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Review Article

Acute Pulmonary Embolism

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Abstract

Pulmonary embolism (PE) is globally recognized as the third most frequent acute cardiovascular syndrome next to myocardial infarction and stroke. Annual incidence rates for PE range from 39-115 per 100 000 population. Clinical presentation of acute PE is non-specific and high suspicion is maintained based on various scoring system like Wells scoring system and later will proceed to other required investigation. The treatment at earliest can save lives which prompt to the rule of "HIT HARD, HIT FAST". That is recognize early and treat early.

Keywords: Pulmonary embolism, Deep Venous Thrombosis, Hit Hard Hit Fast.

Introduction

Pulmonary embolism (PE) is globally recognized as the third most frequent acute cardiovascular syndrome next to myocardial infarction and stroke. The classical clinical features of pulmonary embolism include sudden onset of breathlessness and pleuritic chest pain.[1]

Clinicians need to possess a great degree of suspicion for PE in patients presenting with cardiopulmonary symptoms, since any delay in the diagnosis of PE can consequently be deleterious, while at the same time, Rapid intervention decreases fatality rate.[2-5]

Epidemiology

In epidemiological studies, annual incidence rates for PE range from 39-115 per 100 000 population; for DVT, incidence rates range from 53-162 per 100 000 population.[6,7] PE may cause approximately 300 000 deaths per year in the US, ranking high among the causes of cardiovascular mortality.[6] In recent years increased use of optimal therapies and interventions has played a positive effect on the prognosis.

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Predisposing Risk Factors

Pulmonary embolism occurs as a consequence of imbalance between patient related and setting related risk factors. Common risk factors are mentioned in Table 1.

Diagnosis

Clinical presentation of acute PE is non-specific. The vast majority of patients with pulmonary embolism present with features which, in decreasing order of frequency, are:

1. Sudden onset of breathlessness
2. Chest pain
3. Syncope
4. Hemoptysis. Hemodynamic instability is rare, but important as it requires emergency intervention or else it May prove fatal. Clinical decision rules can stratify patients as those with high likelihood of pulmonary embolism, using a set of seven bedside assessment questions known as Wells score for PE Table 2.

Table :1 Predisposing Risk Factors.

Strong Risk Factors (OR>10)
Fracture of lower limb
Hospitalization for heart failure or atrial fibrillation/flutter (within previous 3 months)
Hip or knee replacement
Major trauma
Myocardial infarction (within previous 3 months)
Previous VTE
Spinal cord injury
Moderate Risk Factors (OR 2-9)
Arthroscopic knee surgery
Autoimmune diseases
Blood transfusion
Central venous lines
Intravenous catheters and leads
Chemotherapy
Congestive heart failure or respiratory failure
Erythropoiesis-stimulating agents
Hormone replacement therapy (depends on formulation)
In vitro fertilization
Oral contraceptive therapy
Post-partum period
Infection (specifically pneumonia, urinary tract infection, and HIV)
Inflammatory bowel disease
Cancer (highest risk in metastatic disease)
Paralytic stroke
Superficial vein thrombosis
Thrombophilia
Weak Risk Factors (OR<2)
Bed rest >3 days
Diabetes mellitus, Arterial hypertension
Immobility due to sitting (e.g. prolonged car or air travel), Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity ,Pregnancy,Varicose veins

Table :2 Wells Score For Pulmonary Embolism

Symptoms	**Score**
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate of >100 beats per minute	1.5
Immobilisation or surgery within previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical Prability	**Total Score**
PE Unlikely	≤ 4
PE likely	>4

Chest X-ray is frequently abnormal and, although the findings are usually non-specific in PE, it may be useful for excluding other differentials of dyspnoea or chest pain.[8] Focal oligemia (westermark sign) suggests massive central embolic occlusion. A peripheral wedge shaped density above the diaphragm (Hampton Hump) indicates pulmonary infarction.

Electrocardiogram changes range from normal to abnormal findings such as sinus tachycardia, inversion of T waves in leads V1-V4 and the S1Q3T3 pattern, which in itself is a famous sign of right heart strain. ECG also helps exclude acute MI and acute pericarditis.

D-Dimer is recommended for intermediate /low-risk PE. The negative predictive value of D-dimer testing is high, and a normal D-dimer level renders acute PE unlikely. D-Dimer Titers are age dependent, and as such, they increase with advancing age, leading to a decreased specificity in its value.

Echocardiography is a rapid, practical and sensitive technique for detection of right ventricular overload among patients with acute PE. An RV/LV diameter ratio >1.0 and TAPSE <16mm are associated with poorer prognosis. Two important ECHO findings which have high positive predictive value are; 1. Pulmonary ejection acceleration time (measured in the RV outflow tract) <60 ms with a peak systolic tricuspid valve gradient <60 mmHg ('60/60' sign) and 2. Depressed

contractility of the RV free wall as compared to the 'echocardiographic' RV apex (McConnell sign). In patients who are hemodynamically stable RV dysfunction in ECHO carries poor prognosis.

Multidetector computed tomographic pulmonary angiography (CTPA)

The modality of choice for imaging the pulmonary vasculature in patients with suspected PE. It allows for adequate visualization of the pulmonary arteries down to the subsegmental level with a sensitivity of 83% and a specificity of 95%. A negative CTPA result provides adequate grounds for the exclusion of PE in patients with low or intermediate clinical probability of PE.

Lung scanning

The use of radio labelled aggregates of albumin demonstrates multiple perfusion defects in patients with large pulmonary embolism.

The Three principle indications for obtaining lung scans are:

1. Pregnancy,
2. Renal disease and
3. Anaphylaxis reaction to intravenous contrast agent.

Pulmonary angiography

The reference standard for diagnosing PE however, it is a rarely performed test at present Table 3.

Table 3: Investigations in Diagnosis of pulmonary embolism.

INVESTIGATION	SENSITIVITY & SPECEFICITY	ADVANTAGE	DISADVANTAGE
D-Dimer	Cutoff of - 500mi-crogram/L Sensitivity - 99% Specificity - 20-50%	1. Fast exclusion of PE	1. Specificity decreases with age 2. Low specificity at low cut-off value
CTPA	Sensitivity - 83% Specificity - 96 % 1	1. Readily available around the clock in most centres 2. Excellent accuracy 3. Strong validation in prospec-tive management outcome studies 4. Low rate of inconclusive results (35%) 5. May provide alternative di-agnosis if PE excluded 6. Short acquisition time	1. Radiation exposure 2. Exposure to iodine contrast: • limited use in iodine allergy and hyperthyroidism • risks in pregnant and breast-feeding women • contraindicated in severe renal failure 3. Tendency to overuse because of easy accessibility 4.Clinical relevance of CTPA diagnosis of subsegmental PE unknown
Lung scintigraphy		1. Almost no contraindication 2. Strong validation in prospec-tive management outcome studies	1. Not readily available in all centres 2. Interobserver variability in interpretation 3. Results reported as likelihood ratios 4. Inconclusive in 50% of cases 5. Cannot provide alternative diagnosis if PE excluded
V/Q SPECT		1. Almost no contraindications 2. Lowest rate of non-diagnostic tests (<3%) 3. High accuracy according to available data 4. Binary interpretation ('PE' vs. 'no PE')	1. Variability of techniques 2. Variability of diagnostic criteria 3. Cannot provide alternative diag-nosis if PE excluded 4. No validation in prospective management outcome studies
Pulmonary Angiography		**Historical gold standard**	1. Invasive procedure 2. Not readily available in all centres

Venous ultrasound

It aids in diagnosing DVT, but at least 50% of patients with PE have no imaging evidence of DVT.

Lab Biomarkers

Elevated plasma Troponin concentration at admission is associated with poor prognosis in the acute phase of pulmonary embolism, especially it helps in differentiating between low intermediate risk/high intermediate risk pulmonary embolism. When interpreted along with clinical findings and imaging, it allows for the identification of PE related risk and further prognostic stratification. Elevated BNP or NT pro-BNP concentrations have positive prediction values in a normotensive patient with PE.

Risk Stratification

Risk stratification is an important process in initiating appropriate therapeutic approach. ESC guidelines 2019, provides certain criterion for risk assessment. Initial risk stratification is based on clinical symptoms and signs of hemodynamic instability, indicating a high risk of early death. Risk stratification plays an important role in management of suspected and confirmed PE.

Among the several risk stratification indices that exist, PESI i.e. Pulmonary Embolism Severity Index is the most accepted risk assessment score used Table 4.

Table 4: Original and Simplified Pulmonary Embolism Severity Index.

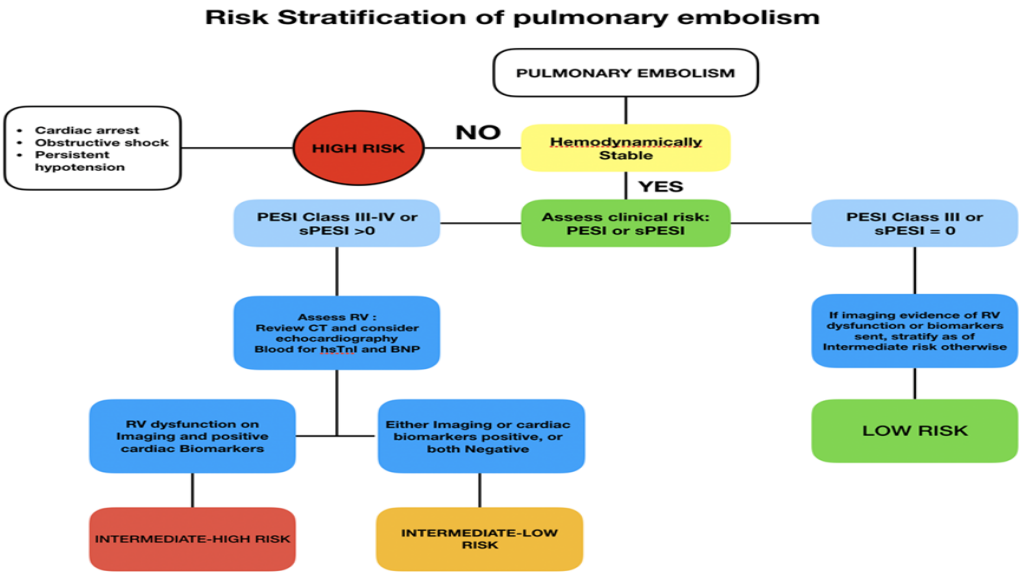
Parameters	Original Version	Simplified Version
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	-
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate >_110 b.p.m.	+20 points	1 point
Systolic BP <100 mmHg	+30 points	1 point
Respiratory rate >30 breaths per min	+20 points	-
Temperature <36 C	+20 points	-
Altered mental status	+60 points	-
Arterial oxyhaemo- globin saturation <90%	+20 points	1 point
	Risk Strata	
	Class I: ≤65 points very low 30 day mortality risk (0-1.6%) **Class II: 66-85 points** low mortality risk (1.7-3.5%)	0 points = 30 day mortality risk 1.0% (95% CI 0.0-2.1%)
	Class III: 86-105 points moderate mortality risk (3.2-7.1%) **Class IV: 106-125 points** high mortality risk (4.0-11.4%) **Class V: >125 points** very high mortality risk (10.0-24.5%)	≥1 point (s) = 30 day mortality risk 10.9% (95% CI 8.5-13.2%)

Original and simplified PESI

Prognostic assessment strategy

Classification of PE severity and the risk of early death (in hospital or 30 day) is summarized in following Figure-1.

Figure 1: Classification of Pulmonary Embolism Severity.[3]



Treatment in the Acute Phase

Initial assessment and Hemodynamic stability

Assess Hemodynamic stability

1. Hemodynamically unstable PE ("massive" PE) is that which presents with hypotension; Here, Hypotension is defined as a systolic blood pressure (BP) <90 mmHg for a period >15 minutes, hypotension requiring vasopressors or clear evidence of shock.
2. Hemodynamically stable PE - These patients are categorized as patients with small PE and stable BP ("low risk") and patients with larger PE who have right ventricular dysfunction and borderline BP (i.e., "submassive" PE/intermediate risk).

Initial Therapies

Respiratory support: Mismatch between ventilation and perfusion, as seen in pulmonary embolism, results in hypoxemia. Administration of supplemental O2 is merited when spO2 is <90%. When hypoxemia is refractory to supplemental O2 further intervention should be considered which include high flow oxygen, mechanical ventilation (non-invasive/invasive).

Mechanical circulatory support and oxygenation: The temporary use of mechanical cardiopulmonary support, mostly with venoarterial extracorporeal membrane oxygenation (ECHMO), may be helpful in patients with high risk PE or circulatory collapse/ cardiac arrest.

Hemodynamic support: The threshold for Hemodynamic support should to centralized to individual patients based on their baseline blood pressure as well as any symptoms and signs suggestive of tissue hypo-perfusion (change in mental status and decreased urine output). Initial therapy of choice is Intra venous fluid (IVF) following which, if the patient's perfusion status does not improve, ionotropes merit consideration. While Norepinephrine is preferred, Dobutamine is sometimes additionally used to increase RV contractility, keeping in mind the special consideration to patients with RV failure wherein excessive IVF administration can worsen RV strain resulting in RV ischemia furthering deterioration of the patient condition. Hence, it is essential to monitor patient's fluid status before administering the IVF.

Initial anticoagulation

Anticoagulation occupies a cornerstone in the treatment of acute Pulmonary embolism. Initial empirical anticoagulation therapy is initiated to those who come under intermediate to high risk clinical probability of PE. This is usually done with subcutaneous low molecular weight heparin (LMWH) or Fondaparinux or IV Unfractioned heparin. Similar effect is also achieved with Non Vitamin K antagonist oral anticoagulants (NOAC), oral drug anticoagulation with higher dose of Apixaban or Rivaroxaban. LMWH or Fondaparinux is preferred over unfractioned

heparin in the initial treatment of PE as it carries a lower risk of causing major bleeding and causing heparin induced thrombocytopenia. Use of UFH is limited to patients with imminent Hemodynamic decompensation in whom primary re-perfusion therapy is necessitated.

NOAC's

NOACs are small molecules that directly inhibit an activated coagulation factor, which is thrombin for dabigatran and factor Xa for apixaban, edoxaban, and rivaroxaban.

The advantages of NOAC's over vitamin K antagonist include 1. rapid onset, 2. Minimal drug to drug interactions. These drugs prescribed in fixed doses, do not require coagulation monitoring at the same time also not requiring bridging when they are stopped for invasive diagnostic or surgical procedures. In addition to being a safer choice than warfarin, it is also on par with warfarin.

Vitamin K antagonist

Vitamin K antagonists are still most commonly used, it is necessary to use Unfractioned heparin, LMWH or fondaparinux concurrently with oral anticoagulants for ≥5 days with monitoring of INR which should be maintained between 2.0-3.0 for 2 consecutive days. Warfarin may be started at dose of 10mg in younger (<60yrs) and at lower dose <5mg in older patients. Self-monitoring in patients on VKA may reduce the risk of thromboembolic event or major bleeding.

Reperfusion treatment.

Systemic Thrombolysis

Immediate systemic Thrombolysis is indicated in massive and high risk sub-massive pulmonary embolism. It results in the rapid improvement of pulmonary obstruction in PE resulting in improved lung perfusion and a decrease in RV dilatation as seen on the echocardiogram. The hallmarks of successful therapy are reduction of right ventricular pressure overload and prevention of release of neuro-humoral factors that exacerbate pulmonary hypertension. Thrombolysis may also improve pulmonary capillary blood flow and reduce the incidence of CTPH (chronic thromboembolic pulmonary hypertension). Thrombolysis has demonstrated a 47% decrease in all-cause mortality rate, A 60% decrease in recurrent pulmonary embolism, A 2.4 fold increase in major bleeding and a 4.6 fold increased risk of intracranial hemorrhage. Drugs used in thrombolytic regimen include recombinant tissue plasminogen activator (rtPA), Streptokinase and urokinase Table 5.

Table 5: Drugs Used in Thrombolytic Regimen in Pulmonary Embolism.

Molecule	Regimen	Contraindications to fibrinolysis
rtPA	100 mg over 2 h	**Absolute** History of haemorrhagic stroke or stroke of unknown origin Ischaemic stroke in previous 6 months Central nervous system neoplasm Major trauma, surgery, or head injury in previous 3 weeks Bleeding diathesis Active bleeding **Relative** Transient ischaemic attack in previous 6 months Oral anticoagulation Pregnancy or first post-partum week Non-compressible puncture sites Traumatic resuscitation Refractory hypertension (systolic BP >180 mmHg) Advanced liver disease Infective endocarditis Active peptic ulcer
	0.6 mg/kg over 15 min (maximum dose 50 mg)a	
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h	
	Accelerated regimen: 1.5 million IU over 2 h	
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h	
	Accelerated regimen: 3 million IU ove	

Percutaneous catheter-based treatment

Pharmacomechanical catheter based therapies including thrombolysis - Pharmacomechanical method where mechanical lysis is combined with low dose intraarterial thrombolysis resulting in a very effective and safe modality associated with lower rates of major bleeding.. These include mechanical fragmentation and aspiration of thrombus through standard pulmonary artery catheter, Rheolytic thrombectomy, clot maceration with rotating basket catheter and pig tail rotational catheter embolectomy.[8,9]

Surgical embolectomy

The usual indication for surgical embolectomy is hemodynamic instability due to acute PE for patients in whom thrombolysis (systemic or catheter-directed) is contraindicated, and becomes an option in whom thrombolysis has failed.[10-12] Additional indications may include echocardiographic evidence of an embolus trapped within a patent foramen ovale, present in the right atrium or right ventricle[11]

Inferior venacava Filters

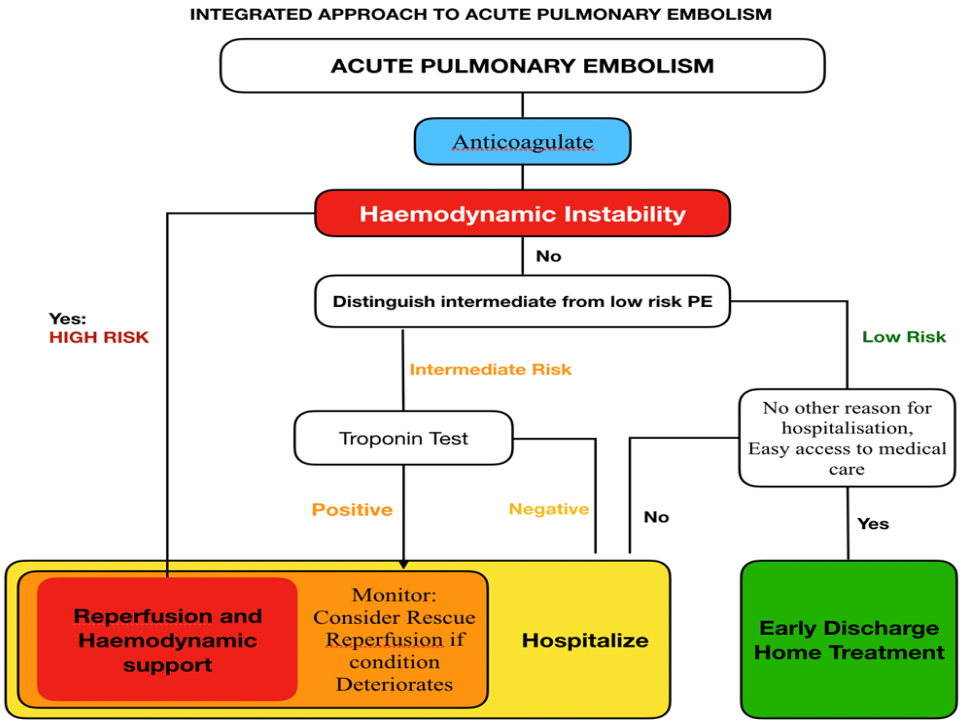
Here the aim is to mechanically prevent the embolus from reaching pulmonary circulation.
Potential indications include:

1. Absolute contraindication to anticoagulant treatment.
2. Recurrent PE despite adequate anticoagulation.
3. Primary prophylaxis in patients with a high risk of PE,
4. Patients undergoing surgical pulmonary embolectomy.

Integrated Management of Acute Pulmonary Embolism

Any patient presenting with a high risk of pulmonary embolism has to be started on empirical anticoagulation and must be assessed for hemodynamic stability. Hemodynamically unstable patients are categorized as high risk and require emergency reperfusion in addition to hemodynamic support. Following reperfusion therapy with parental anticoagulation, a shift to oral anticoagulation can be made. In the setting where patients are eligible for oral anticoagulation, initiation of NOAC's is recommended as per 2019 ERS guidelines. For patients with intermediate risk PE, reperfusion therapy is not recommended as the risk outweighs benefit, instead, parenteral anticoagulation is recommended, which is later converted to oral anticoagulation, with NOAC's as the primary recommendation. In Mild risk PE, early discharge from hospital is recommended with initiation of oral anticoagulants. Figure-2

Figure 2: Integrated approach to Pulmonary Embolism.[4]



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