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Pulmonary Embolism

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Pulmonary embolism (PE) and deep vein thrombosis (DVT) together constitute one of the "big three" cardiovascular diseases, the other two being myocardial infraction (MI) and stroke. Venous thrombombolism (VTE) encompasses PE and DVT and causes more than 100,000 deaths annually in the United States. The in-hospital case fatality rate for patients who present with hemodynamic instability is approximately 30%, 10-fold higher than for patients who are haemodynamically stable. Advances in diagnostic therapeutic and preventive strategies along with a better understanding of pathophysiology have helped us in improving results of therapy.

Availability of new oral anticoagulant such as rivaroxaban allows the management of PE and DVT without any parenteral anticoagulant for a majority of patients. For patients requiring advanced therapy new invasive tools such as ultrasound facilitated and catheter-assisted thrombolysis with low dose tissue plasminogen activator therapy promise a lower rate of hemorrhagic complications than that associated with traditional systemically administered thrombolysis.

AETIOLOGY

Stasis,hypercoagulabilty and endothelial injury (Virchow's triad) activate the pathophysiology cascade leading to VTE (Figure 1). Venous thrombic contain fibrin, red blood cells, platelets and neutrophils. From the leg these clots migrate to the lungs and produce a PE.

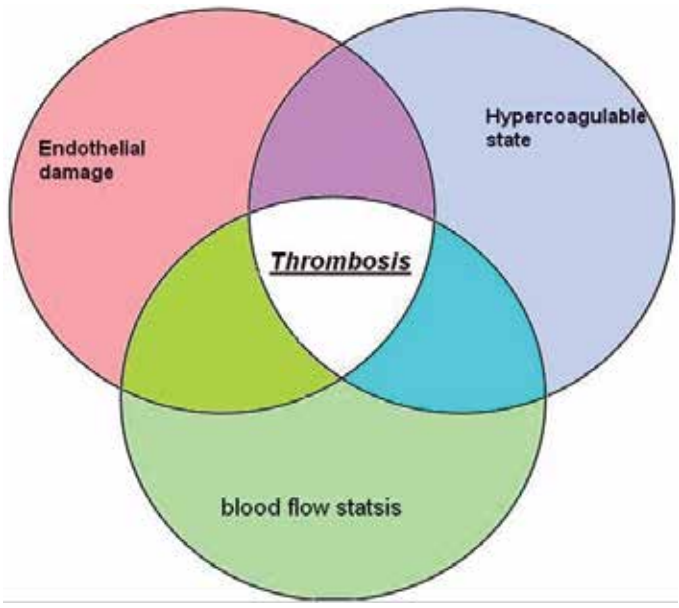

Fig. 1: Virchow's triad

CARDIOPULMONARY DYNAMICS

PE can elicit a complex cardiopulmonary response that includes increased pulmonary vascular resistance due to vascular obstruction, neurohumoral agents, or pulmonary artery baroreceptors; impaired gas exchange caused by increased alveolar dead space from vascular obstruction and hypoxemia from alveolar hypoventilation and right to left shunting as well as impaired carbon monoxide transfer caused by loss of gas exchange surface ; increased airway resistance due to bronchoconstriction and decreased pulmonary compliance due to lung hemorrhage and loss of surfactant.

As obstruction increases pulmonary artery pressure rises. Further increase in pulmonary vascular resistance and pulmonary hypertension result from secretion of vasoconstrictors such as serotonin,reflex pulmonary artery vasoconstriction and hypoxemia. The overloaded right ventricle releases cardiac biomarkers such as pro-B type natriuretic peptide (pro-BNP), brain natriuretic peptide (BNP) and troponin, all of which portend an increased likehood of adverse clinical outcome.

The sudden rise in pulmonary artery pressure abruptly increases right ventricular after load with consequent elevation of right ventricular wall tension followed by right ventricular dilation and dysfunction. As the right ventricle dilates the interventricular septum shifts towards the left leading to underfilling and decreased left ventricular diastolic distensibility. With hampered filling of the left ventricle systemic cardiac output and systolic arterial pressure both decline impairing coronary perfusion and producing myocardial ischemia. Elevated right ventricular wall tension after massive PE reduces right coronary artery flow and increases right ventricular myocardial oxygen demand causing ischemia. Perpetuation of this cycle can lead to right ventricular infarction circulatory collapse and death.

CLASSIFICATION AND RISK STRATIFICATION OF PULMONARY EMBOLISM

Classification of acute PE is based on assessing clinical markers, markers of RV dysfunction and markers of myocardial injury. The classification assists with prognostication and clinical management. Because PE manifests with a wide spectrum of acuity ranging from mild to severe; rapid and accurate risk stratification is of paramount importance. Low risk patients have an excellent prognosis with intensive anticoagulation. High risk patients may require intensive hemodynamic

and respiratory support with inotropes or mechanical ventilation, whereas the PE itself is managed with advanced therapy such as systemic thrombolysis, pharmacomechanical catheter assisted therapy,vena cava filter placement, or surgical embolectomy.

The three key components for risk stratification are given in Table 1.

PE is divided into 3 categories: massive, sub-massive and low risk. Massive PE accounts for 5% to 10% of cases. Submassive PE is more common, occurring in approximately 20% to 25% of patients. Low risk PE constitutes the majority of PE cases-approximately 70%.

MASSIVE PULMONARY EMBOLISM

Patients with massive PE present with cardiogenic shock. Associated renal insufficiency,hepatic dysfunction and altered mentation are common findings. Thrombosis is widespread affecting at least half of the pulmonary arterial vasculature. Clot typically is present bilaterally, sometimes as a "saddle" PE. Dyspnea usually is the most prominent symptom; chest pain is unusual,transient cyanosis is common, and systemic arterial hypotension requiring inotropes occurs frequently. The mortality risk markers and treatment options are given in Table 2.

Table 1: Components for risk stratification in PE

Clinical markers	Shock Hypotension[a]
Markers of RV dysfunction	RV dilatation, hypokinesis or pressure overload on echocardiography RV dilatation on spiral computed tomography BNP or NT-proBNP elevation Elevated right heart pressure
Markers of myocardial injury	Cardiac troponin T or I positive

BNP = brain natriuretic peptide; NT-proBNP = N-terminal proBNP; RV = right ventricle; [a]Defined as a systolic blood pressure <90 mmHg or a pressure drop of ≥ 40 mmHg for > 15 min if not caused by new-onset arrhythmia, hypovolemia or sepsis.

SUBMASSIVE PULMONARY EMBOLISM

Patients with submassive PE present with moderate or severe right ventricular hypokinesia as well as elevations in troponin, pro-BNP, or BNP but they maintain normal systemic arterial pressure. Usually one third or more of the pulmonary artery vasculature is obstructed in these patients. Most survive but may require escalation of therapy with pressure support or mechanical ventilation.

LOW RISK PULMONARY EMBOLISM

Those patients designated as having low risk PE exhibit no markers of an adverse prognosis. They present with normal systemic arterial pressure, no cardiac biomarkers release, and normal right ventricular function. They often prove to have an anatomically small PE and appear clinically stable. Adequate anticoagulation results in an excellent clinical outcome.

PULMONARY INFARCTION

Pulmonary infraction is characterized by pleurtitic chest pain that may be unremitting or may wax and wane. Occasionally it is accompanied by hemoptysis. The embolus usually lodges in the peripheral pulmonary arterial tree, near the pleura. Tissue infraction usually occurs 3 to 7 days after embolism. Signs and symptoms often include fever,leukocytosis, elevated erythrocyte sedimentation rate and radiologic evidence of infraction.

LOWER- EXTREMITY DVT AND THE RELATIONSHIP BETWEEN DVT AND PE

In DVT - the more proximal the thrombus is within the deep leg veins, the more likely it is to embolize and cause acute PE. When venous thrombi detach from their sites of formation, they travel through the right atrium and right ventricle and then enter the pulmonary arterial circulation. An extremely large embolus may lodge at the bifurcation of the pulmonary artery, forming a saddle embolus. In many patients with large PEs ultrasonographic evidence

Table 2: Risk markers of mortality and treatment of PE

PE-related early Mortality Risk		Risk Markers: CLINICAL (shock or hypotension)	Risk Markers: RV dysfunction	Risk Markers: Myocardial injury	Potential treatment implications
High >15%		+	(+)[a]	(+)[a]	Thrombolysis or embolectomy
Non High	Intermediate 3-15%	-	+	+	Hospital admission
			+	-	
			-	+	
	Low <1%	-	-	-	Early discharge or home treatment

[a]In the presence of shock or hypotension it is not necessary to confirm RV dysfunction/injury to classify as high risk of PE-related early mortality. PE = pulmonary embolism; RV = right ventricle.

Table 3: Wells Criteria for DVT Probability

Clinical Characteristic	Score
Active cancer (treatment ongoing, within previous 6 months, **or** palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg Collateral superficial veins (nonvaricose)	1
Alternative diagnosis at least as likely as deep venous thrombosis	-2

of DVT is lacking probably because the clot has already embolized to the lungs.

EPIDEMIOLOGY

Clinical risk factors

Risk factors for VTE include advancing age, cancer, previous VTE, venous insufficiency, pregnancy, trauma, major surgery, frailty and immobility.

Hypercoagulable States

Classically the pathogenesis of PE has been dichotomized as caused by either inherited (Primary) or acquired (secondary) risk factors. A combination of thrombohillia and acquired risk factors, however usually precipitate thrombosis. The two most common identified genetic causes of thrombophilia are factor V Leiden and the prothrombin gene mutation.

Diagnosis

One of the greatest challenges in diagnosis PE is that it can masquerade as other illness, thereby confounding the diagnostic workup. The most useful approach is a clinical assessment of likehood, based on presenting symptoms and signs, in conjunction with judicious diagnostic testing. A normal plasma D-dimer level usually can rule out PE. When PE is strongly suspected, a D-Dimer need not be obtained; in most cases with high clinical suspicion, it is appropriate to proceed directly to chest computed tomography(CT) imaging.

Clinical Presentation

Dyspnea is the most frequent symptom, and tachypnea is the most frequent sign of PE. Severe dyspnea, syncope or cyanosis portends a major life threatening PE, in which the clinical picture often is devoid of chest pain. Paradoxically severe pleurtitic pain often signifies that the embolism is small and not life threatening and located in the distal pulmonary arterial system, near the pleural lining.

PE should be suspected when there is evidence of

1. venous thrombosis or predisposing VTE risk factors;
2. acute cor pulmonale (acute right ventricular failure), with features such as distended neck veins, right sided S3 gallop, right ventricular heave tachycardia, or tachypnea; especially if
3. echocardiographic findings of right ventricular dilation and hypokinesia or electrocardiographic evidence of acute cor pulmonale manifested by a new S1Q3T3 pattern, new right bundle branch block or right ventricular ischemia manifested by inferior T wave inversion or T wave inversion in leads V1 through V4.

Clinical decision rules can stratify patients into groups with high clinical likehood or non-high clinical likehood of PE, using a set of seven bedside assessment questions known as the Wells Criteria (Table 3).

Pretest probability score- low≤ 0, moderate if 1–2, and high if ≥ 3.

If both the legs are symptomatic score the more severe leg

Differential Diagnosis

DD includes - Aortic dissection, Cardiac tamponade, MI, corpulmonale, TR, acute exacerbation of COPD, pneumonia

In critically ill patients one must have a low threshold for entertaining PE esp in the setting of risk factors such as malignancy, recent surgery, central lines or prior VTE/ DVT

Lab testing and Bedside Tools

1. D-Dimer – 95% sensitive for VTE - but also elevated in malignancy, infection, surgery, MI
2. Hypoxia: highly sensitive but poorly specific
3. ECG: tachycardia, S1 Q3 T3 pattern, low voltage, RBBB, P pulmonale. Helps to rule out acute MI and acute pericarditis

IMAGING METHODS

Chest Radiography

A near normal radiographic appearance in the setting of severe respiratory comprise is highly suggestive of massive PE. Major chest radiographic abnormalities are uncommon. Focal oligemia indicates massive central embolic occlusion. A peripheral wedge shaped density above the diaphragam (Hampton hump) – arrow in Fig 1 - usually indicates pulmonary infarction.

Lung Scanning

Pulmonary radionuclide perfusion scintigraphy (lung scanning) uses radiolabedled aggregates of albumin or microspheres that lodge in the pulmonary microvasculature. Patients with large PE often have multiple perfusion defects.

Three principal indications for obtaining a lung scan are :

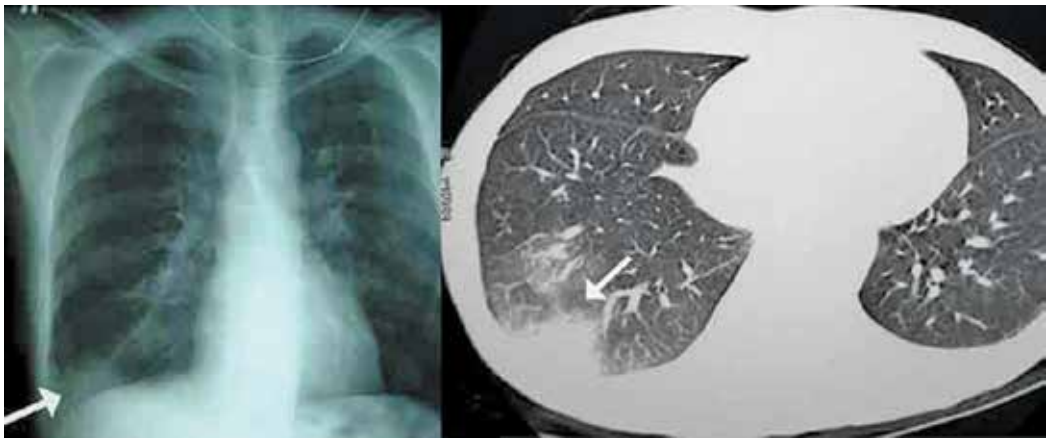

Fig. 1: Chest X-ray and CT showing a peripheral pulmonary infarct (arrow)

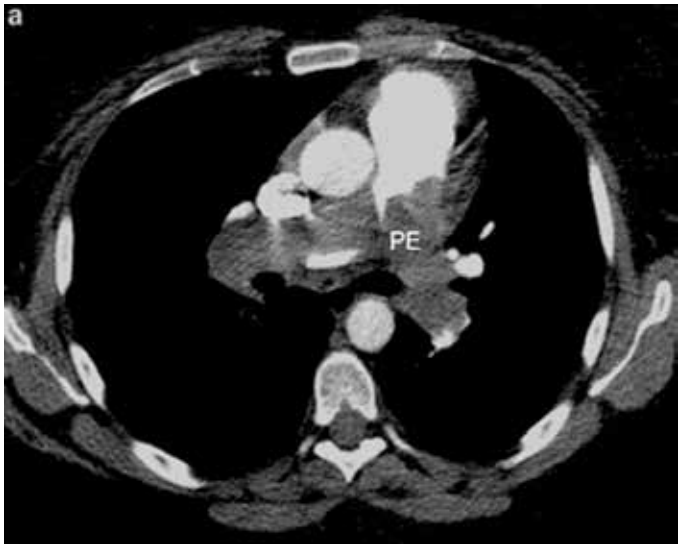

Fig. 2 : CT scan showing a large saddle pulmonary embolus (PE)

- renal insufficiency
- anaphylaxis occurring in reaction to intravenous contrast agent
- pregnancy (lower radiation exposure to the fetus).

Chest computed Tomography (Figures 2 & 3)

Chest CT has supplanted pulmonary radionuclide perfusion scintigraphy as the initial imaging test in most patients with suspected PE, allowing ready visualization of massive PE and confirmation of surgical or catheter accessibility to the centrally located thrombus. The chest CT scan also can detect other pulmonary diseases that manifest in conjunction with PE or explain a clinical presentation that mimics PE. These diseases include dissection aorta,pneumonia, atelectasis, pneumothorax, and pleural effusion.

Echocardiography

Echocardiography findings are normal in approximately one half of unselected patients with acute PE, so echocardiography is not recommended as a routine diagnostic test for PE. Echocardiography is however a rapid practical and sensitive technique for detection of right ventricular overload among patients with established and large PE. Moderate or severe right ventricular

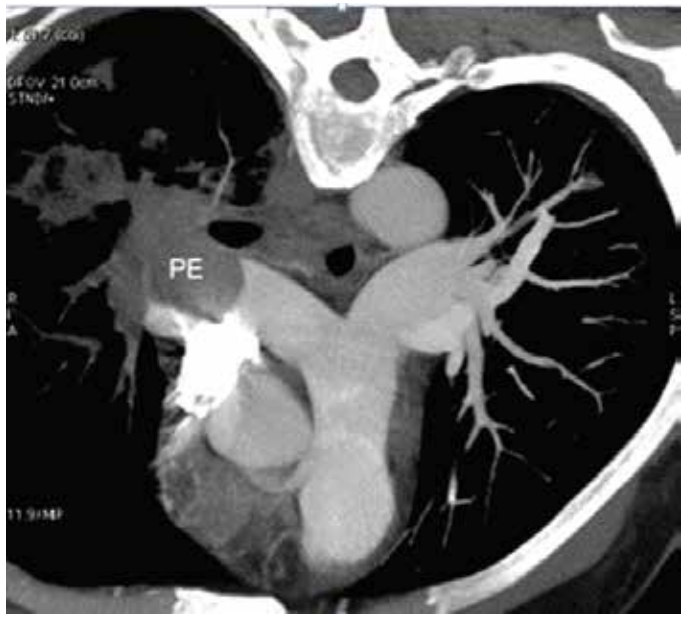

Fig. 3: Large pulmonary embolus (PE) in right pulmonary artery

hypokinesis, persistent pulmonary hypertension, patent foramen ovalen and free floating thrombus in the right atrium or right ventricle are factors associated with high risk of death or recurrent thromboembolism. Echocardiography also can help identify illness that may mimic PE, such as MI and pericardial disease.

Venous Duplex Ultrasonography

The primary diagnostic criterion for DVT on ultrasound imaging is loss of vein compressibility. At least one half of the patients with PE have no imaging evidence of DVT. Therefore if the level of clinical suspicion of PE is moderate or high, patients even without evidence of DVT should undergo further investigation for PE.

Magnetic resonance imaging

Gadolinium enhanced magnetic resonance angiography (MRA) is far less sensitive than CT for the detection of PE but unlike chest CT or catheter based pulmonary angiography, MRA does not require ionizing radiation or injection of an iodinated contrast agent. Pulmonary MRA also can asses right ventricular size and function.

Invasive Pulmonary Angiography

Invasive pulmonary angiography formerly was the reference standard for the diagnosis of PE, but it is now rarely performed as a diagnostic test. Use of this modality is routine however when interventions such as pharmacomechanical catheter assisted therapy are planned.

Contrast Venography

Although contrast phlebography was once the reference standard for DVT diagnosis, venograms are rarely obtained now for diagnostic purpose. Venography is the first step, however for evaluation of patients with large femoral or iliofemoral DVT who will undergo invasive pharmacomechanical catheter-directed therapy.

Overall strategy: An Integrated Diagnostic Approach

Suspected PE can be investigated with a wide array of diagnostic tests. The first step in an integrated diagnostic strategy is a directed history and physical examination to assess the clinical likehood for acute PE. The findings of non-high clinical probability is followed by D-dimer testing. A normal D-dimer assay usually rules out PE. If the D- dimer is elevated chest CT usually provides the definitive diagnosis or exclusion of PE.

THERAPY

Anticoagulation therapy for acute pulmonary embolism: Parenteral Anticoagulation

Unfractionated Heparin

Anticoagulation is the cornerstone of treatment for PE. It prevents additional thrombus formation and permits endogenous fibrinolytic mechanisms to lyse at least some of the clot that has already formed. Heparin does not directly dissolve thrombus. For patients with average bleeding risk, UFH should be started with an intravenous bolus of 80 units/kg, followed by a continuous infusion at 18 units/kg/hr. The aPTT should be targeted between 1.5 and 2.5 times the control value. The therapeutic range commonly is 60 to 80 seconds. The short half life of UFH is advantageous for patients who may require subsequent insertion of an inferior vena cava filter systemic thrombolysis, catheter directed pharmacomechanical therapy, or surgical embolectomy.

Low Molecular Weight Heparin

Low molecular weight heparin (LMWH) has greater bioavailability with a more predictable dose response and a longer half life compared with UFH. These features permit weight based LMWH dosing without laboratory tests, because no dose adjustment is needed in most instances. LMVH has revolutionized the management of DVT and has shortened treatment from a mandatory minimum 5 day hospitalization with intravenous UFH to either an overnight stay or outpatient therapy for most patients.

Warfarin Anticoagulation

Warfarin is a vitamin K antagonist. The full anticoagulant effect of warfarin becomes evident after 5 to 7 days. For patients with VTE, the usual target INR is between 2.0 and 3.0.

Warfarin Overlap with Heparin

Overlapping warfarin for at least 5 days with an immediately effective parenteral heparin (UFH, LMWH) allows quick onset of therapy and counteracts the procoagulant effect of unopposed warfarin.

Novel Oral AntiCoagulants NOAC

Novel oral anticoagulants have a rapid onset of action and provide systemic levels of anticoagulation within several hours of ingestion. They are prescribed in fixed doses without laboratory coagulation monitoring and have minimal drug-drug or drug-food interactions. These agents have a short half life, so when they are stopped for an invasive diagnostic or surgical procedure no bridging is needed. They are noninferior to warfarin for efficacy and are equivalent, or in some cases superior to warfarin for safety.

Oral monotherapy with Rivaroxaban for Acute Deep vein Thrombosis or Acute Pulmonary Embolism

In November 2012, the FDA approved rivaroxaban a direct inhibitor of activated factor x, as oral monotherapy for acute DVT and acute PE. This approval changes the fundamental approach to the treatment of VTE. Completely oral therapy with rivaroxaban is a prudent option for patient with DVT or PE at low or moderate risk for adverse events using a 3 weeks loading dose of 15 mg twice daily, followed by 20 mg once daily thereafter. For most patients the traditional approach using initial parenteral anticoagulation as a bridge to warfarin will no longer be necessary. Home treatment of acute PE will be facilitated.

In the EINSTEIN –PE trial 4833, patient with acute symptomatic PE were treated with either rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily, or with standard therapy using enoxaparin as a bridge to an adjusted dose vitamin K antagonist, usually warfarin. The principal efficacy outcome of symptomatic recurrent venous thromboembolism occurred in 2.1% receving rivaroxaban and 1.8% receving standard therapy achieving statistical noninferiority for rivaroxaban. Rivaroxaban had superior safety. Major bleeding rates were 1.1% for rivaroxaban verus 2.2% for enoxaparin bridging to warfarin (P=0.003). As summarized in the American College of Chest Physicians (ACCP) 2012 Guidelines, "for acute DVT or PE we recommended initial parenteral anticoagulation or anticoagulation with rivaroxaban.

Selection of an Optimal Anticoagulant for extended duration Anticoagulation

The choices for extended-duration anticoagulation have broadened with a wide array of options including warfarin, LMWH, aspirin rivaroxaban, dabigatran and apixaban now available. Standard intensity anticoagulation with warfarin is the conventional time honored approach with a target INR range of 2.0 to 3.0.

Table 4: Advanced therapy for PE

Technique	Description	Comments
Thrombolysis	Catheter in main PA. bolus of thrombolytic followed by infusion Often combined with mechanical fragmentation to increase surface area of thrombus exposed to thrombolytic	No reduced risk of blccdmg documented No evidence of benefit of catheter-directed lysis over systemic unless combined with fragmentation
Fragmentation	Breaking up targe central clot with catheter device: device rotated by operator Fragments migrate distally Often combined with local thrombolysis	Improved rccanalization wim thrombolytics Example: Cook Europe rotatable pigtail catheter
Embolectomy	Catheter directed to thrombus and manual suction used to remove thrombus	Examples: Greenfield embolceiomy device
Balloon angioplasty	Compression of embolus Often combined with local thromboryso	Results in partial fragmentation of embolus Difficult to tell if thrombolytic explains hemodynamic benefits when combined Examples: Wallstent, Giancurco Z stents
Percutaneous thrombectomy	Clot pulverized and removed via catheter by rotation of device or hydrodynam* vortex	Examples: Amplatz thrombectomy device, the Hydrolizcr. Aspirex

Advanced therapy (In addition to anticoagulation) for acute pulmonary embolism

American Heart Association (AHA) and ACCP guideline recommend advanced therapy for patients with massive PE and for patients with submassive PE at the unstable end of the spectrum. These advanced therapy options include full dose systemic thrombolysis, pharmacomechanical catheter directed therapy (usually with low dose thrombolysis), surgical embolectomy, and inferior vena cava filter placement (Table 4).

Table 5: Contraindications to thrombolysis

Absolute Contraindications	Relative Contraindications
Major trauma, surgery, head trauma within 3 weeks	Cancer
Prior hemorrhagic stroke	Age > 75-80 Transient ischemic attack within 6 months
Ischemic stroke within prior 6 months	Oral anticoagulant therapy
Central nervous system neoplasm	Noncomprcssiblc punctures
Gastrointestinal bleeding within one month	Traumatic resuscitation
Active bleeding	Refractory hypertension
	Advanced liver disease
	Infective endocarditis
	Active peptic ulcer
	Pregnancy or within one week postpartum

Systemic Thrombolysis Administered Through a Peripheral Vein

The FDA has approved alteplase for massive PE in a dose of 100mg delivered as a continuous infusion over 2 hours, without concomitant heparin. Unlike that for MI effective use of thrombolysis for PE shows a wide "timewindow "of benefit. Patients who receive thrombolysis up to 14 days after onset of new symptoms or signs can derive benefit, probably because of the effects on the bronchial collateral circulation. Patients being considered for thrombolysis require screening for contraindications (Table 5). Intracranial hemorrhage is the most feared and severe complication.

Advances in pharmacomechanical Catheter Directed Therapy including Thrombolysis

The 1% or greater rate of intracranial hemorrhage in patients with PE receving systemic thrombolysis has dampened enthusiasm for this potential life saving therapy. Pharmacomechanical catheter directed reperfusion, however holds the promise of good efficacy with lower rates of major bleeding owing to lower doses of thrombolytic agent. The typical dose of tissue plasminogen activator (tPA) in a pharmacomechanical catheter based procedure for example is 25 mg or less-compared with 100 mg or systemic administration.

Interventional mechanical techniques usually performed on conjunction with low dose thrombolysis include mechanical fragmentation and aspiration of thrombus through standard pulmonary artery catheter,

Fig. 4: Clots removed from the pulmonary artery in 2 different patients. RA = right atrium, LPAS = left pulmonary artery, RPA = right pulmonary artery

clot pulverization with a rotating basket catheter, rheolytic thrombectomy and pigtail rotational catheter embolectomy. Successful catheter embolectomy rapidly restores normal blood pressure and decrease hypoxemia. Low intensity ultrasound facilitated fibrinolysis is a novel approach. Ultrasound disaggregates fibrin strands increase clot permeability, and disperses infused fibrinolytic drug into the through acoustic microstreaming effects.

Surgical Embolectomy

Emergency surgical embolectomy has reemerged for the management of patients with massive PE and systemic arterial hypotension or submassive PE with severe right ventricular dysfunction in whom contraindications preclude thrombolysis. This procedure also is suitable for patients with acute PE who require surgical excision of a right Atrial thrombus or closure of a patent foramen ovale. Surgical embolectomy also can be used as resuce therapy for patients in whom PE is refractory to thrombolysis. Result are best when patients undergo surgery before they become pressor dependent and before the onset of cardiogenic shock and multisystem organ failure. The surgery is done under hypothermic cardio-pulmonary bypass. The heart is arrested, the pulmonary artery opened and the clots carefully and completely removed – Figure 4. With better methods of myocardial preservation and timely surgery the results are good.

Inferior Vena Cava Filters

The AHA supports the use of inferior vena cava filters for patients with (1) contraindication to anticoagulation ;(2) recurrent PE despite therapeutic levels of anticoagulation

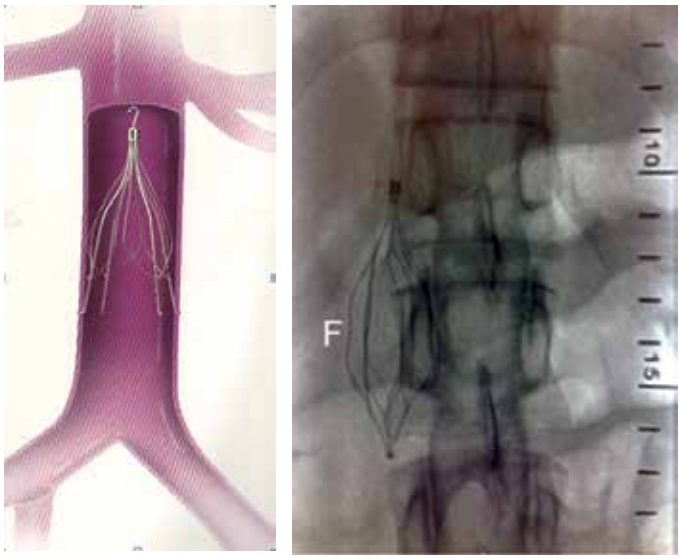

Fig. 5: Filter (F) in IVC

and (3) very poor cardiopulmonary reserve including patients with massive PE. For patients with a temporary contraindication to anticoagulation, placement of a nonpermanent, retrievable filter is appropriate (Figure 5). Retrievable filters can be left in place for weeks to months or can remain permanently, if necessary.

CONCLUSION

PE remains a diagnostic and therapeutic challenge. With advances in understanding of the disease process, a high index of suspicion and quicker and better imaging techniques and therapeutic modalities the results of therapy and likely to get better.