

PULMONARY EMBOLISM - A PULMONOLOGIST'S PERSPECTIVE

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Abstract: Pulmonary embolism is an extremely common and lethal condition. It occurs when an artery in the pulmonary vasculature becomes blocked. Blockage is caused by one or more blood clots that travel to the lungs from another part of the body. Most of these blood clots originate in the legs, but they can also form in the arm veins, the right side of the heart or even at the tip of the catheter placed in the vein. A good clinician actively seeks the diagnosis as soon as any suspicion of pulmonary embolism is warranted. Prompt diagnosis and treatment can dramatically reduce the mortality and morbidity of the disease. Unfortunately the diagnosis is missed more often than it is made, because pulmonary embolism often causes only vague and nonspecific symptoms. It is a leading cause of hospital deaths and an increasing threat to passengers on long airplane flights. But a few simple measures can go a long way towards preventing pulmonary embolism. Immediate full anticoagulation is mandatory for all patients with suspected DVT or pulmonary embolism because effective anticoagulation with heparin reduces the mortality rate of PE from 30% to less than 10%. Anti coagulation is essential but anticoagulation alone does not guarantee a successful outcome. DVT and PE may recur or extend despite full and effective heparin anticoagulation.

INTRODUCTION

Pulmonary embolism (PE) is an extremely common and highly lethal condition that is a leading cause of death in all age groups. It is caused by sudden blockage in a lung artery, usually due to a blood clot that travelled to the lung from the leg. A clot that forms in one part of the body and travels in the bloodstream to another part of the body is called an embolus. In most cases, pulmonary embolism is a complication of a condition called deep vein thrombosis (DVT). In DVT, blood clots form in the deep veins of the body, most often in the legs, these clots can break free, travel to the lungs and cause pulmonary embolism.

Thrombosis in the veins is triggered by venostasis, hypercoagulability and vessel wall inflammation. These three underlying causes are known as the Virchow triad.

Although DVT starts in the calf veins, it has propagated above the knee in 87% of symptomatic patients before the diagnosis is made. Studies suggest that nearly every patient with thrombus in the upper leg or thigh will have a PE if a sensitive enough test is done to look for it. Thrombus in the popliteal segment of the femoral vein is the cause of PE in more than 60% of cases. Fatal PE often result from thrombus that originates in the axillary or subclavian veins or indwelling central venous catheters. One third of the cases of massive PE have their only identified source in the veins of the lower limbs.

INCIDENCE

More than 600,000 people in the United States have a pulmonary embolism each year and more than 60,000 of them die, most by within 30 to 60 minutes after symptoms start. PE is the third most common cause of death in the US and first or second most common cause of unexpected deaths in most age groups. Highest incidence of recognized PE occurs in hospitalized patients. In the absence of prophylaxis acute DVT may be demonstrated in, general medical patients advised bed rest for a week (10-13%), patients in medical intensive care units (29-33%), patients with pulmonary disease kept in bed for 3 or 7 days (20-26%), patients admitted to coronary care units after myocardial infection (27-33%), patients who are

asymptomatic after coronary bypass graft (48%).

In the Framingham study it was observed that about four times more medical patients die from PE than surgical patients, yet we focus on the prevention of thrombosis in postoperative settings, ignoring the medical patients.

Patients who survive an acute PE are at high risk for recurrent PE and for the development of pulmonary hypertension and chronic cor-pulmonale, which occurs in upto 70% of patients and carries its own attendant mortality and morbidity.

Race:- Subtle population differences may exist in the incidence of DVT & PE, but the incidence is high in all racial groups. If the differences are real, whether they are due to generic variation or to population differences in diet and activity is not known.

Sex:- PE is common in all trimesters of pregnancy and puerperium and the incidence of PE is increased in women receiving oral contraceptive or hormone replacement therapy; however sex alone is not an independent risk factor.

Age:- Although the frequency of PE increases with age, it is not an independent risk factor. Rather the accumulation of other risk factors, such as underlying illness and decreased mobility, causes the increased frequency of PE in older patients.

Cause:- *Hypercoagulable states* Prolonged venous stasis or significant injury to the veins can provoke DVT and PE in any person, but increasing evidence suggests that spontaneous DVT and PE nearly always are related to some underlying hypercoagulable state. Other identified causes most likely serve only as triggers for a system that is already out of balance. Hypercoagulable states may be *acquired* or *congenital*. An inborn resistance to activated protein C is the most common congenital risk factor for DVT that has been identified to date. Most patients with this syndrome have a genetic mutation in factor V known as "factor V Leyden," although other mechanisms also can produce a resistance to activated protein C. Primary or acquired deficiencies in protein C, protein S, or antithrombin III are also common underlying causes of DVT and PE.

SIGNS & SYMPTOMS

The classic triad of signs & symptoms of PE are haemoptysis,

dyspnoea and chest pain but these are neither sensitive nor specific. They occur in fewer than 20% of patients in whom the diagnosis of PE is made. Nonetheless, the presence of any of these classic signs & symptoms is an indication for a complete diagnostic evaluation. Many patient with PE are initially completely asymptomatic and those who do have symptoms, have an atypical presentation. They may present as seizures, syncope, abdominal pain, high fever, productive cough, new onset of reactive airway disease, new onset atrial fibrillation or pleuritic chest pain.

Differential Diagnosis :- Although PE is known as a great masquerader, quite often other illness simulate PE . PE is likely diagnosis when dyspnoea, pain chest and an abnormal lung scan are present. In situations wherein pneumonia or heart failure coexist with PE, clinical improvement will often fail to occur despite standard medical treatment of concomitant illness, indicating possibility of coexisting PE. Whether the presentation is typical or atypical, the list of differential diagnosis remains extensive and the true diagnosis must be sought actively;

1. Acute coronary syndrome, conditions includes unstable angina and acute myocardial infraction.
2. Pneumonia, bronchitis, exacerbation of asthma or chronic obstructive lung disease..
3. Congestive heart failure, pulmonary edema.
4. Pericarditis.
5. Pleurisy, costochondritis, musculoskeletal discomfort.
6. Rib fracture, pneumothorax , pneumo-mediastinum
7. Primary pulmonary hypertension.
8. Anxiety, hyperventilation.

Laboratory Studies: Unfortunately no known blood or serum test can confirm pulmonary thromboembolism or vise versa.

■ **D-dimer** is a unique degradation product produced by plasma-mediated proteolysis of cross linked fibrin. It is measured by latex agglutination or by an enzyme linked immunosorbent assay (ELISA) test that is considered positive if the level is greater than 500 ng/ml.

■ **Latex agglutination tests** are notoriously unreliable with sensitivity of only 50-60% for DVT & PE. **ELISA test** is more sensitive than latex test. Under the best of circumstances, D-dimer study misses 10% of patients with positive pulmonary angiograms, while only 30% of those with a positive d-dimer will have a positive angiogram.

D-dimer alone is not sensitive or specific enough in diagnosing PE but it has a high negative predictive value and thus can be used to help exclude PE.

■ **White cell counts** (WBC) may be normal or elevated. A count as high as 20,000 is not uncommon in PE.

■ **Clotting studies** are normal in most patients of PE.

■ **Contrary** to classic teaching the PO₂ on **arterial blood gases** analysis has a zero or even negative predictive value in clinically suspected cases of PE. The reason for this is that other etiologies that masquerade as PE (eg COPD, pneumonia, CHF) are more likely to lower the PO₂ than is PE. It holds true not only for arterial PO₂ but also for the alveolar-arterial oxygen gradient and for the oxygen saturation level as measured for by pulse oximetry

Electrocardiogram:- Classic abnormalities include sinus tachycardia, new onset atrial fibrillation or flutter, and an S wave

in lead I, a Q wave in lead III and an inverted T in lead III. Often the QRS axis is greater than 90°. T inversion in leads V₁ to V₄ reflects right ventricular strain. One fourth of patients with proven PE have ECGs that are unchanged from their baseline state. An absence of ECG abnormalities has no significant predictive value

Noninvasive Imaging Modalities

The initial chest Xray findings of a patient with PE are virtually always normal. On rare occasions they may show the westermark sign, a dilatation of pulmonary vessels proximal to an embolism along with collapse of distal vessels, sometimes with a sharp cutoff. Later changes include a small pleural effusion and an elevated hemidiaphragm or focal infiltrates indistinguishable from an infectious pneumonia. Rare late finding of PE is 'Hampton hump' – a triangular or rounded pleural based infiltrate with apex pointed towards the hilum, frequently located adjacent to the diaphragm.

Chest CT:- Computer tomography (CT) of the chest with intravenous contrast (100ml administered at 3 to 4ml/sec via an antecubital vein) superseding lung scanning as the principal imaging test for diagnosis of PE. New generation multi slice scanners image the entire thorax with 1mm thin sections during a single 12 to 15 sec breath hold and can detect peripherally located thrombi in the fifth order branches.

Lung scanning:- Small particulate aggregates of albumin labeled with a gamma emitting radionuclide are injected intravenously and are trapped in the capillary bed. The perfusion scan defect indicates absent or decreased blood flow, possibly due to PE. Ventilation scans are obtained with radiolabeled inhaled gases such as Xenon or krypton, improve the specificity of the perfusion scan. A high probability scan for PE is defined as having two or more segmental perfusion defects in the presence of normal ventilation.

The diagnosis of PE is unlikely in patients with normal and near normal scans but is about 90% certain in patients with high probability scans. As many as 40% of patients with high clinical suspicion for PE and 'low probability' scans do in fact, have PE at angiography. A repeat V/Q scan is indicated before stopping anticoagulants in a patient with irreversible risk factors for DVT and PE because recurrent symptoms are common and a reference 'post treatment V/Q scan' can serve as new baseline for comparison , often sparing the patient the need for a future angiogram.

Magnetic Resonance (MR) pulmonary angiography utilizes gadolinium contrast agent, which unlike iodinated contrast agents used in CT angiography, is not nephrotoxic. Usually reserved test for pregnant woman and nephrocompromised patients MR also assesses right ventricular function, thus making it a promising single test for both diagnosis for PE and assessment of hemodynamic effect .

Echocardiography :- More than half of patients with PE will have normal echocardiograms. Mc Connell's sign ie right ventricular free wall hypokinesis with normal right ventricular apical motion, appears to be specific for PE. Detection of right ventricular dysfunction due to PE helps to stratify the risk, delineate the prognoses and plan optimal management.

Venous Ultrasonography :- Confirmed DVT is usually an adequate surrogate for PE. Ultrasonography of the deep venous system relies upon loss of vein compressibility as the primary criterion for DVT. About one half of the patients with PE have no

imaging evidence of DVT because the clot has already embolised to the lung or in the pelvic veins, where ultrasonography is inadequate.

Invasive Diagnostic Modalities

Pulmonary Angiography:- Is the most specific examination available for establishing the definitive diagnosis of PE and can detect an embolus as small as 1 to 2 mm. A definitive diagnosis of PE depends upon visualisation of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion (Cuf off) of vessels; segmental oligemia or avascularity, a prolonged arterial phase with slow filling or tortuous tapering peripheral vessels. Chest CT scanning is replacing diagnostic pulmonary angiography because it is less invasive. In the current era of chest CT with contrast, pulmonary angiography is reserved for (1) patients with technically inadequate CT scans (2) scans performed on older machines which cannot image fourth or fifth order pulmonary arteries and (3) patients who will undergo interventions such as catheter embolectomy or catheter – directed thrombolysis.

Contrast Phlebography :- Venous ultrasonography has virtually replaced contrast phlebography, which is costly, uncomfortable and occasionally results in contrast allergy or contrast induced phlebitis.

TREATMENT

Primary therapy consists of clot dissolution with thrombolysis or removal of PE by embolectomy. Secondary prevention constitutes anticoagulation with heparin and warfarin and placement of inferior vena caval filter.

Risk Stratification:- is crucial for determining treatment strategy. The presence of hemodynamic instability, right ventricular dysfunction or elevation of troponin level due to right ventricular micro infarction can identify high risk patients. Such patients would warrant primary therapy to prevent adverse clinical outcome. When right ventricular function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone.

Drug Therapy:- Fibrinolytics:- therapy has been the standard of care for patients with massive or unstable PE. Unless contraindicated, a rapidly acting fibrinolytic agent should be administered immediately to every patient who has suffered hypotension (even if resolved) or is significantly hypoxic from PE. Fibrinolytic therapy has replaced surgical embolectomy as the primary mode of treatment for hemodynamically unstable patients with pulmonary thromboembolism. Surgical thromboembolectomy is now reserved for patients in whom fibrinolysis has failed or cannot be tolerated. Fibrinolytic regimen currently in use for PE include two forms of recombinant tissue plasminogen activator –t PA (alteplase) and r PA(reteplase) along with urikinase and streptokinase.

Retaplaste (r-PA, Retavase) –Second –generation recombinant tissue – type plasminogen activator. As fibrinolytic agent, seems to work faster than its forerunner, alteplase, and also may be more effective in patient with larger clot burden. Also has been reported more effective than other agents in lysis of older clots. Two major differences help explain these improvements. Compared to alteplase, reteplase does not bind fibrin so tightly, allowing drug to diffuse more freely through clot. Another advantage seems to

be that reteplase does not compete with plasminogen for fibrin – binding sites, allowing plasminogen at site of clot to be transformed into clot- dissolving plasmin.

Adult Dose :- Two, 10 Units, IV boluses, given 30 min apart In setting of cardiac arrest or impending arrest due to PE, single IV bolus of 20 U has been used successfully in small number of cases .

Contraindications :-Active internal bleeding; history of cerebrovascular accident; recent intracranial or intraspinal surgery or trauma; intracranial neoplasm, arteriovenous malformation, or aneurysm; known bleeding diathesis; severe uncontrolled hypertension.

Alteplase (rt-PA, Activase) – Drug most often used to treat PE in ED. One advantage of alteplase is that, it is used so widely for treatment of patients with acute MI that most ED personnel are familiar with its use.

Adult Dose :- 100mg IV infusion over 2 h (FDA- approved regimen for PE)

Accelerated 90- min regimen is used widely, and most authors believe it is both safer and more effective than 2-h infusion; for accelerated regimen, recommended total dose based upon patient weight, not to exceed 100 mg.

Heparin therapy should be instituted or reinstated near end of or immediately following alteplase infusion, when aPTT over thrombin time return to twice normal or less.

Contraindications :- Documented hypersensitivity : active internal bleeding ; history or cerebrovascular accident; recent intracranial or intraspinal surgery or trauma intracranial neoplasm, arteriovenous malformation, or aneurysm, known bleeding diathesis; severe uncontrolled hypertension

Urokinase (Abbokinase)- Direct plasminogen activator produced by human fetal kidney cells grown in culture . Relatively low in antigenicity.

When used for localized fibrinolysis, given as local catheter – directed continuous infusion directly into area of thrombus with no loading dose, When used for PE, loading dose necessary.

Adult Dose :- Loading Dose : 2000 U/lb infused IV over 10 min, maintenance dose : 2000 U/lb/h IV for 24 h.

Contraindications :- Active internal bleeding ; history of cerebrovascular accident ; recent intracranial or intraspinal surgery or trauma ; intracranial neoplasm, arteriovenous malformation, or aneurysm; known bleeding diathesis; severe uncontrolled hypertension.

Anticoagulants :- Heparin augments the activity of antithrombin III and prevents the conversion of fibrinogen to fibrin. Full – dose LMWH or full dose unfractionated IV heparin should be initiated at the first suspicion of DVT or PE. With proper dosing, several LMWH products have been found safer and more effective than unfractionated heparin both for prophylaxis and for treatment of DVT and PE. Monitoring with aPTT is neither necessary nor useful when giving LMWH. Because the drug is active in a tissue phase and does not exert most of its effects on coagulation factor IIa

Fractionated LMWH administered subcutaneously is now the preferred choice for initial anticoagulation therapy . Unfractionated IV heparin can be nearly as effective but is more difficult to titrate for therapeutic effect. Warfarin maintenance therapy may be initiated after 1-3 d of effective heparinization.

Enoxaparin (Lovenox)—First LMWH released in US. Approved by FDA for both treatment and prophylaxis of DVT and PE.

LMWH has been used widely in pregnancy, although clinical trials not yet available to demonstrate that it is as safe as unfractionated heparin. Except in overdoses, checking PT or aPTT has no utility, as aPTT does not correlate with anticoagulant effect of fractionated LMWH.

Adult Dose:- Treatment of DVT and PE: 1 mg/kg SC q12h or 1.5 mg/kg SC qd

DVT prophylaxis: 30 mg SC q12h

DVT prophylaxis in abdominal surgery: 40 mg SC qd, with first dose given 2 h prior to surgery

Contraindications :- Documented hypersensitivity; major bleeding; thrombocytopenia

Dalteparin (Fragmin)—LMWH with many similarities

Except in overdoses, checking PT or aPTT has no utility, as aPTT does not correlate with anticoagulant effect of fractionated LMWH.

Adult Dose:- DVT prophylaxis in patients undergoing abdominal surgery : 2500 U SC qd.

Tinzaparin (Innohep)—Approved for treatment of DVT in hospitalized patients. Enhances inhibition of factor Xa and thrombin by increasing antithrombin III activity. In addition, preferentially increases inhibition of factor Xa.

Adult Dose:- For treatment of acute DVT : 175 IU/kg SC qd; give drug at same time each day and continue for at least 6 d and until long-term anticoagulation established with warfarin or another agent.

DVT prophylaxis in patients undergoing hip and knee surgery:- 50 U/kg SC q12h

Unfractionated heparin—when unfractionated heparin used, aPTT should not be checked until 6 h after initial heparin bolus, as an extremely high or low value during this time should not provoke any action

Adult Dose:- Initial bolus:- 120-140 U/kg IV or approximately 10,000 U/70-kg person Initial infusion:- 20 U/kg/h IV

After bolus, check aPTT q6h until stable, and heparin dosing should be adjusted as follows: if aPTT is low (<1.5 times control value), administer second bolus of 5000 U and increase drip by 10%. If aPTT is high (>2.5 times control value), decrease drip 10%. If aPTT is extremely high (>100s), hold heparin drip for 1 h and decrease drip 10%

Contraindications :- Documented hypersensitivity; subacute bacterial endocarditis; active noncompressible bleeding; any history of heparin-induced thrombocytopenia the drug is usually safe but benefits must outweigh the risks.

Warfarin (Coumadin):- The drug interferes with hepatic synthesis of vitamin K-dependent coagulation factors. Never give to patient with thrombosis until after patient has been anticoagulated fully with heparin, because first few days of warfarin therapy produce hypercoagulable state. Failing to anticoagulate with heparin before starting warfarin will cause clot extension and recurrent thromboembolism in about 40% of patients, compared with 8% of those who receive full-dose heparin before starting warfarin. Heparin should be continued for first 5-7 d of oral warfarin therapy regardless of PT, to allow time for depletion of procoagulant vitamin K-dependent proteins. Anticoagulant effect of warfarin adjusted by varying dose to keep INR within target range. An INR target range

of 2.5 to 3.5 makes sense for DVT and PE because rate of recurrence increases dramatically when INR drops below 2.5 and decreases when INR is kept above 3.0 the risk of serious bleeding (including hemorrhagic stroke) is approximately constant when INR is between 2.5 and 4.5 but rises dramatically when INR is 5.0 or higher. Patients who have difficulty maintaining adequate anticoagulation while taking warfarin may be asked to limit their intake of foods that contain vitamin K. Foods that have moderate to high amounts of vitamin K include brussels sprouts, kale, green tea, asparagus, avocado, broccoli, cabbage, cauliflower, collard green, liver, soybean oil, soybeans, certain beans, mustard greens, peas (black-eyed peas, split peas, chick peas), turnip greens, parsley, green onions, spinach and lettuce.

Adult Dose:- Initial dose: 5-15mg/d PO qd After initial anticoagulation obtained, adjust dose according to desired INR

Contraindications : Avoid or use extreme caution in patients with hereditary or acquired deficiencies of protein C or protein S, because these deficiencies are associated with higher incidence of tissue necrosis following warfarin administration. Warfarin is teratogenic and contraindicated in pregnancy

Prevention

Graduated compression stockings steadily squeeze legs, helping veins and leg muscles move blood more effectively. They offer a safe, simple and inexpensive way to keep blood from stagnating after general surgery. Compression stockings used in combination with heparin are much more effective than is heparin alone.

Pneumatic compression treatment uses high cuffs that automatically inflate every few minutes to massage and compress the veins in the legs. Pneumatic compression can dramatically reduce the risk of blood clots, especially in people who have had hip replacement surgery.

Physical activity :- Early mobilization as soon as possible after surgery can prevent pulmonary embolism and hasten recovery.

Preventive steps while traveling.

- Move around the aeroplane cabin once an hour or so. If driving, stop every hour and walk around the car a couple of times or do a few deep knee bends.
- Exercise while sitting- flex and rotate ankles or press feet against the seat in front or try rising up and down on your toes; Don't sit with crossed legs for long period of time.
- Wear support stockings as they help promote circulation and fluid movement
- Drink plenty of fluids before and during the trip to avoid dehydration as this can contribute to development of blood clots. Avoid alcohol which contributes to fluid loss.
- In high risk individuals planning to fly six hours or more, low molecular weight heparin 2 to 4 hours before departure is recommended.

CONCLUSION

In most cases, a pulmonary embolism is not fatal. Still, pulmonary embolism is a leading cause of hospital deaths and an increasing threat to passengers on long aeroplane flights. A few simple measures can go a long way towards preventing pulmonary embolism. When pulmonary embolism does occur, treatment with anti-clotting medications can greatly reduce the risk of death.

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IMSA News

IMSA CHAPTER ACTIVITIES - Oct. to Dec. 2006

Tamil Nadu Chapter

- 8-10-2006 : Dr. S. Ganapathy Ramanan, "Tumour Markers"
 22-10-2006 : Dr. P.Rajendra, "Etiology and Epidemiology of Chikungunya and Dengue Fever"
 : Dr. Ramasubramanian, "Tackling Chikungunya and Dengue"
 12-11-2006 : Dr. Thangam Varma, "Current Thoughts about HRT & Alternative"
 10-12-2006 : Dr. Leonard Ponraj, "Knee and Shoulder Injuries, Management"

Rural CME T.N. Chapter

- 29-10-2006 : Dr. Khurja, "Hypertension and Diabetes"
 Delhi Chapter
 29-10-2006 : Dr. Khurja, "Hypertension and Diabetes"

Fellows and Members elected during the quarter Oct.-Dec. 2006

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Dr. Vinod Kumar	New Delhi	Prof. Khalid Javed Rabbani	Lahore, Pakistan	Dr. Hasnat Butt	Lahore, Pakistan
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HONOUR

- **Dr. K. Jagadeesan**, President IMSA, has been re-elected as President of International Medical Sciences Academy (IMSA) for another term of 5 years w.e.f. 1/12/2006 by the IMSA governing body in its meeting held recently at Lahore, Pakistan
- **Dr. R.R. Thukral**, Vice President IMSA, ENT Specialist, has been re-elected as Vice President of International Medical Sciences Academy (IMSA) for another term of 5 years w.e.f. 1/12/2006 by the IMSA governing body in its meeting held recently at Lahore, Pakistan

IMSACON 2007 at Manipal, Karnataka

IMSA is pleased to inform its Fellows and Members that Annual Conference IMSACON 2007 will be held at Manipal, Karnataka on 3,4,5 November 2007. Manipal Academy of Higher Education (MAHE) will organize the conference, Dr. Ramdas M. Pai, President of MAHE and Trustee of IMSA will be the Patron.

The organisers will be issuing the first information brochure shortly. IMSA would like its Fellows and Members to participate in the conference in large numbers and derive benefit of latest medical scientific inventions. They should register themselves with the organizers well in time to avoid any confusion at the last moment regarding arrangements for their stay etc.

Dr. R.R.Thukral
Vice President