Deep Vein Thrombosis and Pulmonary Embolism

HPI, Signs and Symptoms

DVT:
- leg pain in one leg only
- worse when walking
- leg tenderness in one leg only
- extending proximally over time
- swelling (edema) of only one leg
- increased warmth of one leg
- changes in skin color of one leg, redness
An examination may reveal a red, swollen, or tender leg.

PE:
- Tachycardia esp. with signs of DVT
- Tachypnoea/Dyspnoea of sudden or intermittent onset
- Pleuritic chest pain
- General non pleuritic retrosternal chest pain
- Haemoptysis
- Syncopy
  - acute onset of shortness of breath;
  - sometimes the patient even pinpoints the moment of distress

Differential Diagnoses (DDx)

DVT
- Intermittent claudication
- Torn tendon
- Hemarthrosis
- ruptured Baker cyst,
- arterial insufficiency,
- hematoma,
- trauma,
- muscle strain,
- arthritis,
- tendonitis,
- iliac vein compression,
- lymphedema,
- sciatic nerve compression.

PE
- Myocardial infarction, unstable angina
- Pneumonia, bronchitis, COPD exacerbation
- Congestive heart failure
- Asthma
- acute respiratory distress syndrome,
- Pericarditis
- Primary pulmonary hypertension
- Rib fracture, pneumothorax
- Costochondritis, “musculoskeletal pain,” anxiety
- cardiac tamponade,
- right-sided heart failure
- pulmonary infection,

HISTORY:

Seek the chronology of symptoms:

DVT will progress into more continuous, more proximal pain
- How rapid the onset of shortness of breath;
- Can the patient pinpoint the moment of distress.
- Complaints related to the signs of DVT,
  - lower extremity swelling and warmth to touch or tenderness may be present.
- Dyspnea is the most frequent symptom of PE.
- With a smaller PE near the pleura, the patient may complain of pleuritic chest pain, cough, or hemoptysis. Sometimes, massive PE can present with syncope.
- The patient may have a sense of impending doom with apprehension and anxiety.
- History may reveal presence of one or more causes or risk factors
Risk factors:

Hereditary haemostatic disorders:
- Factor V Leiden,
- prothrombin G20210A variant,
- protein C deficiency,
- antithrombin III deficiency,
- protein S deficiency,
- abnormal fibrinogen,
- abnormal plasminogen.

Hereditary or acquired haemostatic disorders:
- raised plasma levels of factor VII, VIII, IX or XI,
- raised plasma levels of fibrinogen/ homocysteine,
- coagulation factor IX concentrates,
- lupus anticoagulant,
- oestrogen therapy (oral contraceptive and HRT),
- heparin induced thrombocytopenia,
- pregnancy and puerperium,
- surgery especially orthorpedics,
- major trauma,
- malignancy,
- myocardial infarct,
- thrombocythaemia

Related to stasis and unknown factors:
- Age,
- obesity,
- sepsis,
- paroxysmal nocturnal haemoglobinuria,
- Behçet's disease,
- females,
- Blood group (A>O)
- Cardiac failure,
- stroke,
- prolonged immobility,
- pelvic obstruction,
- nephritic syndrome,
- dehydration,
- hyperviscosity,
- polycythaemia,
- varicose veins

Findings on Examination:
- Tachypnea, R.R > 18 = most common sign of PE.
- Tachycardia often is present.
- The second heart sound can be accentuated.
- Fever may be present.
- Lung examination findings frequently are normal.
- Cyanosis may be present.
- Some patients have signs of DVT, lower extremity swelling, and tenderness and warmth to touch.

HOMANS SIGN:
forcibly dorsiflex the ankle while knee is in flexed position: pain in the calf is suggestive of DVT

SIGNS OF DVT:
- lower extremity swelling,
- pitting oedema
- tenderness
- warmth to touch

SIGNS OF PE:
- Tachypnoea
- Tachycardia
- Cyanosis
- Loud P2 heart sound
- Syncope

2nd pulmonary sound = Only with huge PEs

WORK UP of suspected PE and DVT

Clinical Model for Predicting Pretest Probability for DVT

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Score*</th>
</tr>
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<tbody>
<tr>
<td>Active cancer within six months</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis or cast of lower extremity</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for more than three days or major surgery within the past four weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along distribution of deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Calf diameter more than 3 cm larger than opposite leg§</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely or more likely than that of DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis.
§--Measured 10 cm below tibial tuberosity.

Interpretation:
0 = low probability—3% frequency of DVT;
1 to 2 = medium probability--17% frequency of DVT;
>3 = high probability--75% frequency of DVT
Tests and Investigations: BIOCHEMISTRY

D-Dimers - is there fibrinolysis happening?

- latex agglutination test
- OR ELISA immunoassay (much more accurate and expensive)

\[ \text{D-dimer} = \text{degradation product produced from cross-linked fibrin by plasmin-mediated proteases} \]

\[ \Rightarrow \text{WILL MISS 10\% OF PULMONARY EMBOLISMS!!} \]
\[ \text{ONLY 30\% OF PATIENTS WILL ACTUALLY HAVE A PE} \]

Arterial Blood Gases – to know just how concerned you should be

Looking for Hypoxemia; Hypocapnia; Respiratory alkalosis.

Tests and Investigations: IMAGING

Doppler ultrasound

- Scan the leg! **BEST ACCURACY ABOVE THE KNEE**
- Will show direction of flow, degree of occlusion, size + position of the thrombus.
- Next to useless for PE

Venogram

**DANGEROUS**: INVASIVE and with DYE CONTRAST but is the gold standard for demonstrating occlusion.

Plethysmography

measures the **systolic blood pressure** (maximum pressure exerted when the heart contracts) of a lower extremity as compared to the upper extremity. The test is usually performed to rule out blockages in the extremities (usually lower extremities).

Chest X-ray

May be totally useless BUT MAY DEMONSTRATE A HUGE P.E.

- enlarged right descending pulmonary artery,
- decreased pulmonary vascularity (Westermark sign),
- a wedge-shaped infiltrate,
- an elevation of the hemidiaphragm (Hampton hump).

**PULMONARY ANGIOGRAPHY = gold standard, but increases mortality.**

Invasive, THUS \( \Rightarrow \) increased risk of haemorrhage and dye reactions; increases mortality by 2-3%

**VENTILATION-PERFUSION SCANNING**

Test of choice! Always follow D-dimer assay with the V/Q scan!

- **Negative V/Q scan findings indicate an absence of any perfusion defects. Four percent of these patients still may have PE.**

Shows nicely the areas which are not being perfused (though still being ventilated) and thus will show moderately large PE, but may miss little segmental PEs

ECG to rule out Myocardial Infarction

- Sinus tachycardia often is present.
- Right axis deviation,
- Right bundle branch block,
- Deeply inverted T waves in V_1-V_3 may be present.
- An S\_1Q\_3T\_3 pattern may be seen.

Disease Definition

Hypercoagulability or obstruction leads to the formation of thrombus in the deep veins of the legs, pelvis, or arms. As the clot propagates, proximal extension occurs, which may dislodge or fragment and embolize to the pulmonary arteries. This causes pulmonary artery obstruction and the release of vasoactive agents (ie, serotonin) by platelets increases pulmonary vascular resistance. The arterial obstruction increases alveolar dead space and leads to redistribution of blood flow, thus impairing gas exchange due to the creation of low ventilation-perfusion areas within the lung.
Management of DVT

ESPECIALLY IF PROXIMAL

Distal DVTs have 20% chance of sailing down the bloodstream within 1 week.
INSIDE THE CALF = EVEN LESS CHANCE; can even play the waiting game

Superficial venous thrombosis
- Use duplex scan to screen for involvement of deep system
- Elevation, non-steroidal anti-inflammatory drugs

Deep venous thrombosis
- Begin warfarin on the first hospital day or in the ED
- Low-molecular-weight heparin—more effective and safer than standard heparin
- Enoxaparin recently approved in the United States for treatment of DVT
- Heparin 80 U/kg load, 18 U/kg/hr drip
- Thrombolysis for severe disease in young adults
- Vena cava filter if thrombosis in presence of adequate anticoagulation

Phlegmasia dolens
- Fluid resuscitation
- Heparinization before imaging studies
- Thrombolyis for patients who do not respond rapidly to heparin
- Thrombectomy for patients unresponsive to thrombolysis

Upper extremity thrombosis
- Diagnose with duplex scan
- Catheter directed thrombolysis

Calf thrombi
- Anticoagulate or perform serial studies to detect propagation.
- Consider TED stockings

Pitfalls in the Management of DVT
1. Relying on calf measurements and negative Homans
2. Failure to perform objective testings on patients with presumed cullulitis of the leg
3. Failure to evaluate deep system in patients with superficial thrombophlebitis
4. Failure to consider the clinical likelihood of DVT when interpreting Doppler studies
5. Failure to use a weight-based nomogram to dose heparin
6. Failure to either anticoagulate or perform serial studies on patients with isolated calf vein thrombosis
7. Failure to perform a simple screen for malignancy in patients with unexplained deep venous thrombosis

Management of PULMONARY EMBOLISM

SHORT TERM: prevent cardiopulmonary failure
1. OXYGEN !! restore sats
2. ANALGESIA if PE @ pleural nerves (exquisite pain)
3. THROMBOLYSIS if indicated (eg. massive iliufemoral thrombus)
4. SURGERY (Embolectomy) IF RISKY (eg. Rt Heart Failure)
5. Heparin + oral anticoagulants overlapped for 5 days
6. Monitor clotting time!! Manage UNTIL SATISFACTORY
   (Maintain an APPT between 55 and 90 seconds.)

LONG TERM: address risk factors
1. Oral or subcutaneous anticoagulants for at least 3 months
   (or until temporary risk factors depart)
   Pregnant women: switch to warfarin post-partum
2. TED stockings to prevent recurrent PE
3. QUIT SMOKING

ADMITT TO HOSPITAL IF:
- Concurrent Pulmonary Embolism (PE)
- Serious co-morbid condition
   - Cancer, infection, stroke
- Prior DVT or PE
- Contraindications to anticoagulation
  - Familial bleeding disorder
  - Known deficiency of
    - Antithrombin III
    - Protein C
    - Protein S
    - Pregnancy

HEPARIN THERAPY:
Heparin binds to and accelerates the activity of antithrombin III, an enzyme that inhibits the coagulation factors thrombin (factor IIa), Xa, IXa, XIa, and XIIa. Heparin thus prevents additional thrombus formation and permits endogenous fibrinolytic mechanisms to lyse clot that has already formed. After 5 to 7 days of heparin, residual thrombus begins to stabilize in the endothelium of the vein or pulmonary artery. However, heparin does not directly dissolve thrombus that already exists.

YOU MAY USE THROMBOLYSIS:
streptokinase, urokinase, and tPA
But its not any more effective in preventing PE. BUT IT DOES IMPROVE OUTCOME OF DVT
(fewer sequelae, preserved valves, etc)

IN PREGNANCY:
HEPARIN = SAFE
WARFARIN = DANGEROUS
Prognosis

Most DVT's disappear without difficulty, however there is a risk of recurrence.

!! DVT IS ITS OWN GREATEST RISK FACTOR !!

Some patients may develop some chronic pain and swelling in the leg known as post phlebitic syndrome. This is due to valve destruction, followed by valvular incompetence and thus fluid accumulation in the distal limb.

Untreated acute proximal DVT causes clinical PE in 33-50% of pts

About one third of PE cases are fatal.
Sixty-seven percent of these are not diagnosed premortem.
Death usually occurs within 30 minutes.

Epidemiology

- In the US: 1 in 1000 per year. Approximately 5 million cases of DVT and about 600,000 cases of PE occur per year.
- Internationally: 1.6 in 1000 per year. 3-4% of patients who died within 3 months of a fractured neck of the femur died of fatal PE
- Thromboembolic disease accounts for approximately a quarter of a million hospitalizations in the United States yearly and for about 5-10% of all deaths.

Race: The incidence of thromboembolism is higher in African Americans than it is in whites.
Asians have a lower incidence than both African Americans and whites.

Sex: PE occurs more frequently in men than in women.
Age: Age = risk doubles with each decade in persons older than 40 years.

<table>
<thead>
<tr>
<th>D.V.T. Background Rates</th>
<th>D.V.T. INCIDENCE - MEDICAL PATIENTS (WITHOUT PROHYLAXIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Young</td>
<td>1/100,000</td>
</tr>
<tr>
<td>Young</td>
<td>1/10,000</td>
</tr>
<tr>
<td>Middle Age</td>
<td>1/1000</td>
</tr>
<tr>
<td>Elderly (&gt;80yrs)</td>
<td>1/100</td>
</tr>
<tr>
<td>General Medical</td>
<td>10-26%</td>
</tr>
<tr>
<td>Stroke</td>
<td>11-75%</td>
</tr>
<tr>
<td>Myocardial Infarct</td>
<td>17-34%</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>6-100%</td>
</tr>
<tr>
<td>Congestive Cardiac Failure</td>
<td>20-40%</td>
</tr>
<tr>
<td>Medical Intensive Care</td>
<td>25-42%</td>
</tr>
</tbody>
</table>

Greatest Risk to Pregnant Women

Is for 2 months AFTER delivery!!

Before = 5 times;
After = 10 times!

Fig. 21.3: The genetic basis of factor V Leiden. (a) Activated protein C inactivates factor Va by proteolytic cleavage at three sites in the Va heavy chain. In the factor V Leiden mutation the Arg-506-Gln polymorphism leads to glutamine at position 506 with less efficient inactivation of factor V and increased risk of thrombosis.
The veins store about 60% of the circulating blood volume. ONLY NEED TO REMEMBER 3 THINGS:

Deep veins
- within the muscle compartments
- usually paired veins
- accompany the calf arteries. !!! musculovenous pump !!!

Superficial veins
- in the subcutaneous tissues.
- the long and the short saphenous veins.
- saphenofemoral junction
- saphenopopliteal junction,

Communicating veins
- run between the superficial and deep veins, pass through the deep fascia
MECHANISM OF PE and DVT

Virchow’s Triad

HYPERCOAGULABILITY

STASIS

Endothelial dysfunction

Virchow’s Triad

STASIS

HYPERCOAGULABILITY

Endothelial dysfunction

PREGNANCY:
By nature results in the production of MUCH MORE CLOTTING FACTORS...Because the body prepares to bleed at its completion

Risk Factors for Thrombosis

Genetic:
Deficiencies
- Antithrombin III
- Protein C
- Protein S
Abnormal Proteins
- Factor V Leiden (resistant to activated Pr C)
- Prothrombin 20210
Anomocysteinemias

Acquired:
Virchow’s Triad
1. Stasis of blood flow—Cancer, failure, arrhythmias, immobilisation (travel), pelvic obstruction (pregnancy)
   previous DVT
2. Abnormalities of vessel wall—venous veins, atherosclerosis, trauma, smoking, surgery, tissue infection
3. Changes in blood composition—aging, malignancy, estrogen therapy, pregnancy, anaphylaxis, polycythemia, smoking

Any of these factors may contribute to the thrombotic episode in isolation or in combination. e.g. Oral contraceptives + Factor V Leiden may increase risk by 30 times (See Learning Topic)

Deep Venous Thrombosis

Local turbulence in vicinity of valves in Great Saphenous Vein causes exposure of collagen & tissue factor

Platelets adhere to sub-endothelium via WIF and release ADP & Thromboxane A2

ADP and Thromboxane A2 forming initial plug attract additional platelets

Further Platelet Aggregation and fibrin cross-linking causes further stasis in vicinity of initial thrombus and retards inflow of clotting inhibitors and anticoagulants

Antithrombin III, Protein C, Protein S and Plasmin
Leading to propagation of further thrombus above and below initial thrombus

Vessel Occlusion: Inhibition of flow in Gr. Saphenous Vein, causes a build up of hydrostatic pressure causing extravasation of fluid from vein into ECF

Emboli Formation: Eventually anticoagulants ATIII & Plasmin start working at the edges of the thrombus breaking off emboli

Embolic Dislodgement of part of thrombus is carried to right atrium of heart via inferior vena cava

Pulmonary Embolus: Entry of embolus into pulmonary artery from right atrium

Signs & Symptoms
- Pain
- Godoma
- Rest

Signs, Symptoms & Tests
- Tachypnea
- Tachycardia
- SpO2 & PCO2
- Abnormal V/Q scan
- ECG abnormalities

Obstruction of Pulmonary vessels causes a V/Q mismatch: Severity depends on:
- size of embolus/vessel
- Collateral circulation to that region of lung

References:
3. Refer to Learning Topic

Michelle’s painful calf
Thrombosis prepared by Kosta Calligeros

Its late and Alex is tired

Rudolf Ludwig Karl Virchow
Pathophysiology

- Hypercoagulability or obstruction leads to the formation of thrombus in the deep veins of the legs, pelvis, or arms.
- As the clot propagates, proximal extension occurs, which may dislodge or fragment and embolize to the pulmonary arteries.
- This causes pulmonary artery obstruction and the release of vasoactive agents (ie, serotonin) by platelets increases pulmonary vascular resistance.
- The arterial obstruction increases alveolar dead space and leads to redistribution of blood flow.
- Thus impairing gas exchange due to the creation of low ventilation-perfusion areas within the lung.
- Stimulation of irritant receptors causes alveolar hyperventilation.
- Reflex bronchoconstriction occurs and augments airway resistance.
- Lung edema decreases pulmonary compliance.
- The increased pulmonary vascular resistance causes an increase in right ventricular afterload, and tension rises in the right ventricular wall, which may lead to dilatation, dysfunction, and ischemia of the right ventricle.
- Right heart failure can occur and lead to cardiogenic shock and even death.
- In the presence of a patent foramen ovale or atrial septal defect, paradoxical embolism may occur, as well as right-to-left shunting of blood with severe hypoxemia.

BIOCHEMISTRY: IRON METABOLISM

Veinous emboli grow in the direction of the blood flow, and tend to be amorphous.
Arterial thrombi grow downstream and have a characteristically “laminar” appearance, with rings of red cells interspaced by rings of greyish fibrin strands.

- a 70 Kg man has approximately 4.5g of iron
- Normal dietary intake = 10-15 mg/day
- only about 10% of this is absorbed.
- MAJOR SITE OF ABSORPTION = duodenum
- haemoglobin and myoglobin are well absorbed. (haem iron)
- non haem iron comes from porridge, spinach, eggs, etc.
- DIETARY REGULATION:
  - For a few days after a dietary bolus of iron, the cells in the intestine are resistant to further iron absorption.
- STORES REGULATION
  - sensitive to the total body iron and protects the body from accumulating too much iron which could be toxic.
- ERYTHROPOIETIC REGULATION
  - modulates iron absorption in response to the needs of red cell formation and this regulator has a more powerful effect than the “stores regulator”. 

Table 3.2 Iron absorption

<table>
<thead>
<tr>
<th>Factors favouring absorption</th>
<th>Factors reducing absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haem iron</td>
<td>Inorganic iron</td>
</tr>
<tr>
<td>Ferrous form (Fe²⁺)</td>
<td>Ferric form (Fe³⁺)</td>
</tr>
<tr>
<td>Acids (HCL, vitamin C)</td>
<td>Alkalies—antacids, pancreatic secretions</td>
</tr>
<tr>
<td>Solubilizing agents (eg, sugars, amino acids)</td>
<td>Protuberating agents—phytates, phosphates</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Iron excess</td>
</tr>
<tr>
<td>Increased erythropoiesis</td>
<td>Decreased erythropoiesis</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Infection</td>
</tr>
<tr>
<td>Hereditary haemochromatosis</td>
<td>Tea</td>
</tr>
<tr>
<td>Increased expression of DMT-1 and ferroportin in duodenal enterocytes</td>
<td>Decreased expression of DMT-1 and ferroportin in duodenal enterocytes</td>
</tr>
</tbody>
</table>
Heparin: an acidic, unfractionated mucopolysaccharide (molecular weight 15 - 18,000) is an inhibitor of blood coagulation that is not absorbed from the gastrointestinal tract so is given by injection. Heparin is inactivated by the liver and excreted in urine and has a biological half life of 1 hr. Heparin potentiates the formation of complexes between antithrombin and activated serine protease coagulation factors, thrombin (IIa) and factors IXa, Xa and XIa. The complex formation inactivates these factors irreversibly and it also impairs platelet function.

Low molecular weigh heparin (LMWH) (molecular weigh 2000 – 10,000) is produced by enzymatic or chemical depolymerisation of unfractionated heparin. It has a greater ability to inhibit factor Xa than to inhibit thrombin and interact less with platelets compared to standard heparin. LMWH has a greater bioavailability and a more prolonged half life in plasma making a once daily administration in prophylaxis or treatment feasible.

Heparin does not cross the placenta and LMWH has 50% less complications than standard heparin. Complications include bleeding, heparin induced thrombocytopenia and osteoporosis.

**Pharmacology of ANTICOAGULATION**

**HEPARIN:** improves **ANTITHROMBIN III ACTIVITY**

**LOW MOLECULAR WEIGHT HEPARIN:** smaller than the normal variety which binds both = less effective, but more effective at binding factor Xa and thus more effective overall (Xa is higher up on the cascade).

**WARFARIN:** vit. K antagonist; disables factors 2, 7, 9, 10.

These drugs block the postribosomal γ-carboxylation of glutamic acid residues of vitamin K dependent factors II, VII, IX and X. Initially (within 24 hrs) Factor VII levels drop but prothrombin has a longer plasma half life and only falls to 50% normal at 3 days and so it is after this period that the patient is fully anticoagulated.

Warfarin crosses the placenta and is teratogenic!!

97% warfarin is bound to albumin and the remaining free portion is the active component and can enter the parenchymal cells of the liver.

**Fibrinolytics:** can lyse fresh thrombi = Treatment is most effective in the first 6 hrs after symptoms begin

**side effects of anticoagulants**

Complications include bleeding, heparin induced thrombocytopenia, drug interactions with the anticoagulants, neutropenia or thrombocytopenia and osteoporosis.