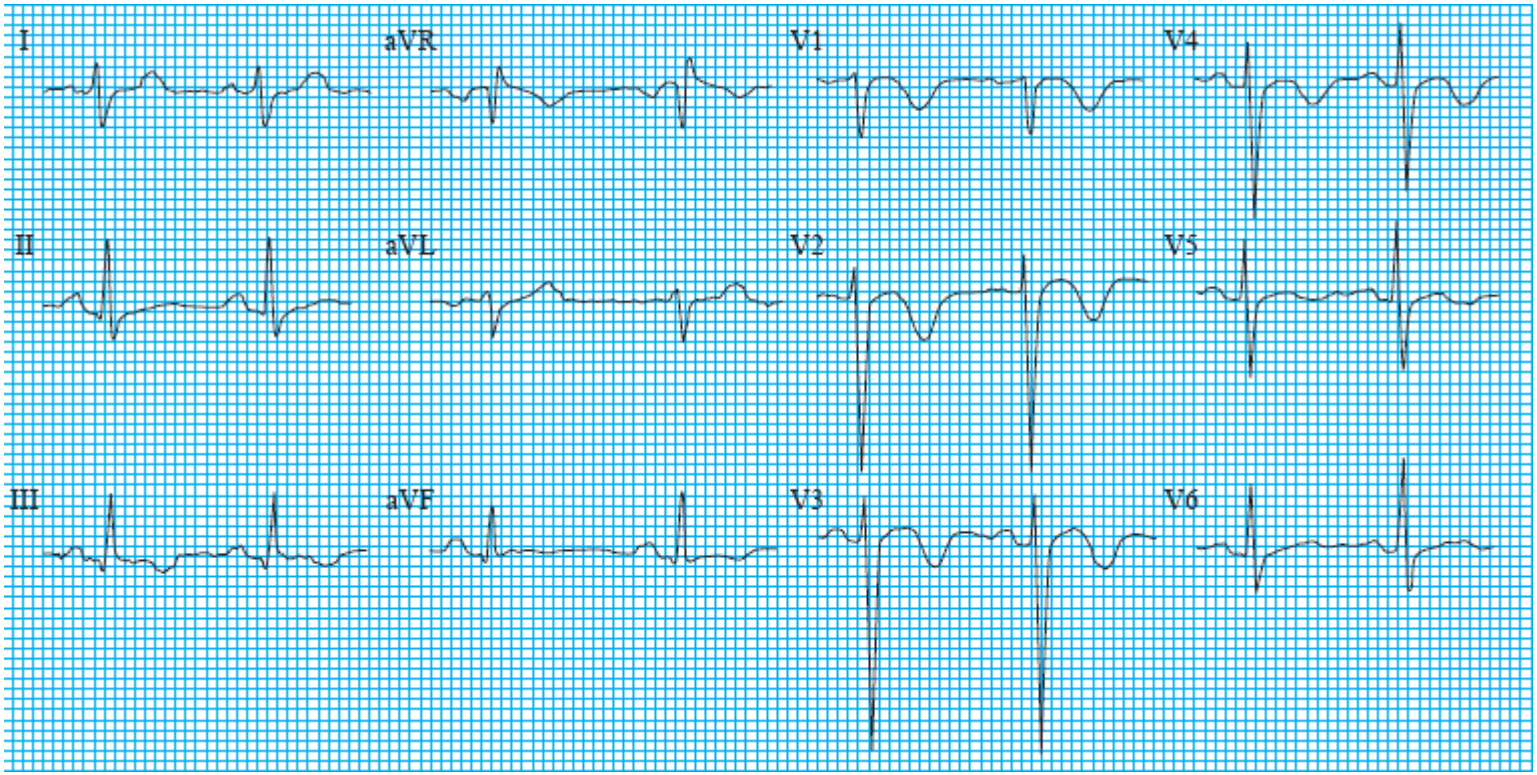
Diagnosis

- CXR
- ABG:
- ECG
- V/Q
- Spiral CT
- Echo
- Angio
- D-dimer

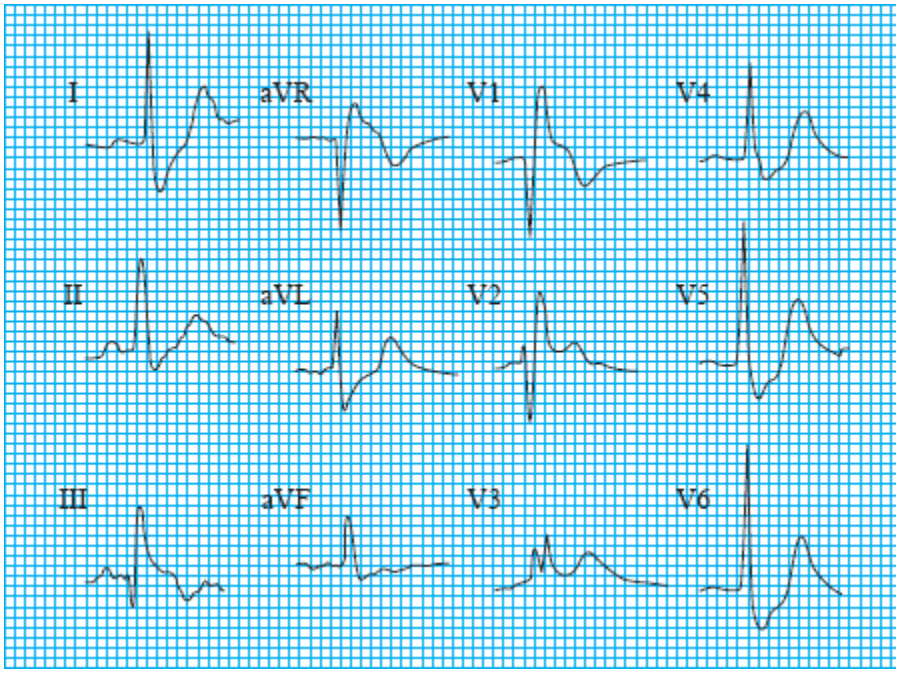
S1 Q3 T3 Pattern



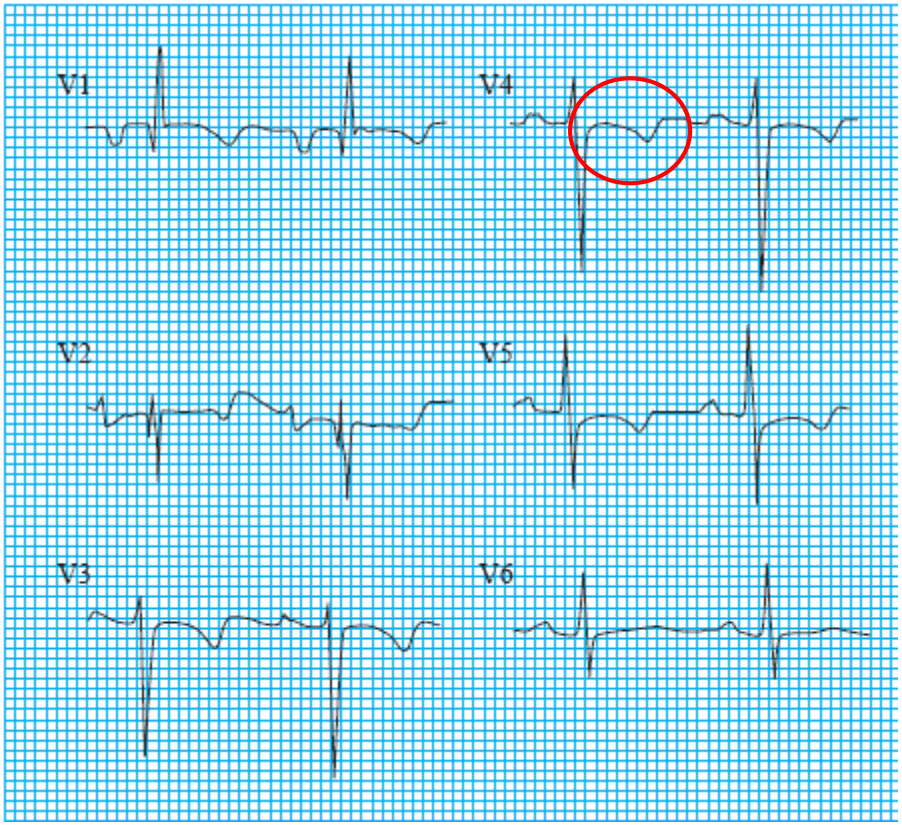
T-wave inversion



Rt. Bundle Branch Block



Rt. Ventricular Strain



D-Dimer

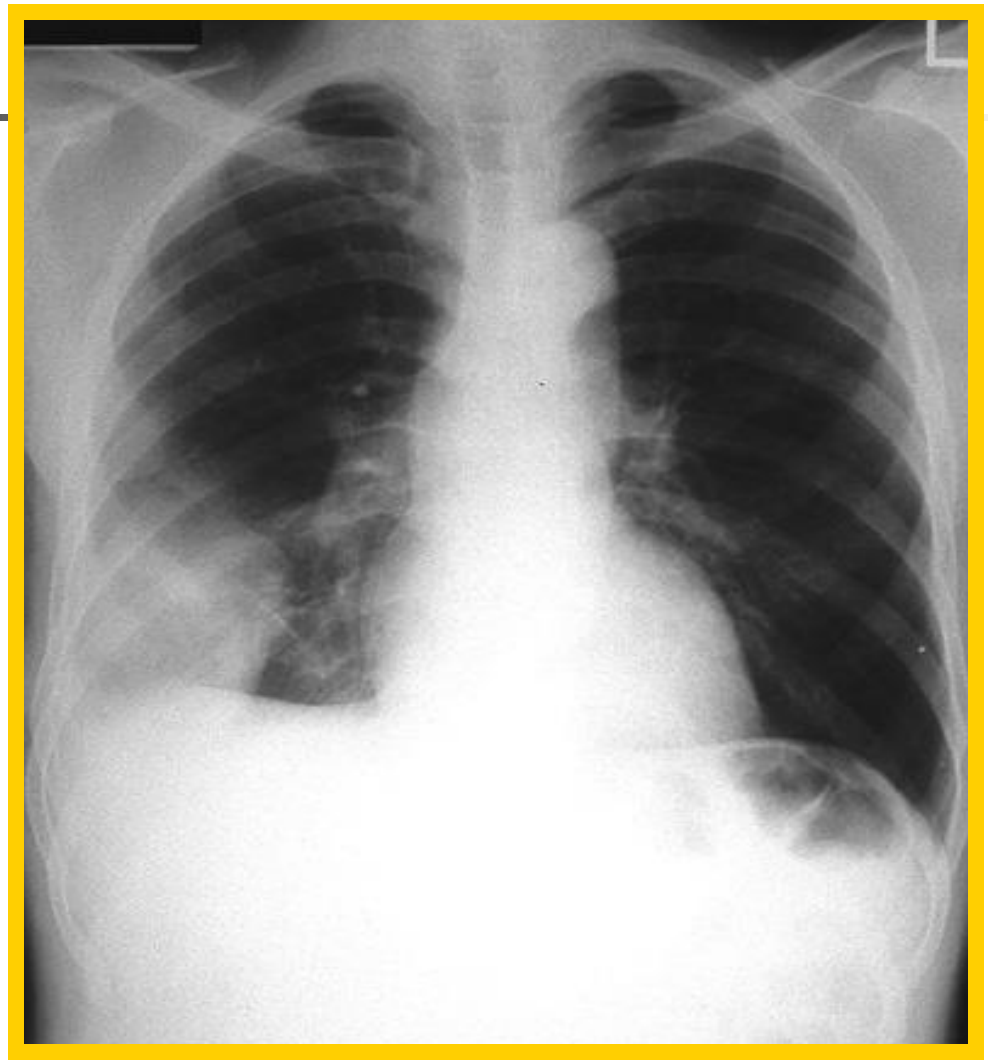
- The D-dimer is a degradation product of fibrinolysis and is increased in patients with acute venous thromboembolism as well other non-thrombotic disorders
- D-dimer is a sensitive but not specific diagnostic test.
- A low clinical probability score is useful for excluding a diagnosis of venous thromboembolism

Diagnosis

The diagnosis of massive PE should be explored whenever oxygenation or hemodynamic parameters are severely compromised without explanation

- CXR
- ABG:
  - Significant hypoxemia is almost uniformly present when there is a hemodynamically significant PE
- V/Q
- Spiral CT
- Echo
- Angio

Chest radiograph showing pulmonary infarct in right lower lobe



Chest radiographic findings in patients with pulmonary embolism

	COPD, % (n= 21)	No prior cardiopulmonary disease, % (n= 117)
Atelectasis or pulmonary parenchymal abnormality	76	68
Pleural effusion	52	48
Pleural-based opacity	33	35
Elevated diaphragm	14	24
Decreased pulmonary vascularity	38	21
Prominent central pulmonary artery	29	15
Cardiomegaly	19	12
Westermark's sign*	5	7
Pulmonary edema	14	4

The use of ventilation perfusion scan in diagnosing pulmonary embolism

High probability

=2 large segmental (>75% of a segment) perfusion defects without corresponding ventilation or radiographic abnormalities or substantially larger than matching ventilation or radiologic abnormalities

OR

=2 moderate segmental (>25% and <75% of a segment) perfusion defects without matching ventilation or chest radiographic abnormalities plus one large unmatched segmental defect

OR

=4 moderate segmental perfusion defects without matching ventilation or chest radiologic abnormalities

The use of ventilation perfusion scan in diagnosing pulmonary embolism

Intermediate probability

Scans that do not fall into normal, very low, low, or high probability categories

The use of ventilation perfusion scan in diagnosing pulmonary embolism

Low probability

Nonsegmental perfusion defects

OR

Single moderate mismatched segmental perfusion defect with normal chest radiograph

OR

Any perfusion defect with a substantially larger abnormality on chest radiograph

OR

Large or moderate segmental perfusion defects involving no more than four segments in one lung and no more than three segments in one lung region with matching or larger ventilation/radiographic abnormalities

OR

More than three small segmental perfusion defects (<25% of a segment) with a normal chest radiograph

The use of ventilation perfusion scan in diagnosing pulmonary embolism

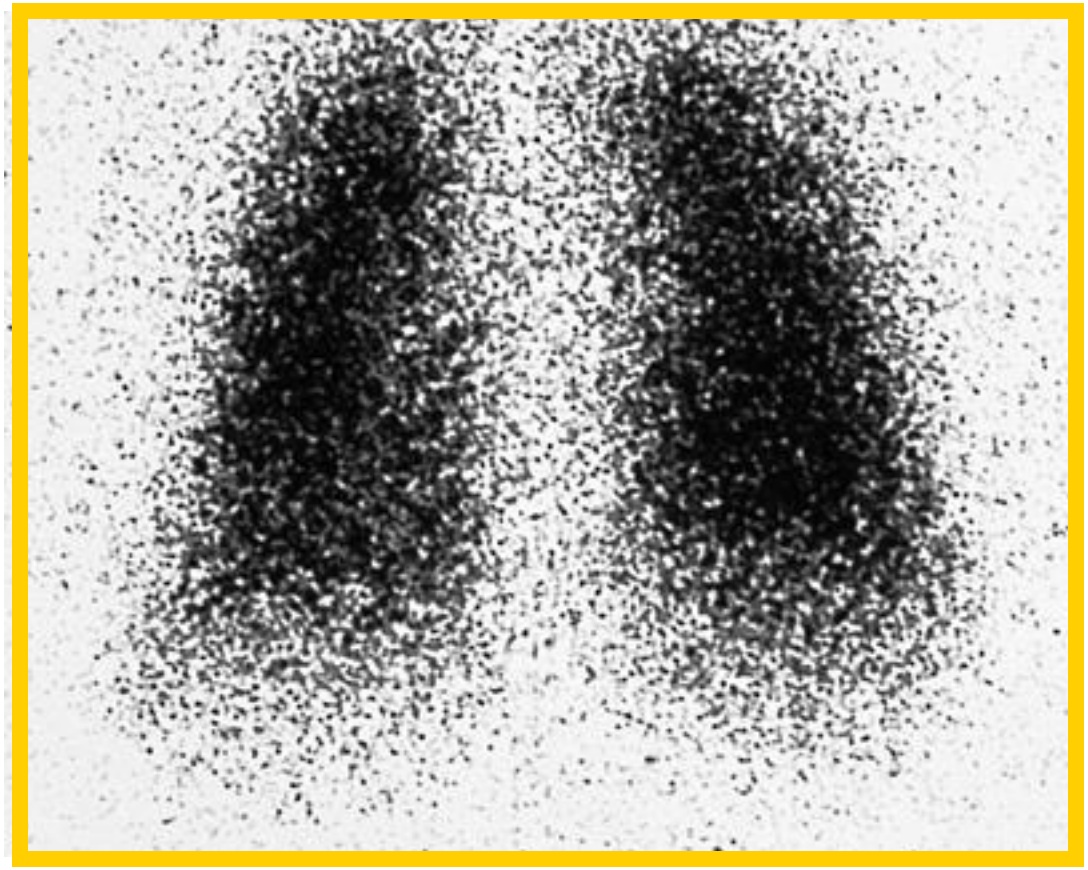
Very low probability

Three or fewer small segmental perfusion defects with a normal chest radiograph

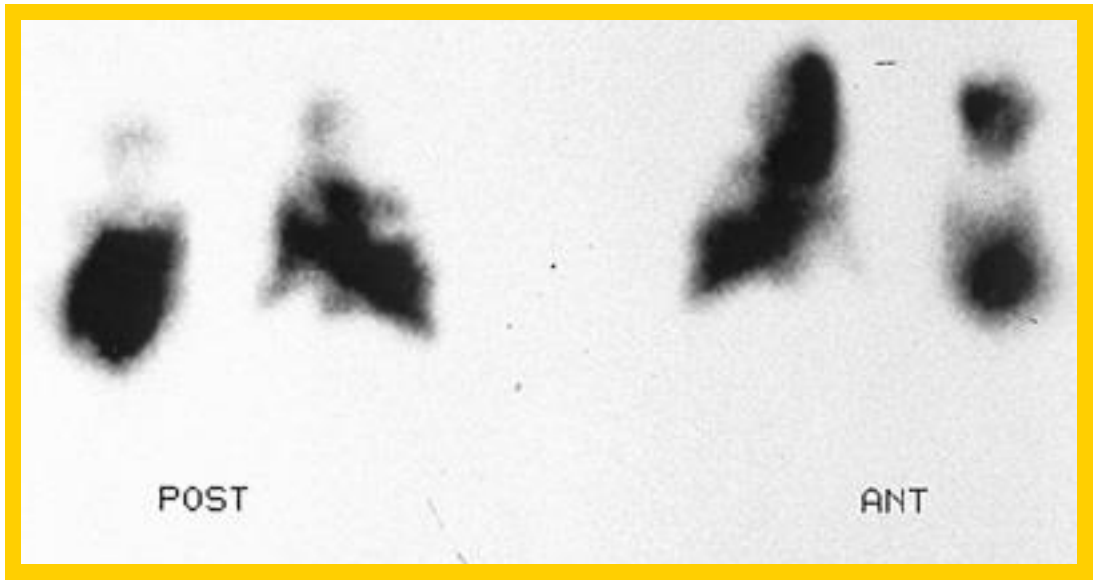
Normal

No perfusion defects present

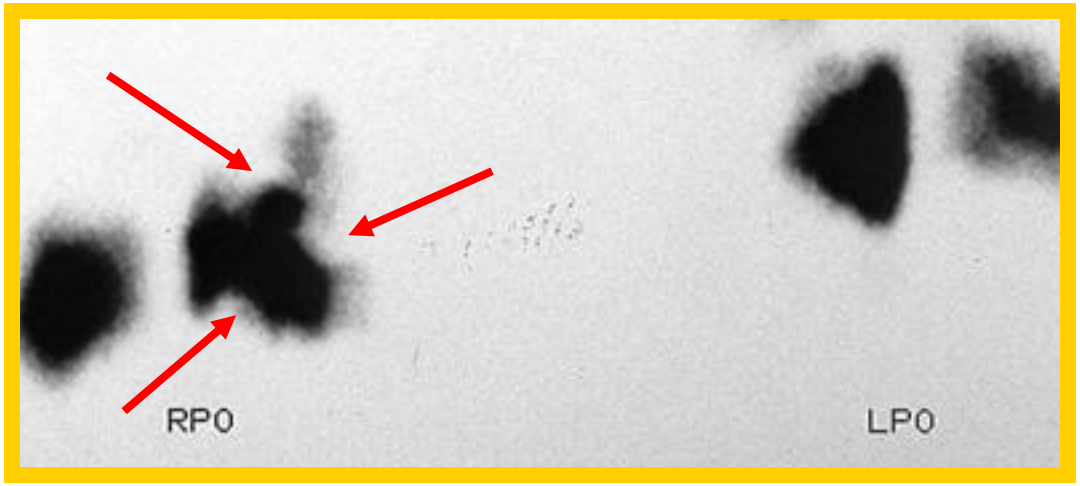
High-probability ventilation-perfusion scan



High-probability ventilation-perfusion scan



High-probability ventilation-perfusion scan



Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) results

Prospective investigation of pulmonary embolism diagnosis results

Scan category	PE present	PE absent	PE uncertain	No angiogram	Total
High probability	102	14	1	7	124
Intermediate probability	105	217	9	33	364
Low probability	39	199	12	62	312
Near normal or normal	5	50	2	74	131
Total	251	480	24	176	931

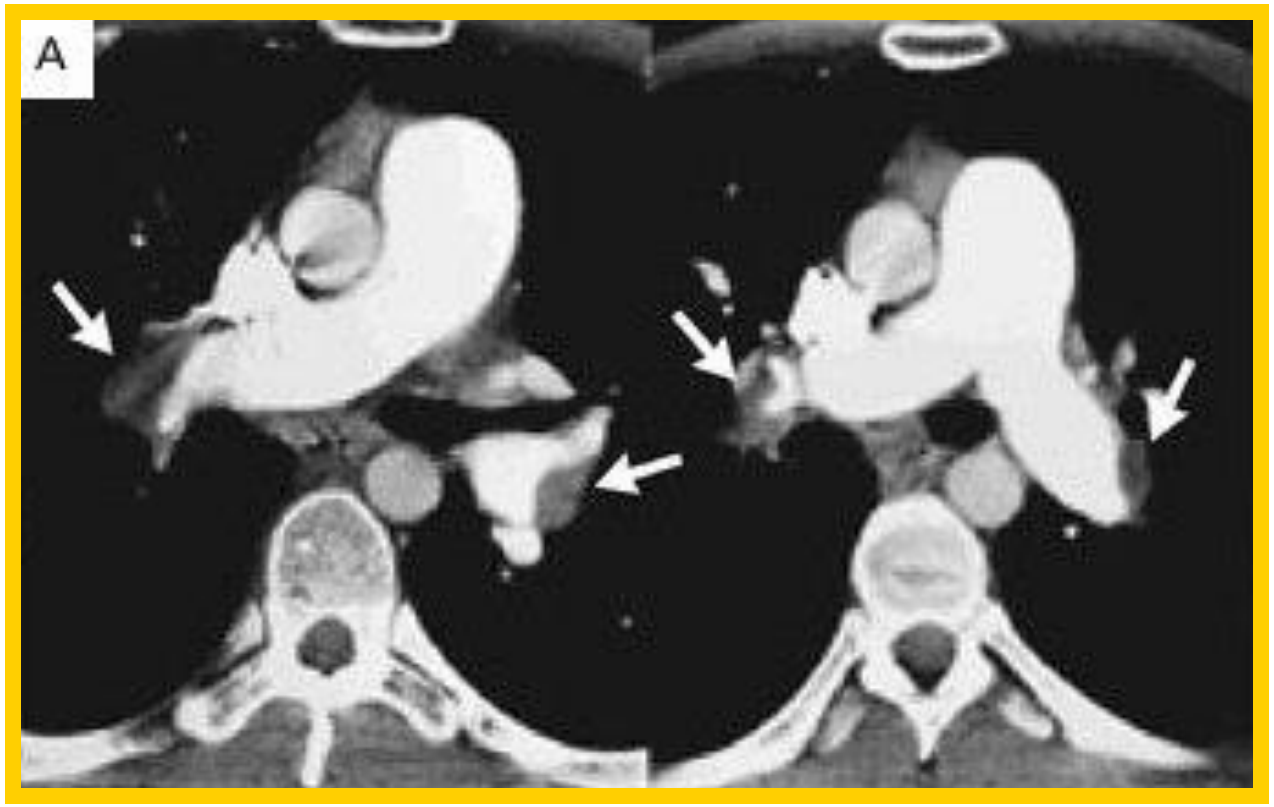
Computed tomography pulmonary angiography (CTPA) (previously Spiral CT)

- **Multidetector computed tomography (MDCT)** is considered the standard imaging modality for diagnosing PE.

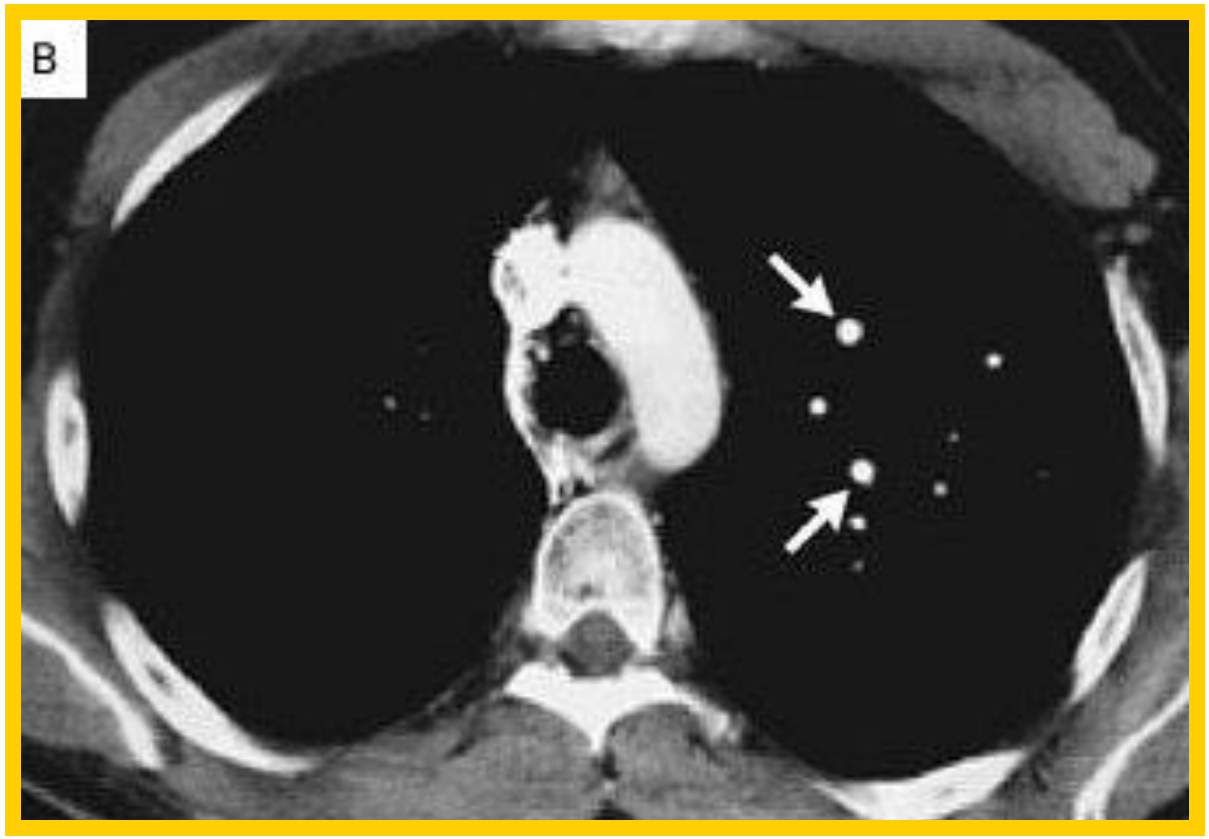
- Technical advancements in CT in the past decade have allowed physicians to obtain images of higher quality, with exposure to lower levels of radiation, which demonstrate small subsegmental pulmonary artery embolisms

- **Dual-energy computed tomography (DECT)** can provide both morphological and functional pulmonary information of the lung in a single contrast-enhanced examination. It uses X-rays with two different energy spectra to detect specific substances according to the material decomposition theory

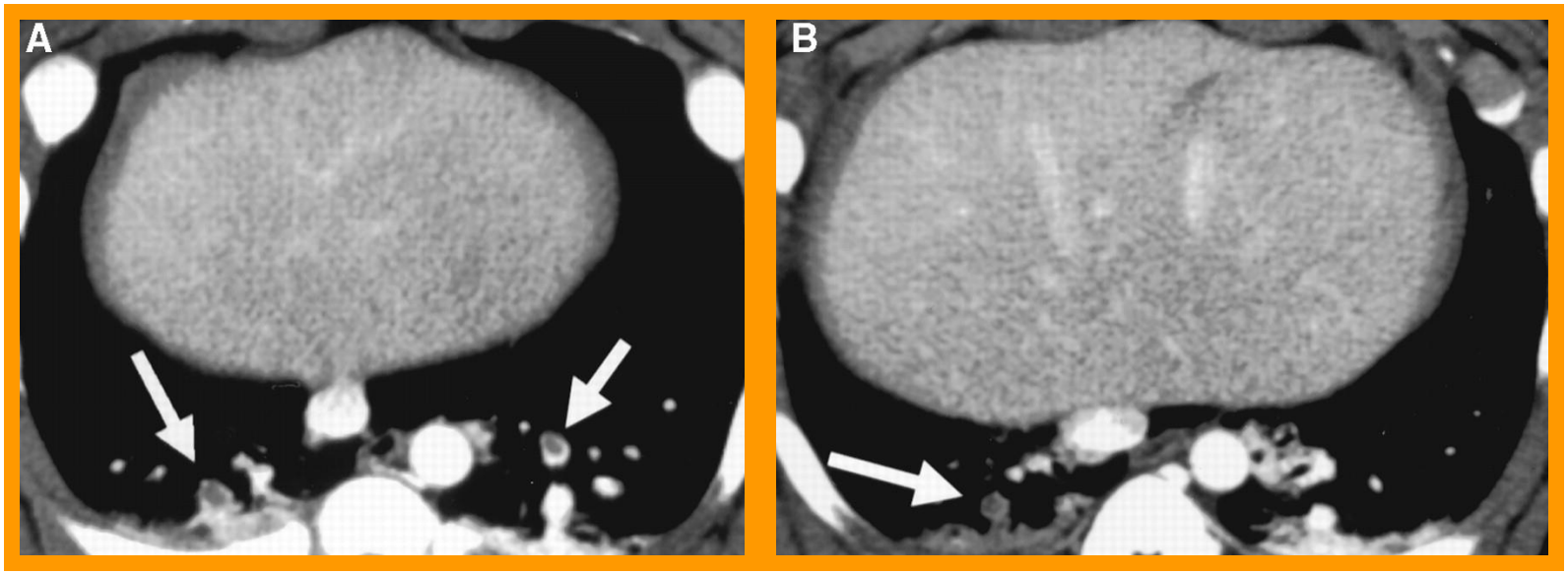
Computed tomography pulmonary angiography (CTPA) (previously Spiral CT)



CT



CTPA



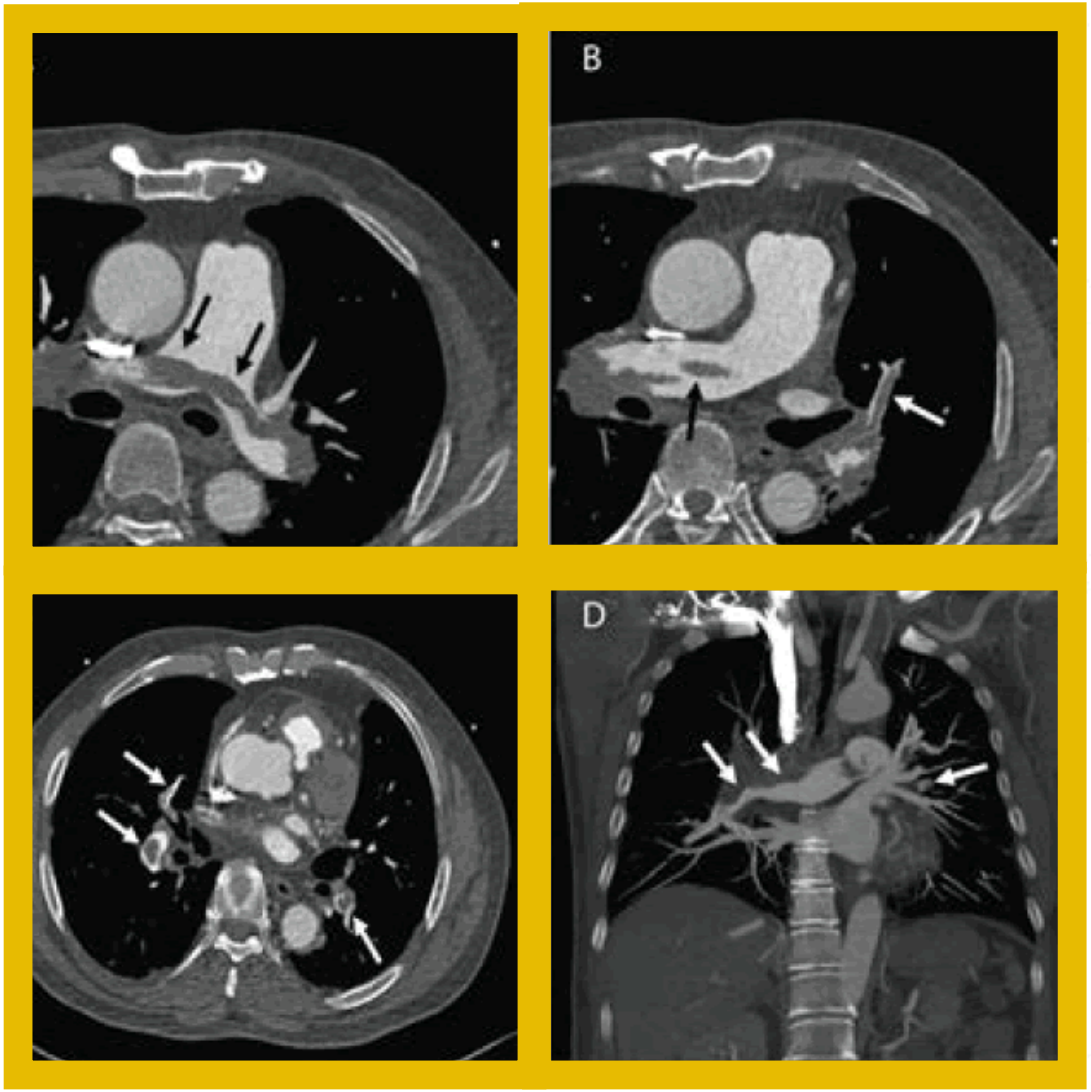
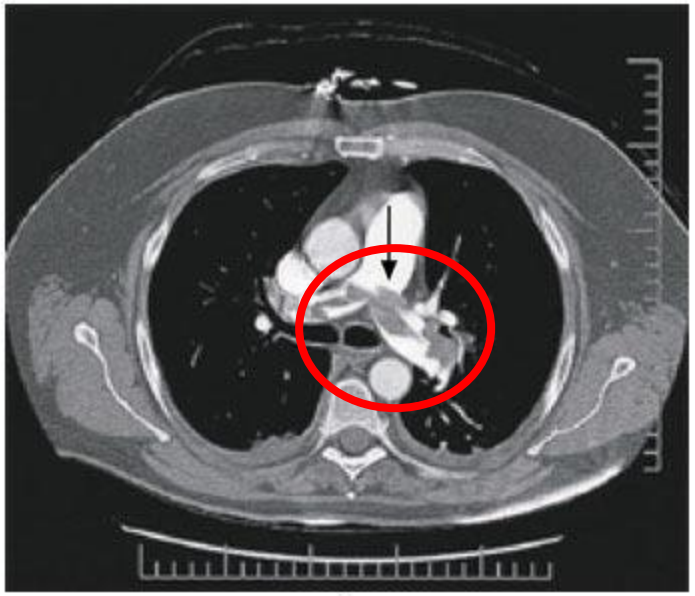


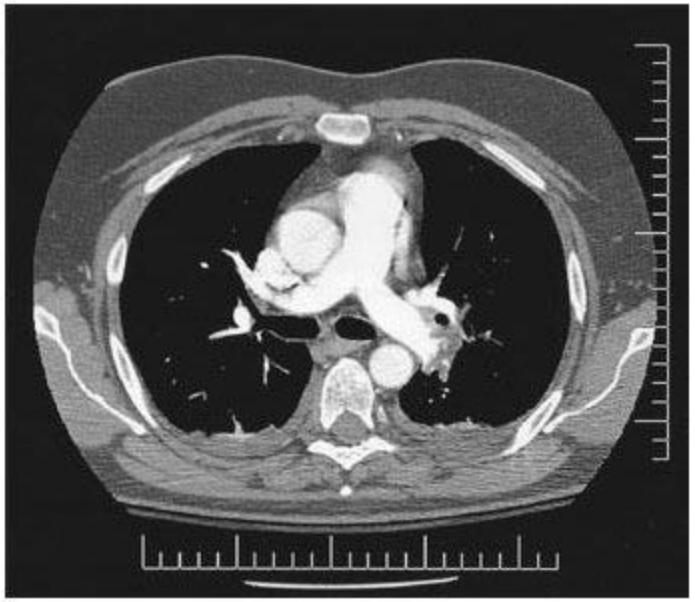
Figure 1: CT pulmonary angiography shows multiple pulmonary emboli in a 63-year-old male with chest pain for 7 days. 2D axial images show presence of thrombus in the main pulmonary arteries with extension to the segmental and subsegmental pulmonary arterial braches on both sides resulting in filling defects (A-C). Coronal reformatted image demonstrates multiple emboli on pulmonary arteries (D). Arrows indicate the thrombi in pulmonary arteries.

Interventional Cardiology (2017) Volume 9, Issue 5



A

Before



B

After

Tomographic scan showing infarcted left lung, large clot in right main pulmonary artery

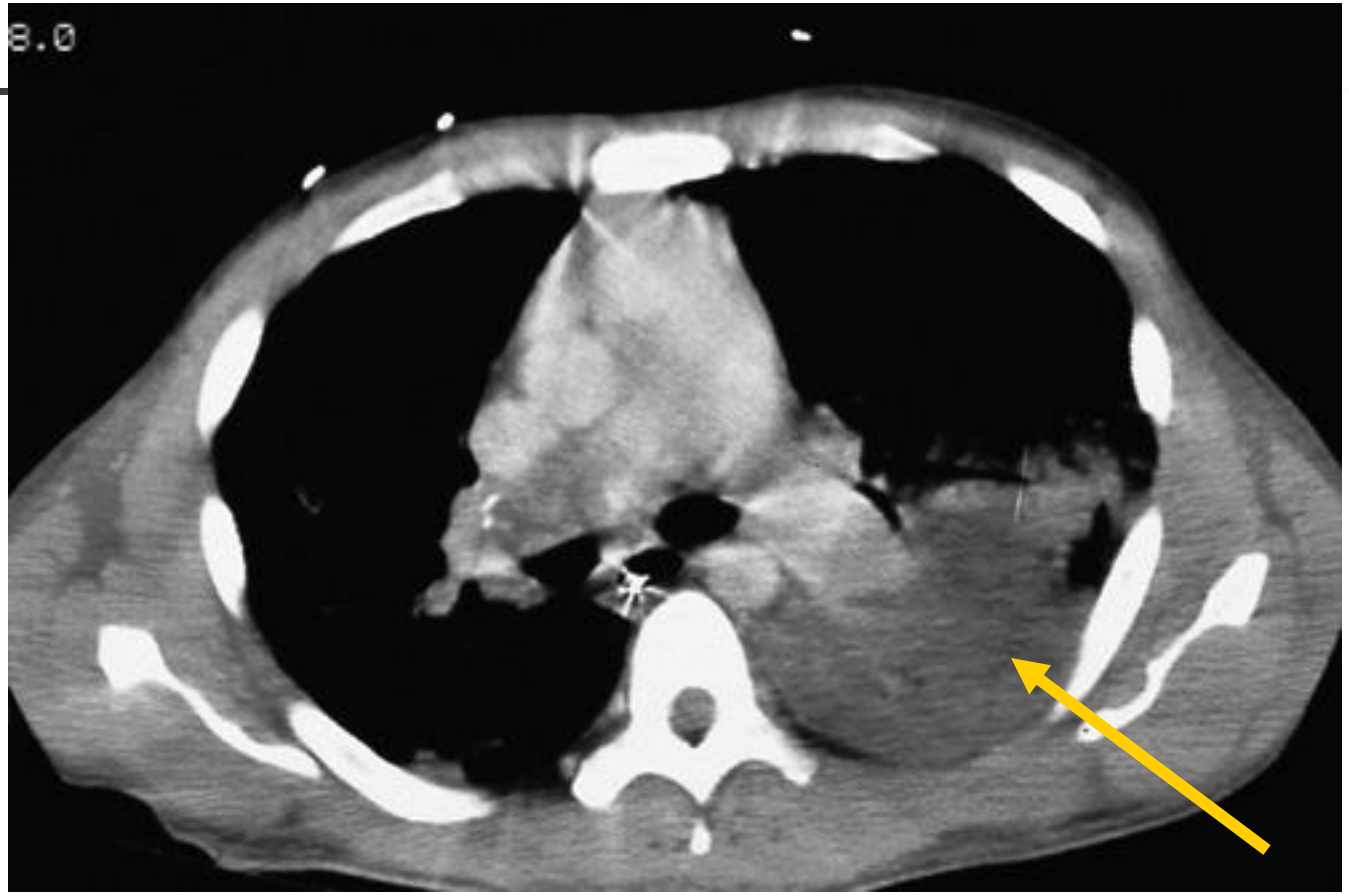
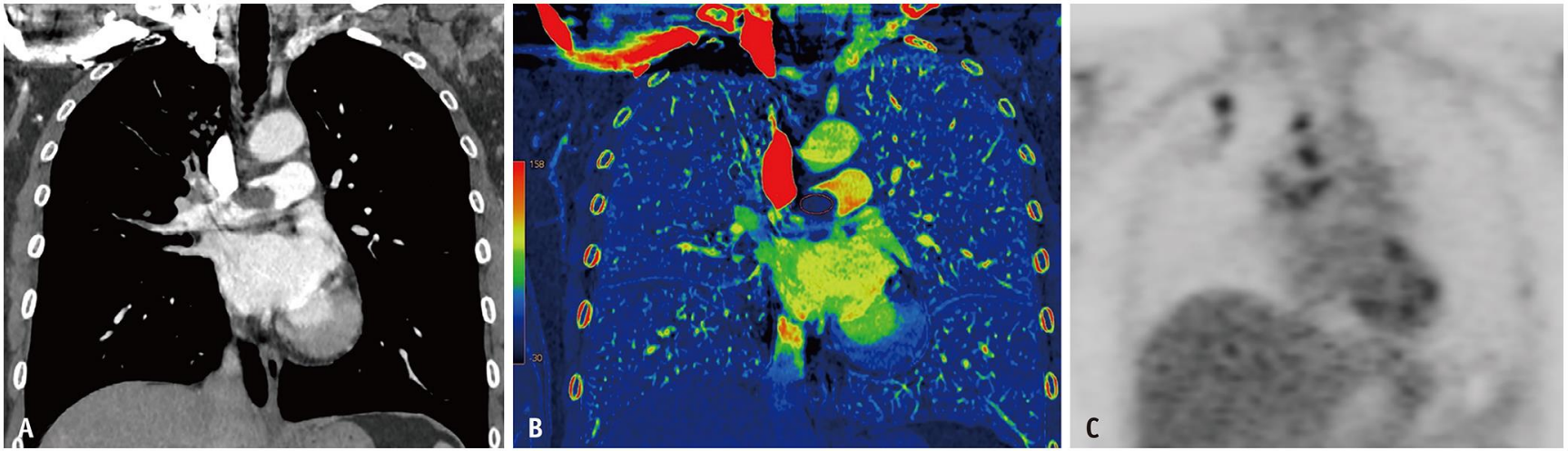


Fig. 3. A 58-year-old female with pulmonary artery sarcoma.



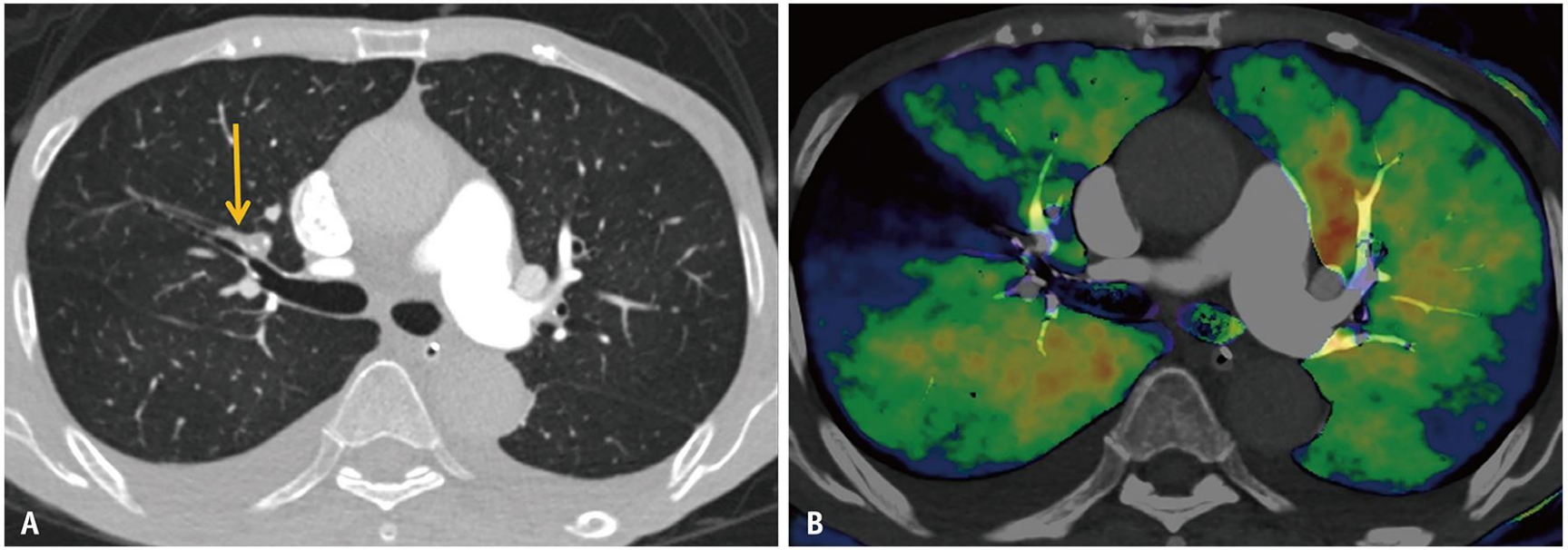
A 58-year-old female with pulmonary artery sarcoma.
A. A coronal contrast enhanced CT image showing an intraluminal mass with an eccentric filling defect in the right main pulmonary trunk.

B. On a coronal color-coded iodine (water) image from dual-energy CT, the mean iodine concentration within the region of interest is 2.6 mg/mL.

C. A coronal PET image showing focal fluorodeoxyglucose uptake in the intraluminal mass and right upper paratracheal lymph nodes.

Korean J Radiol 2021 Sep;22(9):1555-1568. https://doi.org/10.3348/kjr.2020.1512

Fig. 1. A 76-year-old female diagnosed with acute pulmonary thromboembolism.



A 76-year-old female diagnosed with acute pulmonary thromboembolism.
A. CT angiography showing a focal filling defect in the right upper lobar pulmonary artery (arrow) due to acute pulmonary thromboembolism and bilateral pleural effusion
B. The fusion image of CT angiography and a color-coded iodine map showing a thrombus in the right upper pulmonary artery as well as a corresponding wedge-shaped perfusion defect in the right upper lobe.

Korean J Radiol 2021 Sep;22(9):1555-1568. https://doi.org/10.3348/kjr.2020.1512

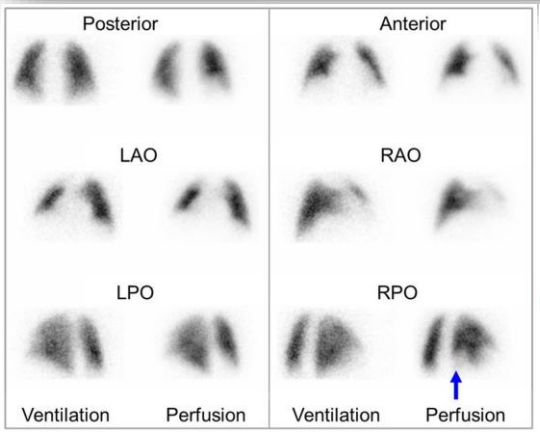
SPECT Ventilation/Perfusion Imaging for Acute Pulmonary Embolism: Meta-analysis of Diagnostic Test Accuracy

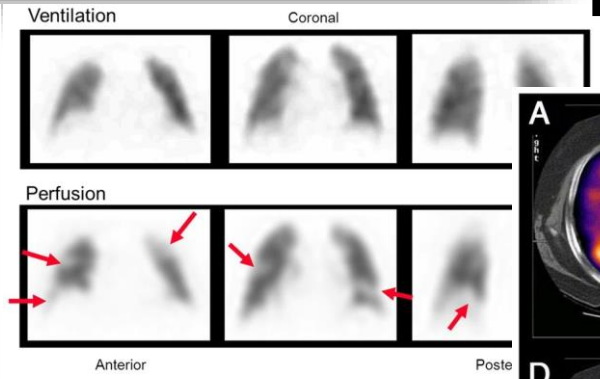
Acad Radiol. 2023 Jul 22;S1076-6332(23)00333-1.

Imran H. Iftikhar, MBBS, Nauman H. Iftikhar, MBBS, Muhammad Naeem, MBBS, Ahmed BaHammam, MD

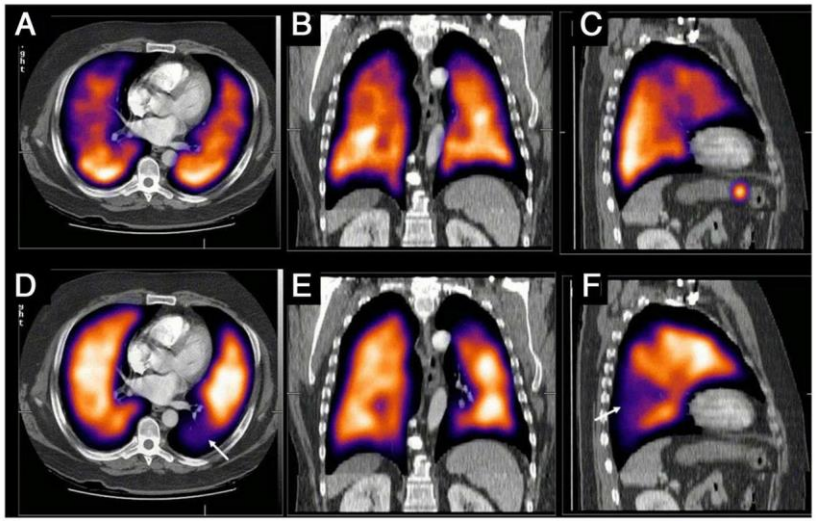
V/Q-SPECT-CT:

- **Sensitivity:** 0.95
- **Specificity:** 0.99
- **Positive Likelihood Ratio:** 76.7
- **Negative Likelihood Ratio:** 0.06

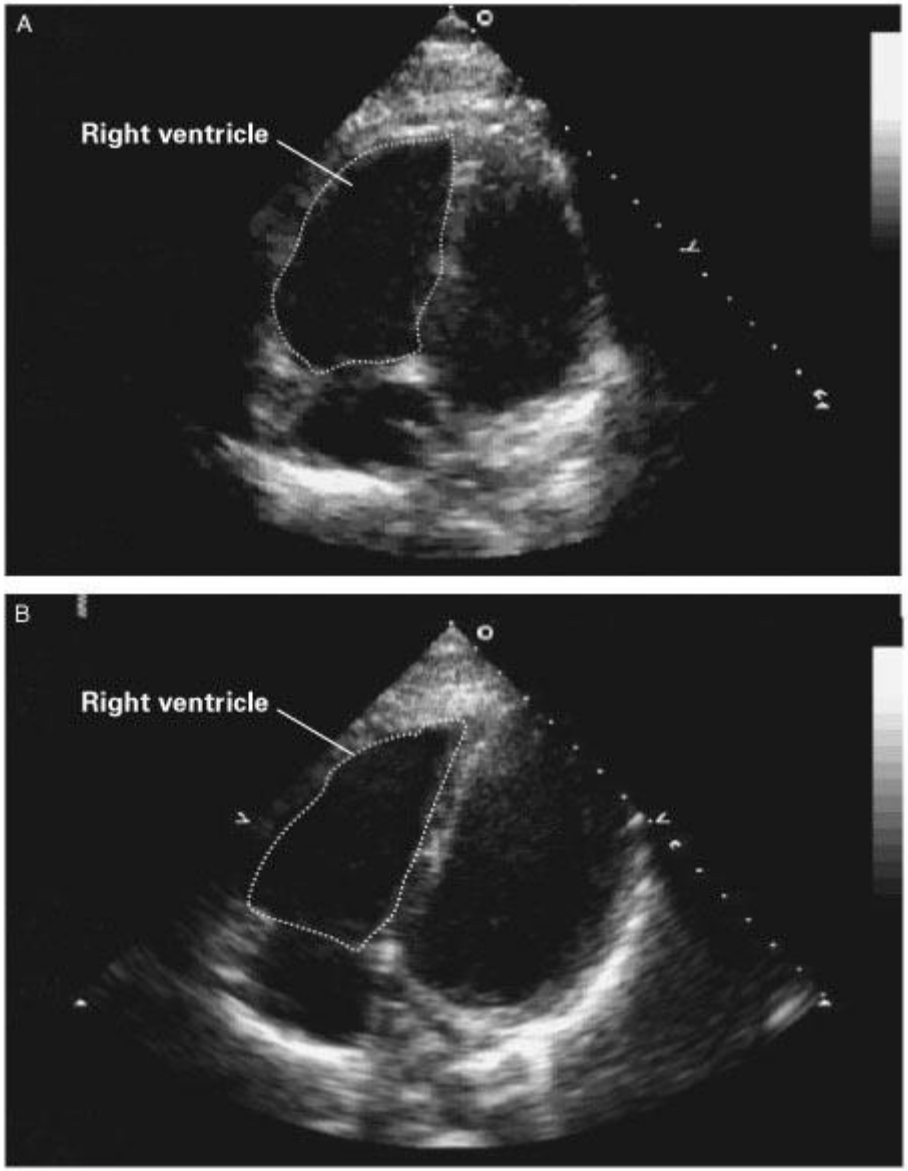




For same patient study as outlined in Figure 1, planar **V/Q scan after SPECT** with representative slices demonstrating multiple defects (arrows), indicating more widespread pulmonary emboli



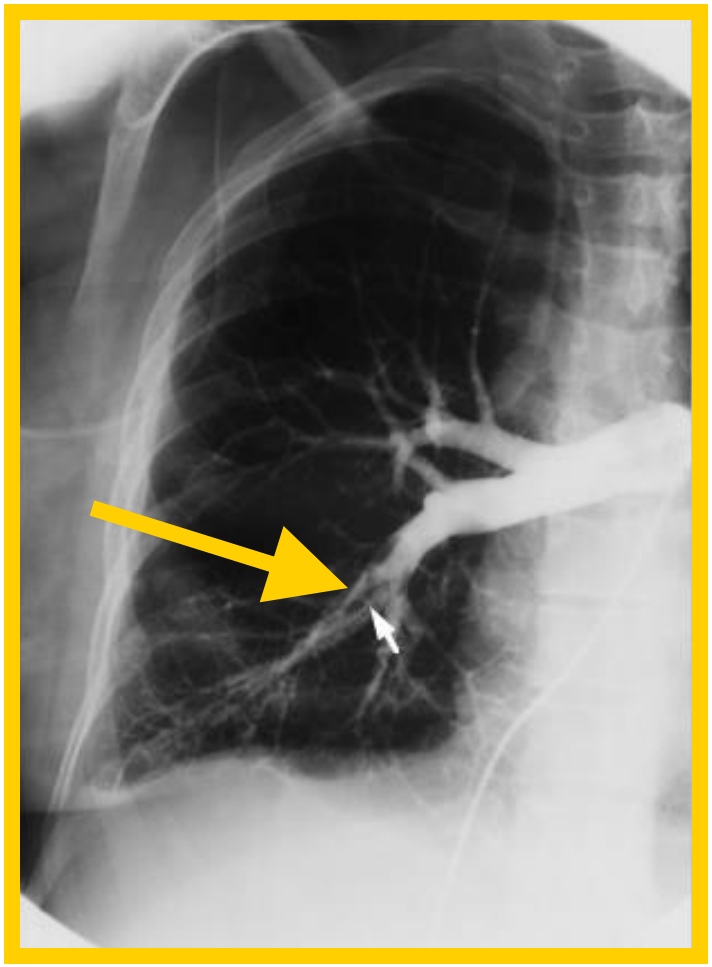
Representative **SPECT/CT** images of lung ventilation (top) and perfusion (bottom) demonstrating segmental perfusion defect (arrow in D and F) in left lower lobe with no CT opacity or matched ventilation defect consistent with pulmonary embolism.



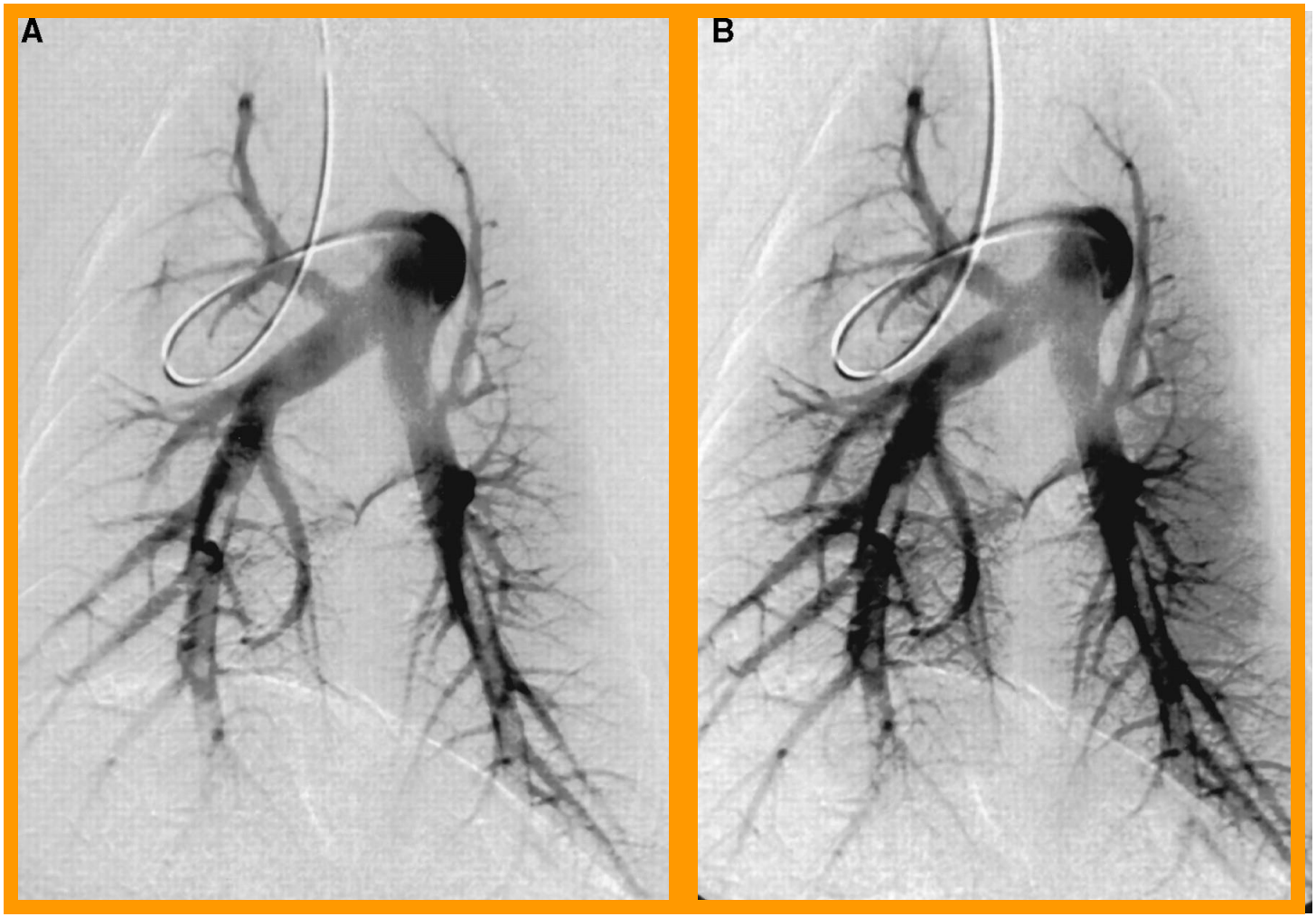
Before

After

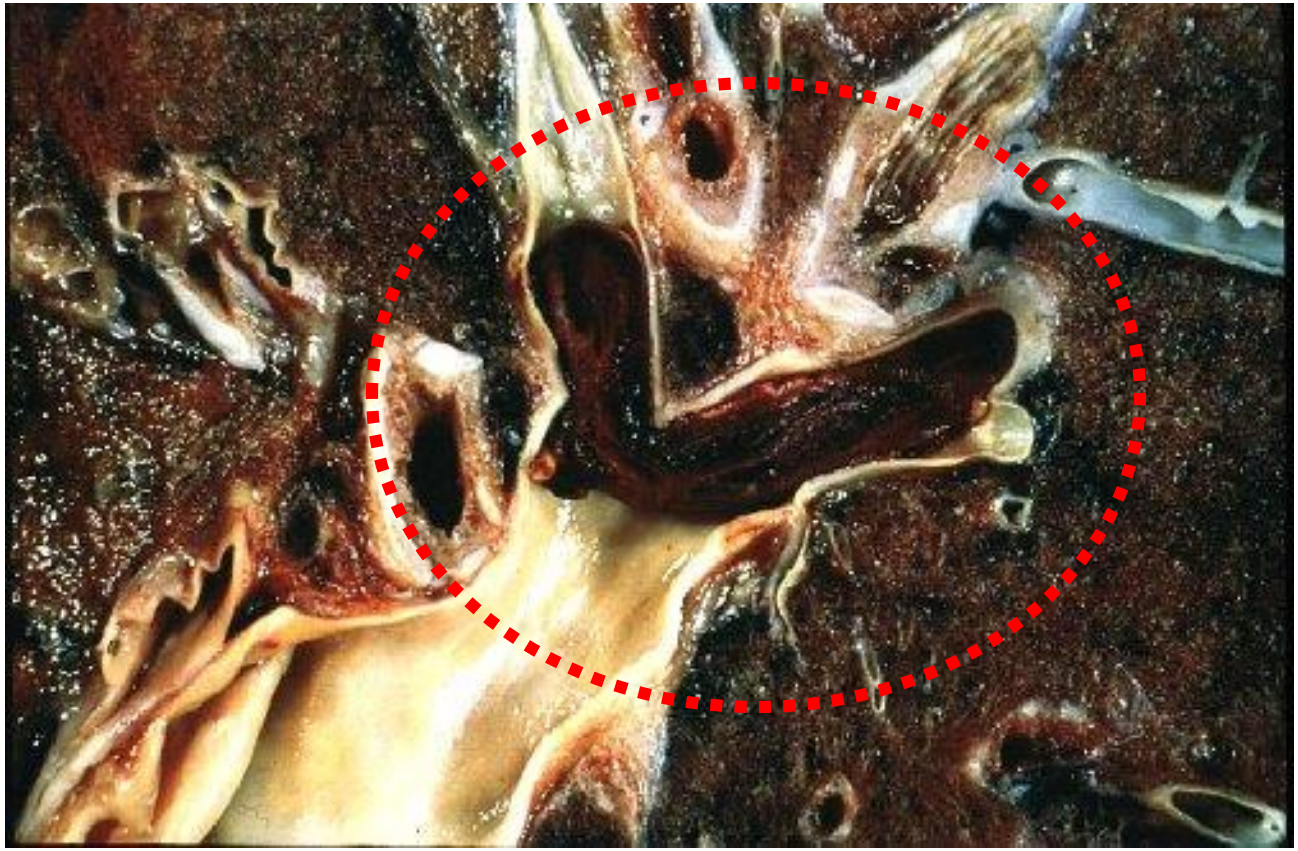
Pulmonary angiogram



Pulmonary Angiogram



PULMONARY EMBOLISM



Suggested diagnostic strategy for venous thromboembolism

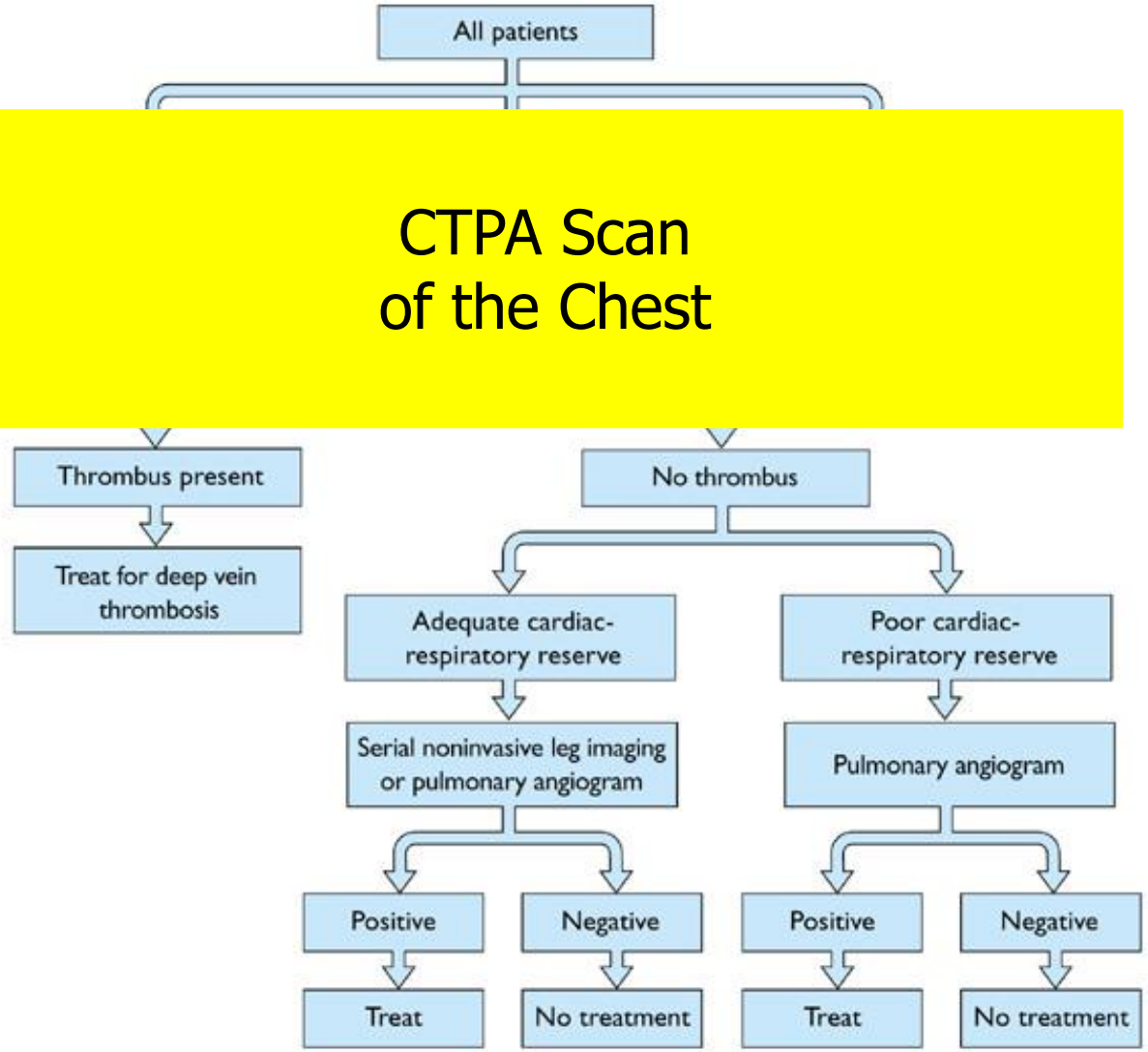


Table 2 | Comparison of pulmonary embolism risk prediction scores

Variable	Points
Pulmonary Embolism Severity Index (PESI)*[87]	
Age, per year	Age, in years
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Pulse rate ≥110/min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30/min	+20
Temperature <36°C	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20
Simplified Pulmonary Embolism Severity Index (sPESI)†[88]	
Age >80 years	1
History of cancer	1
History of chronic lung disease	1
Pulse rate ≥110 beats/min	1
Systolic blood pressure <100 mm Hg	1
Arterial oxygen saturation <90%	1
Hestia criteria‡[89]	
Is the patient hemodynamically unstable?	–
Is thrombolysis or embolectomy necessary?	–
Active bleeding or high risk of bleeding?	–
>24 h of oxygen supply to maintain oxygen saturation >90%?	–
Is pulmonary embolism diagnosed during anticoagulant treatment?	–
Severe pain needing intravenous pain medication for >24 h?	–
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, no support system)?	–
Does the patient have a creatinine clearance of <30 mL/min?	–
Does the patient have severe liver impairment?	–
Is the patient pregnant?	–
Does the patient have a documented history of heparin induced thrombocytopenia?	–

*66-85 class I; 86-105 class II; 106-125 class III; >125 class IV; class V. Class I and II defined as low risk.
†0 low risk; ≥1 high risk.
‡Yes to any question, admission required.

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Treatment

- Prompt initiation of anticoagulation while awaiting investigations is prudent because of the high risk of early mortality with untreated pulmonary embolism

Types of anticoagulants

Direct anticoagulants (DOACs)

- DOACs are given at fixed doses and do not necessitate routine laboratory monitoring
- Each DOAC has been deemed non-inferior to the VKA/LMWH combination for the prevention of symptomatic recurrent venous thromboembolism in patients with an acute venous thromboembolism).
- DOACs have significantly fewer major bleeding events compared with VKAs

DOACs

Table 3 | Characteristics of direct oral anticoagulant drugs

Drug	Target	Peak effect (hours)	Half life (hours)	Renal clearance (%)	Protein binding (%)
Dabigatran	Factor IIa (thrombin)	1.5	14-17	>80	35
Apixaban	Factor Xa	3	8-14	25	85
Edoxaban	Factor Xa	4	8-11	35	55
Rivaroxaban*	Factor Xa	2-3	7-11	33	90

*Rivaroxaban 15 mg and 20 mg tablets should be taken with food for maximum absorption and efficacy.

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Dosage and monitoring of anticoagulant therapy

Warfarin

5 mg/d can be started on day 1 of therapy; there is no benefit from higher starting doses

Platelet count should be monitored at least every 3 d during initial heparin therapy

Therapeutic APTT should correspond to plasma heparin level of 0.2–0.4 IU/mL

Heparin

is usually continued for 5–7 d

Heparin can be stopped after 4–5 d of warfarin therapy when INR is in 2.0–3.0 range

Low molecular weight heparin

Important drug interactions with warfarin

Drugs that decrease warfarin requirement	Drugs that increase warfarin requirement
Phenylbutazone	Barbiturates
Metronidazole	Carbamazepine
Trimethoprim-sulfamethoxazole	Rifampin
Amiodarone	Penicillin
Second- and third-generation cephalosporins	Griseofulvin
Clofibrate	Cholestyramine
Erythromycin	
Anabolic steroids	
Thyroxine	

Complications of anticoagulation

	Complication	Management
Heparin	Bleeding	Stop heparin infusion. For severe bleeding, the anticoagulant effect of heparin can be reversed with intravenous protamine sulfate 1 mg/100 units of heparin bolus or 0.5 mg for the number of units given by constant infusion over the past hour; provide supportive care including transfusion and clot evacuation from closed body cavities as needed.

Complications of anticoagulation

	Complication	Management
Heparin	Heparin-induced thrombocytopenia and thrombosis	Carefully monitor platelet count during therapy. Stop-heparin for platelet counts <75,000. Replace heparin with direct inhibitors of thrombin-like desirudin if necessary. These agents do not cause heparin-induced thrombocytopenia. Avoid platelet transfusion because of the risk for thrombosis.

Complications of anticoagulation

	Complication	Management
Heparin	Heparin-induced osteoporosis (therapy >1 mo)	LMWHs may have lower propensity to cause osteoporosis as compared with unfractionated heparin; consider LMWH if prolonged heparin therapy is necessary.

Complications of anticoagulation

	Complication	Management
Warfarin	Bleeding	Stop therapy. Administer vitamin K and fresh-frozen plasma for severe bleeding; provide supportive care including transfusion and clot evacuation from closed body cavities as needed
	Skin necrosis (rare)	Supportive care.
	Teratogenicity	Do not use in pregnancy or in patients planning to become pregnant.

Treatment phases

Treatment phases:

1. Initial phase from 0-7days,
2. Long term therapy 1 wk – 3 months
3. Extended therapy 3 months - indefinite.

Box 2: Phases of pulmonary embolism treatment[104]

Initial (0-7 days)

- Apixaban 10 mg BID for 7 days
- Rivaroxaban 15 mg BID for 21 days
- LMWH/fondaparinux for minimum 5 days* and INR ≥2 for 2 days

Long term (1 week to 3 months)

- Apixaban 5 mg BID
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily†
- Rivaroxaban 20 mg daily
- Warfarin for INR 2-3

Extended (3 months to indefinite)

- Apixaban 5 mg BID or 2.5 mg BID‡
- Acetylsalicylic acid 81-100 mg daily, if anticoagulation not possible
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily†
- Rivaroxaban 20 mg daily or 10 mg daily‡
- Warfarin for INR 2-3

BID=twice daily; INR=international normalized ratio; LMWH=low molecular weight heparin
*LMWH is needed for 5-10 days before starting dabigatran or edoxaban
†30 mg daily if creatinine clearance is 30-50 mL/min or weight ‹60 kg
‡Dose reduction may be considered after 6 months of therapy

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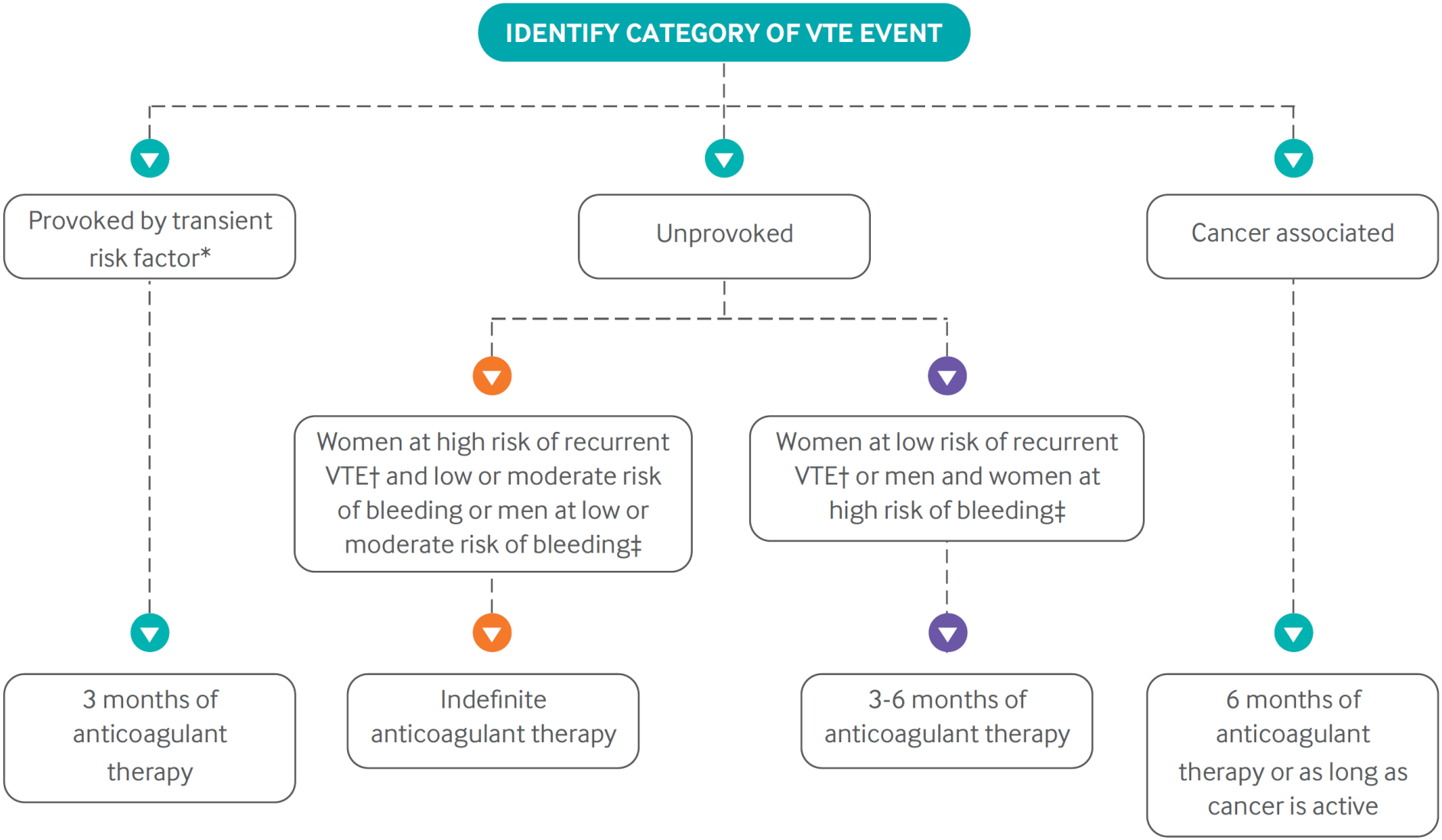
IDENTIFY CATEGORY OF VTE EVENT
Provoked by transient risk factor*
Unprovoked
Cancer associated
Women at high risk of recurrent VTE† and low or moderate risk of bleeding or men at low or moderate risk of bleeding‡
Women at low risk of recurrent VTE† or men and women at high risk of bleeding‡
3 months of anticoagulant therapy
Indefinite anticoagulant therapy
3-6 months of anticoagulant therapy
6 months of anticoagulant therapy or as long as cancer is active

Outpatient vs. inpatient therapy

- RCTs have compared outpatient versus inpatient management of pulmonary embolism and found no difference in outcomes in selected patients.

Approved thrombolytics for pulmonary embolism

Approved thrombolytics for pulmonary embolism

Streptokinase

250,000 IU as loading dose over 30 min, followed by 100,000 U/h for 24 h

Urokinase

4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h for 12-24 h

Recombinant tissue-plasminogen activator

100 mg as a continuous peripheral intravenous infusion administered over 2 h

Indications and contraindications for thrombolytic therapy in pulmonary embolism

Indications

Hemodynamic instability

Hypoxia on 100% oxygen

Right ventricular dysfunction by echocardiography

Contraindications

Relative

Recent surgery within last 10 d

Previous arterial punctures within 10 d

Neurosurgery within 6 mo

Bleeding disorder (thrombocytopenia, renal failure, liver failure)

Ophthalmologic surgery within 6 wk

Hypertension >200 mm Hg systolic or 110 mm Hg diastolic

Placement of central venous catheter within 48 h

Hypertensive retinopathy with hemorrhages or exudates

Intracerebral aneurysm or malignancy

Cardiopulmonary resuscitation within 2 wk

Cerebrovascular disease

Major internal bleeding within the last 6 mo

Pregnancy and the 1st 10 d postpartum

Infectious endocarditis

Severe trauma within 2 mo

Pericarditis

Absolute

Active internal bleeding

Conclusions

- PE is common and under-recognized serious medical problem
- Early diagnosis and treatment is essential for good outcome
- High index of suspicion is needed in high risk patients