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DRUG MANAGEMENT OF PATIENTS WITH PULMONARY EMBOLISM ON THE EXAMPLE OF CLINICAL CASE



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Year 2015

Our patient

- L. O. V.
- Male
- 62 years old
- Retired (Railway attendant by profession)
- A townsman
- Date of admission: November 14

Complains

- Dyspnea (mixed) during exercise and at rest.
- Cough
- Fatigue
- Palpitations
- Chest pain into the right side of the chest at rest and during physical activity
- Heaviness in the legs at night, after physical activity and after long sedentary period.

Medical history

- Dyspnea with cough with transparent sputum appeared a month ago
- There was no treatment for the dyspnea during this period
- On November 14 2015, the condition was deteriorated and the dyspnea became more severe with cough, fatigue ,palpitations and this symptoms disturbed the patient even at rest
- He noted varicose veins in both lower limbs two years ago and he associated it with long term standing
- A month ago he noticed localized redness of limb in the right lower limb and he didn't seek treatment
- He was admitted in the 5th central clinical hospital

Life history

- For 12 years (since 2003), patient has had arterial hypertension (maximum 200/150 mm hg).
- He has no history of stomach or duodenal ulcer, tuberculosis, diabetes, sexually transmitted diseases, viral hepatitis, rheumatism, mental illness.
- Family history is not burdened.
- Allergic history is not burdened
- He has not had any previous surgical operations
- Smoking history :for 40 years he smokes a pack of cigarette or 2 per day. (pack/cig index= 40 pack year smoking index)

Objective status (14 Nov 2015)

The general condition is satisfactory, consciousness is clear, emotionally stable, optimistic mood.

Normosthenic physique. Height -1.7m. Weight -70kg. BMI- 24.2 (normal).

There is peripheral edema in the right tibia. There is no peripheral edema into the left lower limb. There are dilated superficial veins in the both lower limbs, redness of the skin in the inner surface of the right tibia.

Respiratory System: Pulmonary percussion:- dullness on the right side of the chest. Dullness was heard on the IV to VI intercostal space on the posterior axillary line.

Auscultation - vesicular breathing over all the surface of the lungs but there is wheezing into the right side of the chest (posterior axillary line)

Cardiovascular system- accent of 2nd tone of aorta, murmur into the pulmonary artery. Pulse is equal to heart rate at 66 beats/min. Blood pressure is 160/100 mmHg on both hands

Kidney sign is negative on both sides.

Abdomen is soft and painless during palpation.

There is enlargement of the liver by 2 cm below the ribs.

Plan of survey

1. Complete blood count
2. Biochemical blood profile
3. Chest X ray
4. ECG
5. Ultrasound of the heart
6. Ultrasound of the vessels of the lower limbs

Additional recommended

1. Blood lipid profile
2. Coagulogram
3. CT scan
4. D dimer test
5. Holter ECG
6. Urinalysis

Complete blood count

INDEX	RESULT	NORMAL
hemoglobin	138g/l	120-140g/l
erythrocytes	4.52	3.9-4.7
CPU	1.0	0.85-1.15
hematocrit	39.8%	36-42%
thrombocytes	170g/l	160-320g/l
leukocytes	6.3g/l	4.0-9.0 g/l
Stab cells	3%	1-6%
segmented	54.5%	47-72%
eosinophils	3%	0.5-5.0%
basophils	0.9%	0-1.0%
lymphocytes	26%	19-37%
monocytes	7.2%	3-11%
ESR	8mm/h	2-15mm/h

Summary:- there are no changes in the blood

Biochemical blood analysis

Index	Result	normal range
Glucose	5.71mmol/l	3.9-6.4 mmol/l
sodium	140mmol/l	136-146mmol/l
potassium	4.0mmol/l	3.5-5.1mmol/l
INR	1.32	2-3

Summary :- the INR is below the normal range according to the regime of the intake of anticoagulants.

X-ray of the chest (20 Nov 2015)

- There are no infiltrative or local changes in the lung
- There are signs of venous hypertension into the lungs (pulmonary hypertension)
- The root of the lungs are dilated
- The roots are extended due to vessel picture
- The sinus are without liquid
- There is dilation of heart in the left side
- There is sclerosis of aorta in the arch area.

Summary :- Lung hypertension, dilation of the heart on the left and sclerosis of the aorta

ECG of our patient



Summary: sinus rhythm is correct, signs of left ventricle hyperthrophy, QRS complex is normal, two-humped P wave

Ultrasound of the heart

- Left atrium is **dilated**, the diameter is **42.9mm** (< 38 is normal)
- End diastolic volume is **63.1mm** (35-58mm)
- End systolic volume is **49.2 mm** (23-48mm)
- Posterior wall of L.V **16.8 mm** (6-11mm)
- Cavity of L.V is **dilated**
- Intraventricular septum **16.6 mm** (6-11mm)
- R.V dilated **36.6 mm** (9- 26mm)
- R.A dilated **42.9mm**

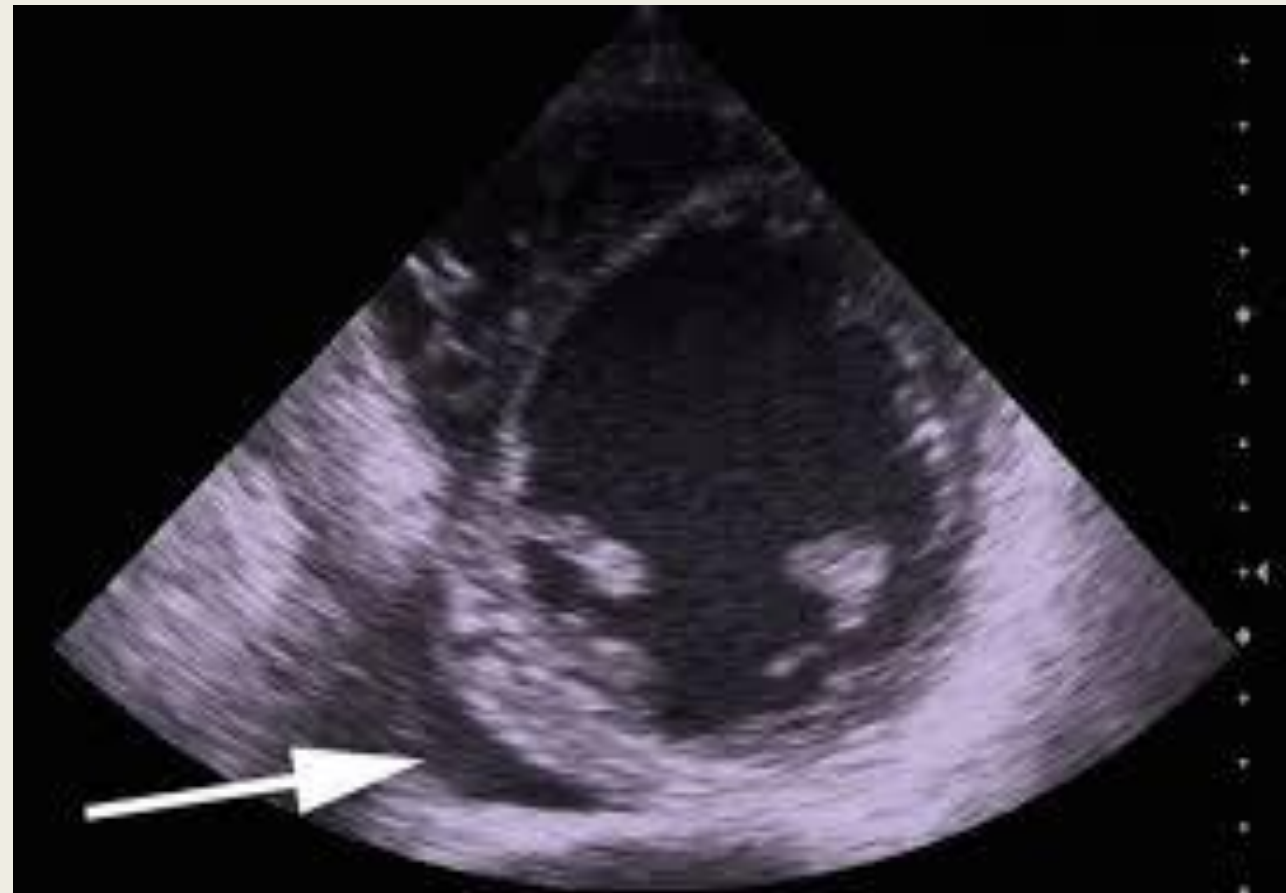
Aortic valve, mitral valve and the aortic walls are sclerotic

Mitral valve, **there is regurgitation of 1st degree**

Aortic **regurgitation of 1st degree**

Ejection fraction **44%** (55-78%) **Lung hypertension of 2nd degree**

Summary -: **there are sclerotic changes of the aortic valve, mitral valve and aortic walls .There is also dilation of all heart cavities. There is regurgitation 1st degree of both mitral and aortic valves. There is evidence of lung hypertension of 2nd degree. Contractile ability of the heart is reduced**



Ultrasound of vessels of lower limbs

- superficial veins thrombophlebitis and valvular insufficiency into the right lower limb.
- varicosis of veins of both lower limbs

Basic clinical syndromes

- Pulmonary embolism
- Infarct pneumonia
- Thrombophlebitis
 - Varicose veins
- Pulmonary hypertension
 - Arterial hypertension
- Acute right ventricular insufficiency
- Congestive heart failure.

Classification of pulmonary embolism

massive - affects more than 50% of the volume of the vascular bed of the lungs (pulmonary embolism trunk and / or the main pulmonary artery) and the disease manifests shock and / or systemic hypotension;

submassive - affects up to 30 - 50% of the volume of the vascular bed of the lungs (embolism many more equity or segmental pulmonary arteries) and manifests symptoms of right ventricular failure;

nonmassive - struck less than 30% of the volume of the vascular bed of the lungs (pulmonary embolism small distal arteries), manifestations are absent or minimal (lung infarction).

Infarct Pneumonia

Pulmonary infarction is localized destruction (necrosis) of lung tissue by blocking (obstruction of) the arterial blood supply. Infarct pneumonia is infection of the infarcted lung tissue.

Thrombophlebitis

Thrombophlebitis is partial or total occlusion of major veins which form in the presence of inflammation of the venous walls.

Classification according localization

- *Superficial*
- *Deep*

Classification according to degree of trophic changes and hemodynamical incompetence

- mild form
- moderate form
- severe form

Classification according to clinical course

- Acute thrombophlebitis
- Subacute thrombophlebitis
- Chronic thrombophlebitis (postphlebitic syndrome)

Varicose veins (chronic venous disorder)

Varicose veins are veins that have become enlarged and twisted.

Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification for

Varicose veins

No visible or palpable varicose veins

C1 -Telangectasia (Thread veins / Spider veins / Broken veins)

C2 is subdivided into

C2A- Varicose veins without any symptoms (Asymptomatic)

C2S- Varicose veins with symptoms

C3- Swollen ankle (oedema) due to varicose veins or hidden varicose veins (venous reflux)

C4- Skin damage due to varicose veins or hidden varicose veins (venous reflux)

C5- Healed venous leg ulcer

C6 - Venous leg ulcer

Pulmonary hypertension classification according to WHO 1

Group 1'.

Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)

Group 2.

Pulmonary hypertension due to left heart diseases

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

Pulmonary hypertension classification according to WHO 2

Group 3 :- Pulmonary hypertension due to lung diseases and/or hypoxemia

Group 4 :- **Chronic thromboembolic pulmonary hypertension (CTEPH)**

Group 5 :- PH with unclear multifactorial mechanisms

- Haematological disorders: myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Clinical classification of hypertension in grades according to European society of cardiology

Category	Systolic blood pressure (mm hg)	Diastolic blood pressure (mm hg)
Optimal blood pressure	< 120	< 80
Normal blood pressure	< 130	< 85
Normal blood pressure	< 130	< 85
Mild hypertension (1 degree)	140-159	90-99
<i>Moderate hypertension (2 degree)</i>	<i>160-179</i>	<i>100-109</i>
Severe hypertension (3 degree)	>180	> 100
Isolated systolic hypertension	>140	> 90

Classification of hypertension in stages with clinical features.

- Stage 1: there are no injuries to target organs
- Stage 2: there are damages to target organs without functional impairment.

Heart : left ventricle hypertrophy.

Eyes: retinopathy

Kidney :micro albuminuria or creatinine elevation less than 177 mmol/l (100-177mmol/l)

Brain: transient ischemic attack

- Stage 3: injuries of internal organ with functional impairment

Heart- heart failure, myocardial infarction, valve dysfunction

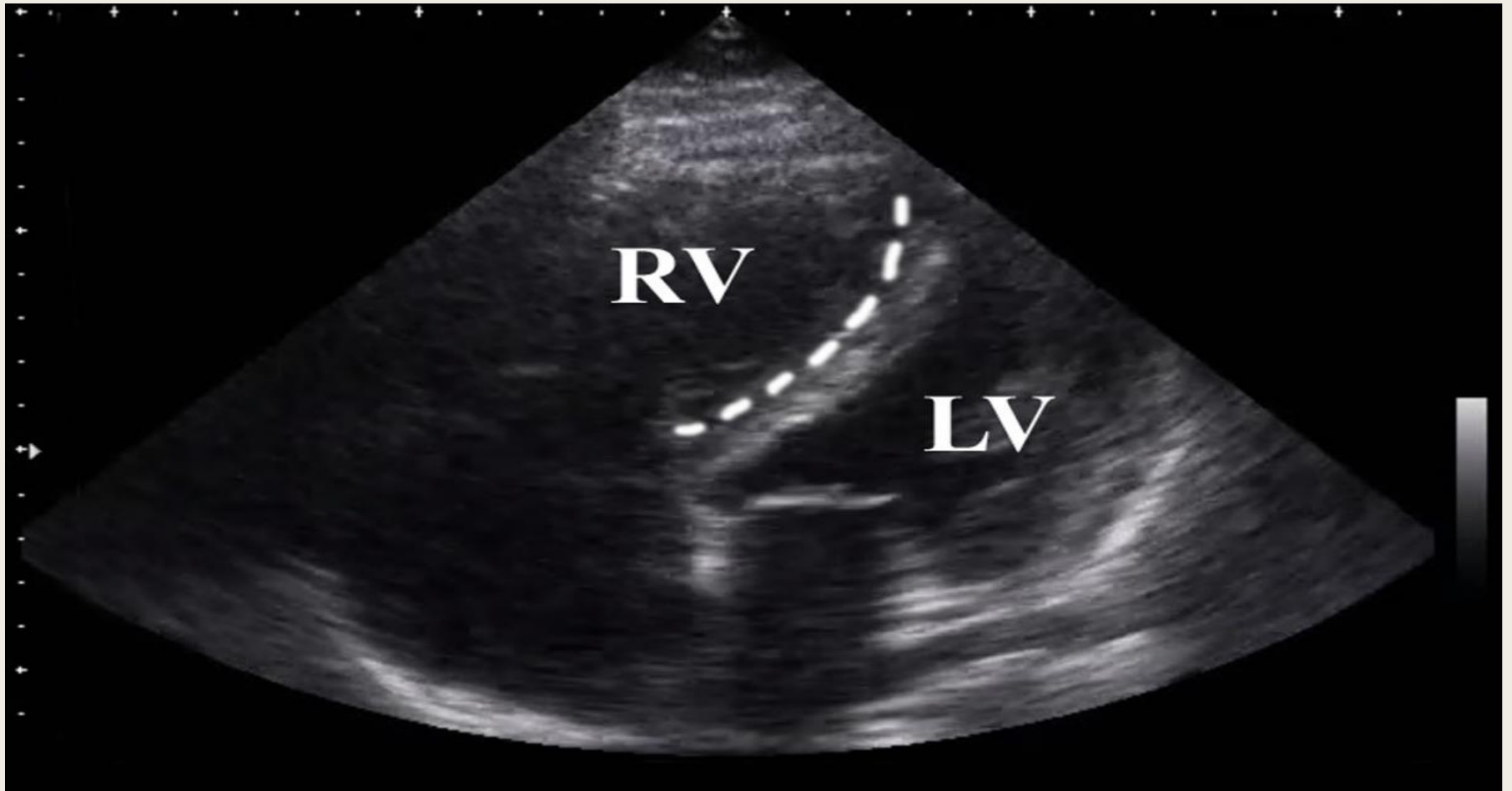
Eyes –retinopathy with the disturbance of vision

Brain –stroke

Liver –hepatomegaly

kidney- chronic kidney disease . Creatine (more than 177mmol/l)
protein in urine

Acute right ventricular insufficiency



Classification of heart failure according to the ACC/AHA

Heart failure stage A	patient is at high risk of developing heart failure in the future but no functional or structural heart disorder
Heart failure stage B	Structural heart disorder but without symptoms of heart failure
Heart failure stage C	Structural heart disorder with prior or current symptoms of heart failure
Heart failure stage D	Refractory heart disorder requiring special interventions

Classification of heart failure (according to New York heart association)

Functional classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Classification of heart failure according to ejection fraction

By LVEF (left ventricle ejection fraction.)

Classification	Ejection fraction
I.Heart failure with reduced ejection fraction (HFrEF)	< or = 40%
II.Heart failure with preserved ejection fraction (HFpEF)	> or = 50%

Clinical diagnosis

Main: Pulmonary embolism. Infarct pneumonia. Arterial hypertension (2nd degree and 2nd stage). Chronic heart failure IIA stage, II FC with abnormal ejection fraction (44%)

Associated disease: Right lower limb superficial vein thrombophlebitis. Varicose veins of both lower limbs

Management of patient

- Lifestyle modification (quit smoking, continuous adherence to physical activity and diet)
- Oxygen treatment
- Clexcane (enoxaparin) -0.4mg (2.4% in 5ml) Warfarin after discharge from the hospital
- Bisoprolol (b-blocker) 10mg once daily.
- Amlodipine (CCB) 10mg once daily
- Rosovalstatin (statins) 10mg/day
- Valsartan(angiotensin II) 160 mg
- Hydrochlorothiazide). 12.5 mg . 2 times a day.
- Cephalosporin -3rd generation to prevent development of pneumonia
- Euphylline (to reduce dyspnea) 5mg/kg
- Lasolvan (mucolytic) 30mg 3times a day for the first 2-3 days and then 30mg 2 times daily afterwards

Additional treatment

1. Lifestyle modification

- the patient is advised to quit smoking
- continuous adherence to physical activity and diet.

2. Drug therapy

- Local therapy with ointment (heparin ointment)
- Surgical treatment to remove varicose vein

Specific diet in patients with warfarin

- They should avoid meals with large amount of vitamin K as that could interfere with the mechanism of warfarin.

Meals like this should be avoided ;-

- Kale
- Spinach
- Brussels sprouts
- Parsley
- Collard greens
- Mustard greens
- Chard
- Green tea

Definition, frequency and clinical significance

- Thromboembolism of pulmonary artery (pulmonary embolism) :- is a blockage of the lung's main artery or one of its branches by a substance that has traveled from elsewhere in the body through the bloodstream (embolism).
- 30% of patients die if untreated usually due to recurrent pulmonary embolism
 - *Up to 60% of autopsies will show some evidence of past PE*

Epidemiology of pulmonary Embolism

- *90-95% of pulmonary emboli originate in the deep venous system of the lower extremities*
- *Other rare locations include*
 - Uterine and prostatic veins
 - Upper extremities
 - Renal veins
 - Right side of the heart

Types of pulmonary embolism

- Acute
 - massive (bp < 90/40 mmhg >15 mins)
 - sub massive
- Chronic
- Saddle embolism
 - embolus lodges at the main P.A bifurcation

Risk factors for pulmonary embolism

Virchow's triad

- Rudolf Virchow postulated more than a century ago that a triad of factors predisposed to venous thrombosis
 - *Local trauma to the vessel wall*
 - *Hypercoagulability*
 - *Stasis of blood flow*

Most patients who suffer a P.E have an underlying disposition until it gets triggered

Pathophysiology

- Clot from deep veins of leg breaks off
- Travels via venous system to right side of heart
- Fragments in right side of heart
- Showers lung with emboli varying in size
- On average > 6-8 vessels are embolized

Pathogenesis

- When venous emboli become dislodged from their site of origin, they embolize to the pulmonary arterial circulation or, paradoxically to the arterial circulation through a patent foramen ovale.
 - *About 50% of patients with pelvic or proximal leg deep venous thrombosis have PE*
 - *Isolated calf or upper extremity venous thrombosis pose a lower risk for PE*

Risk factors for pulmonary embolism 1

- Superficial and deep vein thrombosis
- Inherited thrombophilia
- Smoking
- Long bone fracture
- Long bed rest (after surgery or sedentary obese people)
- Malignancy
- Surgery
- Trauma
- Oral contraceptives
- Obesity
- Pregnancy

Risk factors for pulmonary embolism 2

- Orthopedic surgery
- Congestive heart failure
- Sickle cell disease
- Hypertension
- Inflammatory bowel disease
 - Presence of central vein catheter

Signs and Symptoms of pulmonary embolism

- Dyspnea with rest or with movement
- Plueritic pain (pain with breathing)
- Calf or thigh pain and swelling
- Cough
- Orthopnea
- Wheezing
- Excessive sweating
- Cyanosis (blue colored skin)
- Weak pulse
- Tachypnea , tachycardia , crackles, decreased breath sounds
- Loud s2, raised jugular vein pressure

Laboratory investigations

- Arterial blood gases (hypoxemia, hypocapnia, respiratory alkalosis, hypercapnia, respiratory and metabolic acidosis if massive)
- Troponin levels
- Complete blood count
- Clotting status (PT, aPTT, TT), and some screening tests (erythrocyte sedimentation rate, renal function, liver enzymes, electrolytes).

D dimer

- Fibrin degradation product found in a blood test
- It is elevated in most patient with P.E
- Normal range is less than 250ng/ml
- D-dimer is highly sensitive but not specific (specificity around 50%). In other words, a positive D-dimer is not synonymous with PE, but a negative D-dimer is, with a good degree of certainty, an indication of absence of a PE
- It provides supporting evidence for the need for imaging

Imaging of P.E

■ Chest X-ray

It is mostly abnormal but it doesn't differentiate P.E from other diagnosis.

Radiologic signs include Hampton's hump, fleischner sign, knuckle sign, westermark sign.

Hampton's hump(wedge shaped infarct that can be found on x ray)



VQ scan(ventilation perfusion scan)

A lung ventilation/perfusion scan, or VQ scan, is a test that measures air and blood flow in a patient's lungs. A VQ scan most often is used to help diagnose or rule out a pulmonary_embolism

The ventilation scan shows where air flows in the lungs. The perfusion scan shows where blood flows in the lungs.

Both scans use radioisotopes (a low-risk radioactive substance). For the ventilation scan, the patient inhales a small amount of radioisotope gas. For the perfusion scan, the radioisotopes are injected into a vein in the arm.

Normal VQ scan virtually excludes PE

It is particularly useful in people who have an allergy to iodinated contrast, impaired renal function, or are pregnant (due to its lower radiation exposure as compared to CT)

VQ scan results

Perfusion Scan: Pulmonary Emboli



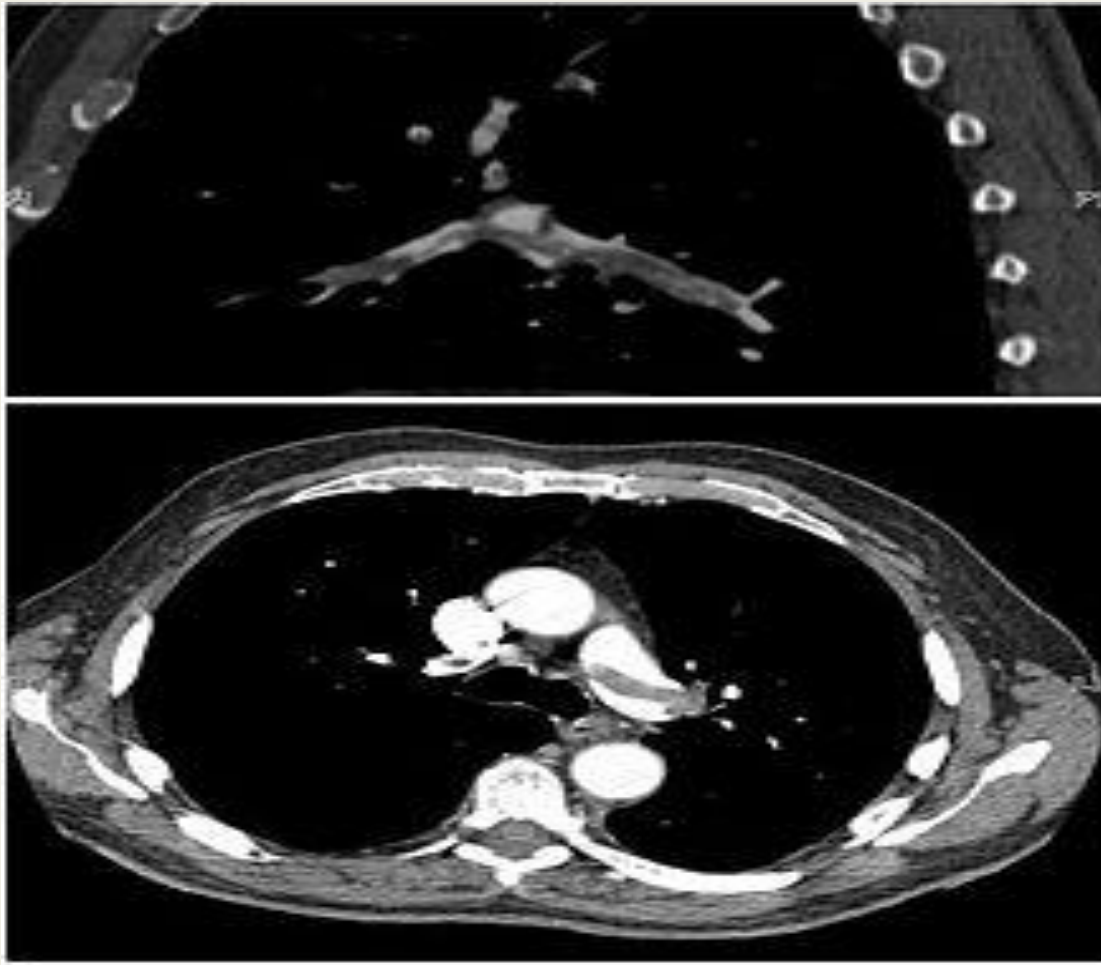
Normal Scan



CT scan

- CT pulmonary angiography (CTPA) is a pulmonary angiogram obtained using computed tomography (CT) with radio contrast rather than right heart catheterization.
- Its advantages are its high specificity, rapidity, and diagnosis of other diseases
- Its disadvantages are availability, expenses, and contrast load

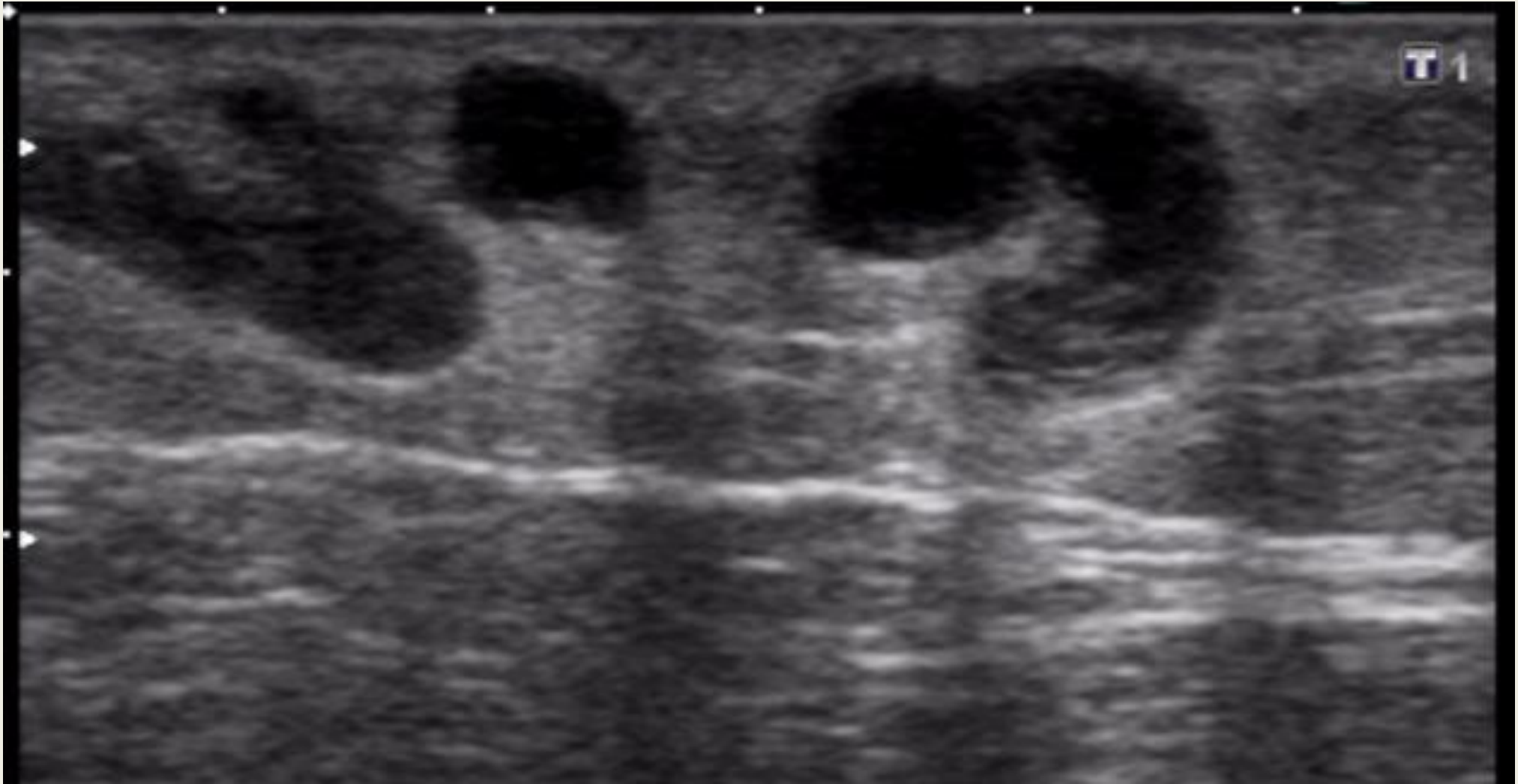
CT SCAN



Ultrasound of the legs (leg Doppler)

- This is done in search of deep vein thrombosis . Absence of this doesn't exclude the diagnosis of P.E but the presence of it could be enough to start anticoagulation therapy and this is particularly useful in pregnant women as this prevents risk to unborn child from radiologic methods.

Varicose vein Ultrasound.



Wells criteria to determine DVT

Table 1

Modified Wells Criteria: Clinical Evaluation Table for Predicting the Probability of a DVT

Clinical Characteristic(s)	Score
Active cancer	+1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	+1
Recently bedridden for three days or major surgery within the last 12 weeks	+1
Localized tenderness along the deep venous system	+1
Entire leg swollen	+1
Calf swelling ≥ 3 cm larger than asymptomatic side	+1
Pitting edema confined to symptomatic leg	+1
Collateral superficial veins	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as a DVT	-2
Clinical Probability of DVT	Total Score
Likely	< 2
Unlikely	≥ 2

Wells criteria to determine pretest probability

Variable	Score
DVT symptoms and signs	3.0
PE as likely or more likely than alternative diagnosis	3.0
Heart rate >100 beats/min	1.5
Immobilization or surgery in previous 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Cancer	1.0

Total Score

<2.0	low pretest probability
2.0 to 6.0	moderate pretest probability
>6.0	high pretest probability

Management of Pulmonary Embolism

■ Anticoagulation therapy(main treatment)

Acute treatment

1. Unfractionated heparin
2. Low molecular weight heparin
3. fondaparinux

Chronic treatment

1. Warfarin (use international normalized ratio to monitor)
2. Acenocoumarol or phenprocoumon (coumarin derivatives and vitamin k antagonists)

International normalized ratio

- This blood test looks to see how well the patient's blood clots.
- The international normalized ratio (INR) is a standardized number that's figured out in the lab. If a patient is on blood thinners, also called anti-clotting drugs or anticoagulants, it's especially important to check the INR. The INR is figured out using the results of the prothrombin time (PT) test, which measures the time it takes for blood to clot. The INR is an international standard for the PT.

I.N.R

International Normalized Ratio (I.N.R.)

- I.N.R. of 3.0 – 4.5 is required for patients with a H/O:

Mechanical Valves

D.V.T. (deep vein thrombosis)

Recent massive M.I. (myocardial infarction)

Atrial fibrillation (AF) associated with Stroke or M.I.

Pulmonary embolism (PE)

International Normalized Ratio (INR)

- $INR = \frac{\text{Patients PT}}{\text{Control PT}} \text{ ISI}^*$
- The normal INR range is 0.9-1.2
- The INR is monitored during Coumadin therapy
- The INR is repeated every 4-6 weeks

*ISI: International Sensitivity Index of Thromboplastin

Thrombolysis

■ Indication

- Massive PE (SBP <90 mmhg for >15mins)

Catheter-directed thrombolysis (CDT) is a new technique found to be relatively safe and effective for massive PEs. This involves accessing the venous system by placing a catheter into a vein in the groin and guiding it through the veins by using fluoroscopic imaging until it is located next to the PE in the lung circulation.

Medication that breaks up blood clots is released through the catheter so that its highest concentration is directly next to the pulmonary embolus. CDT is performed by interventional radiologists, and in medical centers that offer CDT, it should be considered first-line treatment.

Controversial indication

- Severe hypoxemia
- Large thrombus burden
- RV dysfunction
- Saddle embolus
- Non massive P.E

Absolute contraindications

- intracranial neoplasm
- recent (<3 months) intracranial surgery or ischemic stroke
- hemorrhagic stroke
- active or recent bleeding

Relative contraindications

- Bp > 180 systolic
- h/o ischemic stroke
- Recent (<4 weeks) internal bleeding
- thrombocytopenia

Thrombolytic agents

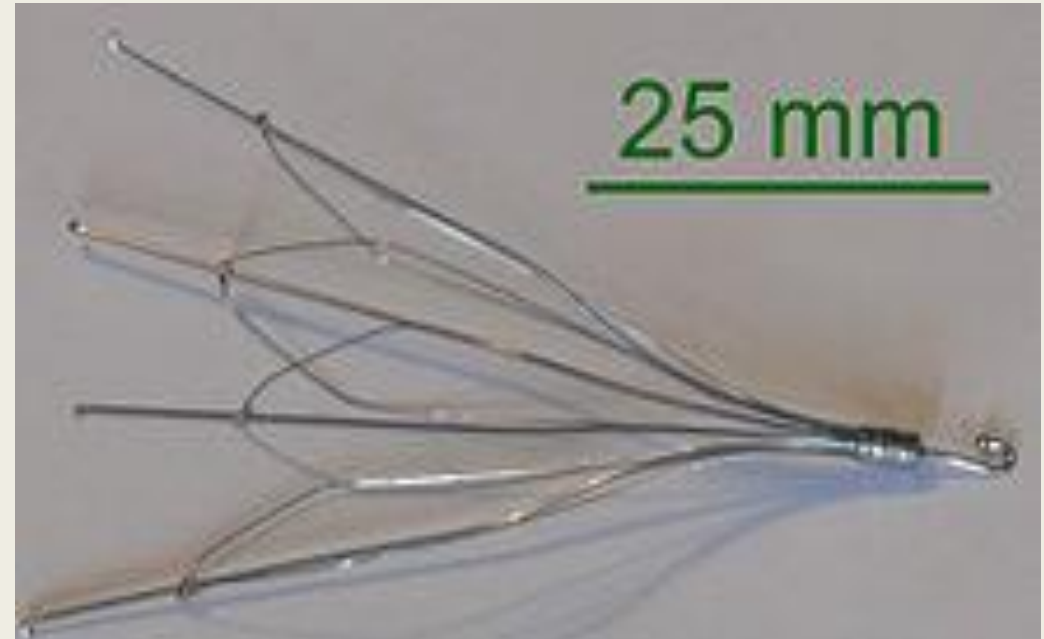
- Tissue plasminogen activator (tpa)
 - Alteplase
 - lv drip 100 mg over 2 hours
 - reteplase
 - tenecteplase
- Streptokinase
 - IV drip 250,00 units over 30mins
 - followed by 100,000 u/hr for 24 hours
- urokinase

Side effects of thrombolysis

- Bleeding (intracranial hemorrhage)
- Allergic reaction and hypotension to streptokinase

Inferior vena cava filter

The advantages of using IVCF are if anticoagulant therapy is contraindicated or if the person still has a pulmonary embolus in spite of being anticoagulated. In these instances, it may be implanted to prevent new or existing DVTs from entering the pulmonary artery and combining with an existing blockage



Surgical embolectomy

- Must be done by an experienced surgeon
- Requires cardiopulmonary bypass
- Indicated as an alternative to thrombolysis or when thrombolysis is contraindicated.

Prevention of blood clots formation

- Blood thinners to help prevent DVT in people at high risk
- Pressure stockings for people who previously had a DVT or varicose veins. They will improve blood flow in the legs and reduce risk of blood clots .
- Smoking cessation
- People who are at very high risk of blood clots may need shots heparin when they take long flights

THANK YOU FOR YOUR
ATTENTION.