Hypercoagulable states DVT

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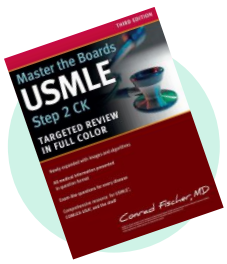
Objectives:

- **Not given yet!**

References:
Slides - Black
Doctor's notes - Red
Step up / davidson - Blue
Extra explanation - Grey

Optional:



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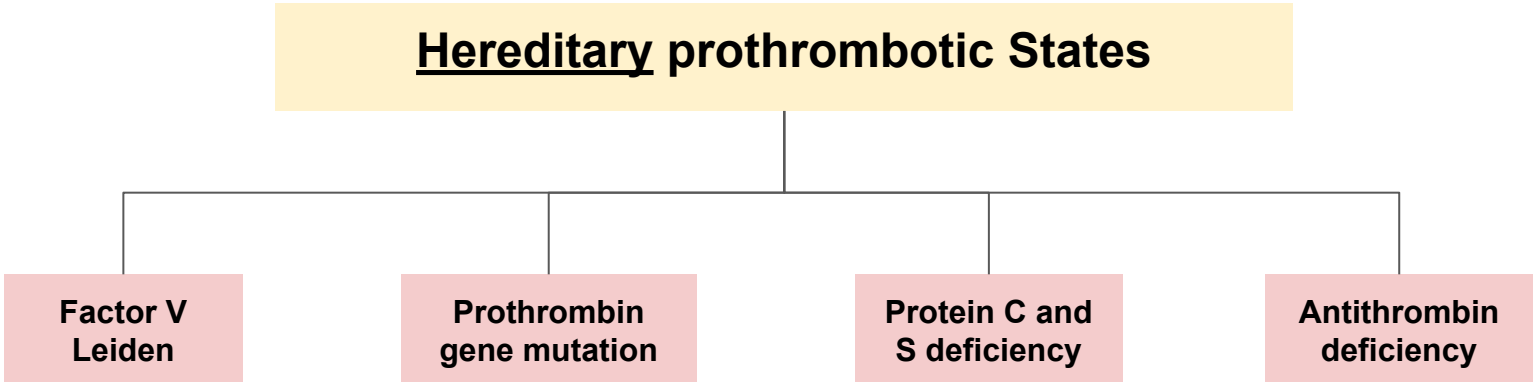
❖ Introduction

- ❑ **Hypercoagulable states "Thrombophilia"** is any state that can increase the tendency of clot formation "thrombosis"
- ❑ It's an Alteration in the hemostatic balance between blood fluidity and clot formation due to genetic or acquired disorders which shift the balance toward excessive platelet aggregation and thrombin generation (Clot formation) that lead to thrombosis.
- ❑ there are Synonyms that describe this condition which we want you to keep in mind because **ALL HAVE SAME MEANING** like:-
  - Hypercoagulable state
  - Prothrombotic state
  - Prothrombogenic state
- ❑ There are two types of thrombus that can arise:- either **Arterial** OR **Venous**
- ❑ In our lecture we would focus about the thrombus that happen in **veins (venous thromboembolism)** which is the most common in people who have Prothrombotic state.
- ❑ Prothrombotic state can happen if:
- ★ Vascular (Endothelial dysfunction) →Although vessels initiate the coagulation process, it's also have antithrombotic mechanism. it's not just a pipe!
- ★ Platelets (↑ activity and/or numbers)
- ★ Coagulation factors (↑)
- ★ Natural anticoagulants (↓ and/or dysfunction)
- ★ Fibrinolytic system (↓)
- ★ Pathological conditions → EX:(hyperhomocysteinemia, antiphospholipid syndrome, Contraceptive pills, etc.)
- ❑ Mention that about the vessels, these are substances that secreted by Endothelial cells and it has a physiological **antithrombotic effects**:-
- ★ Prostacyclin (PGI2) → prevents formation of the platelet plug
- ★ Nitrous oxide (NO2) → vasodilation to avoid the stasis of blood and ↓ the chance of thrombus
- ★ Tthrombomodulin
- ★ Heparans (proteoglycans)
- ★ Tissue factor pathway inhibitors (TFPI) →inhibit the tissue factor to stop the coagulation
- ❑ Now, there are two groups of venous thrombosis disorders in people who have prothrombotic states:- **Hereditary** OR **Acquired**. **and you should know that the most common complication of both groups would be either DVT OR PE** as we are going to discuss them in the upcoming slides!



1) Factor V Leiden

(Estrogen + FV Leiden → ↑↑↑ thrombosis)

Dual pro thrombotic state of Factor V Leiden

1. **Increased coagulation**
2. **FVa Leiden → ↑ thrombin generation, (↓ anticoagulation)**
   ↓ inactivation of factor FVIIIa

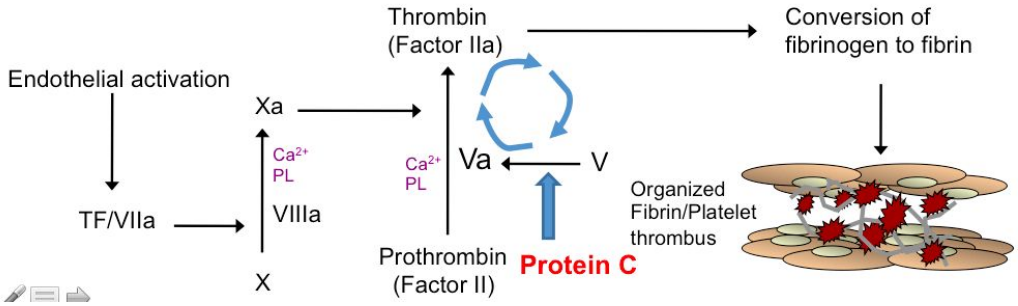
(also ↓ PAI inactivation → ↓ fibrinolysis)

Factor V Leiden: "Protein C resistance"

- **A mutation in factor V gene**
- **Most common hereditary hypercoagulable disorder in caucasian. However, it's not common in KSA**
- **Protein C can no longer cleave factor V, leading to unregulated prothrombin activation →increase risk of thrombotic events**

Q: What are vit K dependents factors?

- **Factor II, VII, IX, X**
- **Protien C&S**



2) Prothrombin gene mutation

- **Normal prothrombin (Factor II) circulates as Vitamin K-dependent cofactor w/ ½ life of 3-5 days.**
- **Heterozygotes have a 30% higher plasma prothrombin level compared to normals.**
- **So, in this mutation.. we get elevated prothrombin (FII) which lead to more thrombotic events.**

Prothrombin 20210A mutation is the 2nd most common prothrombotic mutation (→ ↓ thrombin inactivation)

3) Protein C & S deficiency

- **Are the 2 major cofactors responsible for regulating the amplification of the clotting cascade.**
- **Autosomal dominant inheritance**
- **Inhibit activated cofactors Va and VIIIa, respectively.**
- **Protein C is consumed and levels are low in vitamin K deficiency, DIC , liver disease, etc.**
- **Could be Heterozygous, homozygous, Congenital or Acquired.**
- **Clinical expression of hypercoagulability variable, and do not necessarily correspond with absolute concentration of Protein C.**

Some people may have low levels of protein s and c and they don't develop thrombosis

- **In case of deficiency; the factor V & VIII will still active leading to more thrombotic events**
- **Protein C & S deficiency are Autosomal dominant disease**
- **Protein C & S deficiency can also be acquired in case of:- Oral contraceptive, pregnancy, and nephrotic syndrome**

4) Antithrombin deficiency (AT)

- **AT is a potent inhibitor of thrombin and other serine proteases of the coagulation cascade (e.g., FXa, FIXa).**
- **AT deficiency typically occurs in an Autosomal Dominant inheritance pattern, thereby affecting both sexes equally.**
- **Overall incidence of AT deficiency is low.**
- **Females with AT deficiency are at particularly high-risk for VTE* during pregnancy.**
- **DVT occurred in 18% of pts with AT deficiency, and in 33% in the postpartum period.**
- **They don't respond to Heparin. Heparin needs Antithrombin III to do its action.**
- **Can be Acquired :- (after trauma or surgery, nephrotic syndrome).**

❖ Combined effect of inherited thrombophilias on tendency for VTE* Important!

- Pooled analysis of 2310 cases and 3204 controls amongst 8 case-control studies (from UK, Denmark, France, Italy, Sweden, Brazil) evaluating the risks in patients with FVL and/or prothrombin 20210A
- Of patients with VTE,
- 23% were heterozygous for prothrombin gene mutation
- 12% were heterozygous for Factor V Leiden
- 2.2% were double heterozygotes

The higher odd ratio, the more chance to get the disease

Fifty percent of thrombotic events in patients with inherited thrombophilia are associated with the additional presence of an acquired risk factor (eg, surgery, prolonged bed rest, pregnancy, oral contraceptives). Some patients have more than one form of inherited thrombophilia or more than one form of acquired thrombophilia and appear to be at even greater risk for thrombosis

VTE = Venous thromboembolism

Acquired prothrombotic States

❖ Acquired prothrombotic States important

- Prior thrombotic event or family of VTE.
- Recent major surgery (Especially orthopedic).
- Presence of a central venous catheter - cause impaired of the blood flow.
- Immobilization.
- Trauma.
- Malignancy.
- Heart failure.
- Obesity & older age (>60).
- Pregnancy.
- Oral contraceptive or hormone replacement therapy.
- Antiphospholipid antibody syndrome.
- Myeloproliferative disorders
- Polycythemia vera or essential thrombocythemia
- Heparin use and heparin induced thrombocytopenia & thrombosis (HIT)
- Hyperviscosity syndromes
- Multiple myeloma or Waldenstrom's macroglobulinemia is a type of non-Hodgkin lymphoma (NHL). The cancer cells make large amounts of an abnormal protein (called a *macroglobulin*)

Unfortunately the exact known mechanism is unknown..but the theory said that the are antibodies that against platelet factor IV. The risk of venous and arterial veins thrombosis. risk of limb gangrene is high.

- **How to treat it? stop heparin**
- **special test to diagnosis: HIT assay (definite)**
- **could be developed from small doses**

❖ Virchow's Triad Important

- Alterations in blood flow (i.e., stasis)
- Disrupted laminar flow allows greater interaction between platelets and endothelial surface.
- Prevents dilution of locally activated clotting factors.
- Prevents inflow of clotting factor inhibitors.
- Promotes endothelial cell damage and activation.
- Vascular endothelial injury
- Causes exposure of sub-endothelium and release of tissue factor, thereby activating coagulation cascade ^ increase RBC's mass (polycythemia vera).
- Alterations in constituents of blood (i.e., hypercoagulability)
- Acquired vs inherited coagulopathies.
- Predisposing factors for thrombus formation.

❖ Hyperhomocysteinemia Important

- Homocystinuria or severe hyperhomocysteinemia is a rare autosomal recessive disorder characterized by developmental delay, osteoporosis, ocular abnormalities, VTE, and severe premature CAD (coronary artery disease)
- Less marked elevations of homocysteine are more common, occurring in 5-7% of the population, and are associated with a number of clinical factors
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- Acquired Hyperhomocysteinemia is caused by Vitamin deficiencies (i.e., folate, Vit B6, and/or Vit B12)
- Homocysteine has primary atherogenic and prothrombotic properties
- Meta-analyses of case-control studies have found an odds ratio of 2.5-3 for VTE in pts with homocysteine levels > 2 standard deviations above the mean value of control groups

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❖ Antiphospholipid Syndrome

Do mixing study to know if there is a factor deficiency or antibody against the factors

- Antiphospholipid syndrome (APS) is an autoimmune multisystem disorder characterized by arterial, venous, or small vessel thromboembolic events
- And/or pregnancy morbidity (recurrent abortions) in the presence of persistent antiphospholipid antibodies (aPL). aPLs are a heterogenous group of autoantibodies which are directed against phospholipid-binding proteins.
- Autoimmune disorder, either primary or secondary, associated with an increased risk for arterial and venous thrombosis.
- It can be primary (with no other disorders) OR secondary (eg: SLE)
- there are many antibodies have been recognized in patients with Antiphospholipid syndrome but the most common Three are :-

1- Antibody against cardiolipin. (ELISA assay) is used for detection

2- Antibody against *beta* 2 glycoprotein 1. A subset of anti-cardiolipin antibodies

3- lupus anticoagulants (prolonged APTT and/or PT).

Patients with antiphospholipid antibody syndrome usually have a prolonged PTT during laboratory testing. This is because the antibody interferes with the test, and is a false prolongation

❖ Clinical criteria (manifestations)

- Thrombosis (venous, arterial, small vessel)
- Recurrent abortions
- Skin rash
- Livido reticularis (skins patches)
- Thrombocytopenia

! how to diagnosis?
1 clinical criteria and 1 laboratorial criteria (At least one of the antibodies should be present)

❖ Common complications:

- Deep vein thrombosis (31.4%),
- Pulmonary embolism (23.8%),
- Stroke (14.9%),
- Transient ischaemic attack (11.9%),
- Early spontaneous abortions (67.1%),
- Stillbirths (62.5%),
- Prematurity (25.1%)
- Pre-eclampsia (25.1%).

❖ Malignancy

- **Risk for thrombosis is multi-factorial.**
- **Predominantly venous thrombosis - stasis,DIC, tumor invasion of vessels, chemotherapy effects superimposed on acquired or primary defects in hemostasis.**
- **Increased production of tissue factor by tumours found in many patients which can activate FX directly.**

! **GASTRIC AND PANCREATIC CARCINOMA IS ONE OF THE HIGH RISK**

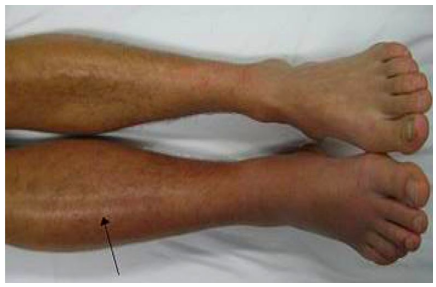
Thrombosis Manifestations

Clinical presentation:

- **Venous – superficial vein or deep veins**
- **Deep vein thrombosis Doesn't kill**
- **swollen, painful extremity**
- **Pulmonary embolus kill**
- **Arterial – coronary, carotid and femoral**
- **Acute MI, Angina**
- **CVA, TIA**
- **Claudication**

Clinical presentation of DVT

- **Lower limb is the most common site**
- **Can happen in upper limb, abdominal veins, cerebral veins & sinuses**
- **Symptoms & signs depend on the site**
  - **Limb swelling**
  - **Pain**
  - **Redness**
  - **Skin changes**



A right-sided acute deep vein thrombosis (to the left in the image). The leg is swollen and red due to venous outflow obstruction

Thrombosis Manifestations

Clinical presentation: Pulmonary embolism (PE)

- **Shortness of breath that may occur suddenly.**
- **Sudden, sharp chest pain that may become worse with deep breathing or coughing (can be pleuritic type-n).**
- **Palpitation (tachycardia).IMPORTANT**
- **Rapid breathing (tachypnea).**
- **Sweating & anxiety.**
- **Hemoptysis or pink, foamy mucus.**
- **Dizziness and fainting (low BP).**
- **PE with low BP (<90 mmHg) is called massive PE. IMPORTANT (THROMBOLYTIC INDICATED)**

Not all the patient has chest pain

❖ Diagnosis of Thrombosis

- DVT and pulmonary embolism are the two most common manifestations of the same disease: VTE.
- 90% of cases of acute PE are due to emboli emanating from the proximal veins of the lower extremities;. proximal DVTs are clinically most significant due to high morbidity and mortality.
- Consider the differential diagnosis of DVT.
- Differential diagnosis: Popliteal (Baker) cyst"outpouching of the back of the knee", superficial thrombophlebitis, muscle pulls/tears, chronic venous insufficiency, cellulitis "comes with fever".
- Consider pre-test probability for VTE before proceeding further in diagnostic evaluation.
- Among those with suspected of DVT of the lower extremity, a minority (17-32%) actually have the disease.

Pre-test probability: it's a criterias that used to tell you the probabilities of the presence of a condition (such as a disease) before a diagnostic test.
The most used for PE is: Wells criteria

Wells' score	Original	Simplified
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Previous PE or DVT	1.5	1
Heart rate >100 bpm	1.5	1
Surgery or immobilisation within 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical probability		
PE unlikely	≤4	≤1
PE likely	>4	>1

- Clinical examination (non-specific)
  - Physical findings may include a palpable cord over the calf, ipsilateral edema, warmth, and/or superficial venous dilatation
- Contrast venography
- Non-invasive testing
  - Impedance plethysmography
  - Compression ultrasonography
  - Recommended in moderate to high pre-test probability
  - D-dimer
    - Useful in low pre-test probability to exclude diagnosis of VTE
    - Sensitivity and negative predictive value are high (~99%)
    - hIGH D-dimer in: trauma, pregnancy and malignancy
- Magnetic resonance venography
- Computed tomography
- Echocardiography, ventilation-perfusion (V/Q) scanning (useful for pregnancy / small clots) and pulmonary angiography

upper limb DVT are not common proximal DVT are most likely to cause PE

Spiral CT scan is the gold standard test for pulmonary embolism

❖ Treatment of VTE

- **Anticoagulation** Anticoagulation is contraindicated in hepatic vein thrombosis
  - **Unfractionated (UFH) and low-molecular weight heparin (LMWH(sc) Ex: enoxaparin, tinzaparin, dalteparin, etc).**
    - **Enable antithrombin to accelerate many-fold its inactivation of thrombin.**
    - **LMWH should be avoided in CKD; contraindicated in Stage-V CKD.**

- **UFH : is the IV anticoagulant, the rest are Oral or SC**
- **UFH is Suitable for unstable patient because the absorption won't be good from SC root (LMWH)**

  - **Vitamin K antagonists (warfarin)**
    - **Heparin + warfarin is more effective than warfarin alone; all cases of VTE should be "<u>bridged</u>" with heparin.**

why we can just start with warfarin?

- **Takes time**
- **Protein c and s is vit k dependent if we inhibit them there will be a thrombosis deficiency initially before the anti coagulation effect**

  - **Factor Xa inhibitors (fondaparinux).**
  - **Hirudins (lepirudin).**
  - **Direct oral Anticoagulants (DOACs)** **instead of warfarin.**
- **Thrombolysis (Usually reserved for massive PE)** thrombolytics only in massive PE .. even if we see a patient with a large emboli but the blood pressure remained above 90 .. this doesn't mean he should take thrombolytics .
- **Tissue plasminogen activators (t-PA, u-PA, urokinase, alteplase).**
- **Thrombectomy (arterial) if the medication is not effective (by the interventional radiologist).**

for heparin induced thrombocytopenia:

1. **stop heparin**
2. **don't use one of the vitamin k antagonist because it takes time**
3. **use fondaparinux or lepirudin**

- **Conventional Anticoagulation**
  a. **Treatment always started with heparin (immediate action)**
  b. **Warfarin can be started at the same time**
  c. **Around 4 days of warfarin & heparin overlap needed**
  d. **Heparin can be stopped when INR reaches therapeutic levels**
  e. **LMWH (SC) in stable cases of VTE but UNH (IV) needed in hemodynamically unstable patients or pts who need procedures**

! **In pregnancy we give LMWH and heparin**

❖ Warfarin Treatment & Monitoring

- **No fixed dose of warfarin, every patient needs a different dose (loading dose+maintenance)**
- **INR (International normalized ratio)**
- **Therapeutic INR 2-3 in most cases**
- **Initially heparin is a must as warfarin slow to act and initially pro-thrombotic**
- **Treatment continued for 3-12 months mostly but longer or life long AC may be needed in recurrent cases of VTE**

We keep it higher in prosthetic valves patients and with those who has risk of thrombosis

❖ Treatment & Monitoring

- **In patients beginning warfarin therapy for initiation of oral anticoagulation, doses between 5 and 10 mg for the first 1 or 2 days are recommended for most individuals and subsequent dosing based on the INR response**
- **A loading dose (*ie,* > 10 mg) of warfarin is not recommended**
- **A starting dose of < 5 mg might be appropriate in elderly patients; in patients with impaired nutrition, liver disease, or congestive heart failure (CHF); and in patients who are at high risk of bleeding e.g have had recent major surgery or on amiodarone**

- **major surgeries 2 mg**
- **PE 6 mg**

- **Don't need to remember the warfarin color**

Tablet strength	Tablet color
1 mg	Pink
2 mg	Lavender (light purple)
2.5 mg	Green
3 mg	Tan
4 mg	Blue
5 mg	Peach (light orange)
6 mg	Teal (blue-green)
7.5 mg	Yellow
10 mg	White

In unprovoked patients we treat for longer period of time

- **polycythemia vera (all life treatment)**
- **Cancer (treat until cure))**

❖ Overdose & Antidotes

- **For heparin > protamine sulphate.**
- **For warfarin > vitamin K but may take time (many hours) to act (Risk of bleeding).**
- **An actively bleeding patient may also need fresh frozen plasma (FFP) or prothrombin complex (useful drug) for GI and intracranial hemorrhage.**

● Direct oral anticoagulants (DOACs)

- **Direct thrombin inhibitors (DTI)**
  - Dabigatran
- **Factor X inhibitors**
  - Rivaroxaban
  - Apixaban
  - Adoxaban

What is the drug that used for cancer patient with thrombosis?

LMWH

❖ Pros & Cons of DOACs

	
• **Fixed daily dose** • **No need for monitoring** • **Quick onset of action** • **Bleeding risk similar to warfarin (GI bleed more common)**	• **More expensive// wafarin is cheap** • **Reversal a problem (Antidote available now)** • **Can not be used in end stage renal failure// expect ufh and warfarin it's ok** • **contraindicated in pregnancy** • **use UFH first followed by wafarin**

NOT IMPORTANT

Reversal of DTI (Dabigatron)

Idarucizumab

- Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with 350-fold higher affinity than that of dabigatran for thrombin.
- In addition to binding dabigatran, idarucizumab also binds the active glucuronide metabolites of dabigatran to form essentially irreversible 1:1 stoichiometric complexes.
- Idarucizumab and idarucizumab-dabigatran complexes are cleared by the kidneys, as is dabigatran.
- After intravenous infusion, the half-life of idarucizumab is about 45 min in subjects with normal renal function

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Reversal of Factor-X Inhibitors

Andexanet alfa

- Andexanet alfa is a recombinant human FXa variant with the active-site serine residue replaced with alanine to eliminate catalytic activity and with the membrane-binding domain deleted to prevent incorporation into the prothrombinase complex.
- Andexanet serves as a decoy for the oral FXa inhibitors because it binds them with affinities similar to those of native FXa. Because andexanet also binds tissue factor pathway inhibitor (TFPI) to form a non-productive andexanet–TFPI complex, it reduces TFPI activity.

MCQ's

Q1:A previously healthy 47-year-old woman comes to medical attention because of loss of sensation in her right hand for 2 days. Physical examination is unremarkable other than confirming the presence of right hand hypoesthesia. CT and MRI scans demonstrate a focal lesion in the left parietal cortex. Laboratory investigations show high levels of antiphospholipid antibodies, prolonged activated partial thromboplastin time (aPTT), and normal prothrombin time (PT). Which of the following complications is most likely to develop?

(A) Glomerulonephritis
(B) Lymphoma
(C) Pulmonary fibrosis
(D) Recurrent bleeding
(E) Recurrent thrombosis

Q2:A 32-year-old woman presents to the emergency department with edema and pain of the right lower extremity that began after a 6-hour car ride. A Doppler ultrasound was completed in which a deep vein thrombosis (DVT) was noted. The patient has no prior history of DVT or pulmonary emboli. The patient has been taking oral contraceptive pills for the past 2 years and currently has stopped her medication. Her family history is significant for a maternal grandmother, mother, and sister with recurrent DVT. Her temperature is 36.2°C (97.2°F), blood pressure is 112/78 mm Hg, heart rate is 86/min, and respiratory rate is 14/min. There is no clinical evidence indicating a pulmonary embolism. Which of the following is the most likely cause of her DVT?

(A) Oral contraceptives
(B) Coagulation factor V gene mutation
(C) Protein C excess
(D) Protein S abnormality
(E) Antiphospholipid syndrome

Q3: A 40-year-old retired professional football player com- plains of the sudden onset of palpitations and shortness of breath 5 days after having knee replacement surgery. His pulse is 100/min and regular. Oxygen saturation is 90% room air. An ECG reveals sinus tachycardia. A chest x-ray film is unremarkable, which of the following is the most appropriate next step in management?

(A) Order an arterial blood gas
(B) Schedule a duplex Doppler examination of the lower extremities
(c) Schedule a ventilation-perfusion scan
(D) Administer supplemental oxygen
(E) Administer IV heparin

Answers: 1.E, 2.B, 3.E

Thank you

If you have any question please contact with us at:
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