ACUTE PULMONARY EMBOLISM (PE)

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I DEFINITION AND THE "SPIRAL OF DEATH" PATHOPHYSIOLOGY

- **Definition:** Acute Pulmonary Embolism (PE) is the mechanical and vasoconstrictive obstruction of the pulmonary arterial tree by a thromboembolus (originating in 80 to 90 percent of cases from proximal **Deep Vein Thrombosis [DVT]** of the iliofemoral or popliteal veins).
- **The Right Ventricular "Spiral of Death" (ESC 2019):**
  - **Abrupt Afterload Spike:** Mechanical occlusion of >30 to 50 percent of the pulmonary vascular bed combined with platelet release of **Thromboxane A2 and Serotonin** causes an abrupt surge in **Pulmonary Vascular Resistance (PVR)**.
  - **RV Dilatation and Ventricular Interdependence:** Because the thin-walled, unconditioned Right Ventricle (RV) cannot acutely generate a mean PA pressure above **40 mmHg** (Peak RVSP >60 mmHg suggests chronic pre-existing PH), the RV dilates acutely, stretching the tricuspid annulus (causing functional TR) and shifting the **interventricular septum leftward into the Left Ventricle ("D-shaped LV")** within the rigid pericardium—impairing **LV diastolic filling (underloading)** and dropping systemic cardiac output.
  - **RV Myocardial Ischemia and Obstructive Shock:** Elevated RV wall tension compresses the intramuscular branches of the **Right Coronary Artery (RCA)** while systemic arterial hypotension reduces aortic root coronary perfusion pressure, precipitating **RV myocardial ischemia/infarction**, cardiovascular collapse, and Pulseless Electrical Activity (PEA) arrest.

II DIAGNOSTIC PROBABILITY SCORES AND D-DIMER ALGORITHMS

- **Pre-Test Probability Clinical Prediction Rules (Applied BEFORE Imaging):**
  - **Wells Score for PE: Clinical signs/symptoms of DVT (3.0 pts)**, **PE is #1 diagnosis or equally likely (3.0 pts)**, **Heart rate >100 bpm (1.5 pts)**, **Immobilization >=3 days or surgery in prior 4 weeks (1.5 pts)**, **Previous objectively diagnosed DVT or PE (1.5 pts)**, **Hemoptysis (1.0 pt)**, and **Malignancy treated within 6 months or palliative (1.0 pt)**. **Two-Level Cut-off: Score <=4.0 = "PE Unlikely"** (order high-sensitivity D-dimer); **Score >4.0 = "PE Likely"** (proceed directly to **CTPA**).
  - **Revised Geneva Score:** Fully objective 8-variable score (excludes the subjective "PE more likely" item).
  - **PERC Rule (Pulmonary Embolism Rule-Out Criteria):** Applied **only when pre-test probability is low (<15%)**; if all **8 criteria are negative** (**Age <50 yr, HR <100 bpm, SpO2 >=95% on room air, no hemoptysis, no exogenous estrogen use, no prior DVT/PE, no surgery/trauma requiring hospitalization within 4 weeks, no unilateral leg swelling**), PE is safely excluded **without ordering a D-dimer**.
  - **Specificity-Enhanced D-Dimer Rules (Class IIa):**
  - **Age-Adjusted D-Dimer:** In patients **over 50 years of age** with non-high pre-test probability, the normal D-dimer cut-off of 500 ng/mL (ug/L) is replaced by **Age (in years) x 10 ng/mL** (e.g., 750 ng/mL in a 75-year-old).
  - **YEARS Algorithm:** Assesses 3 items (**Clinical signs of DVT, Hemoptysis, PE most likely diagnosis**): if **0 YEARS items** are present, PE is excluded if **D-dimer <1,000 ng/mL**; if **>=1 YEARS item** is present, PE is excluded if **D-dimer <500 ng/mL**.
  - **Pregnancy-Adapted YEARS Algorithm (*NEJM* 2019 / ESC Class IIa):** Combines proximal lower-extremity compression ultrasonography (if DVT symptoms exist) with the 3 YEARS criteria + variable D-dimer (<1,000 ng/mL if 0 items; <500 ng/mL if >=1 item), safely avoiding CTPA radiation in 39 to 65 percent of pregnant women.

III PROGNOSTIC RISK STRATIFICATION (ESC 2019 FOUR-TIER MODEL)

- **Abandonment of "Massive / Submassive":** Replaced by the **ESC 4-Tier Risk Classification** integrating (1) **Hemodynamic Stability**, (2) **Clinical Severity (PESI Class III–V or sPESI >=1)**, (3) **Right Ventricular Dysfunction on TTE or CTPA**, and (4) **Elevated Cardiac Troponin (hs-cTnI/T)**:
- **Simplified PESI (sPESI — 1 Point Each; Score 0 = Low Risk [~1.0% 30-day mortality]; Score >=1 = High Risk [~10.9% mortality]): Age >80 years**, **History of Cancer**, **Chronic Cardiopulmonary Disease (HF or COPD)**, **Heart Rate >=110 bpm**, **Systolic BP <100 mmHg**, and **Arterial SpO2 <90%**.
- **Bova Score (0 to 7 Points for Normotensive PE Sub-Stratification): SBP 90–100 mmHg (2 pts)**, **Elevated cardiac troponin (2 pts)**, **RV dysfunction on Echo or CTPA (2 pts)**, and **Heart rate >=110 bpm (1 pt)**; Stage III (**>4 points**) predicts a >25 to 40 percent risk of 30-day PE-related complications/hemodynamic collapse.

ESC Risk Category	Shock or Hypotension	PESI Class III–V or sPESI >=1	RV Dysfunction (TTE or CTPA)	Elevated Cardiac Troponin	Primary First-Line Management Strategy (ESC Class I)
High-Risk PE (~5% of PE; >15–30% mortality)	**YES** (Arrest, obstructive shock, or persistent SBP <90 mmHg)	(+)	**YES**	(+)	**Immediate IV UFH + Systemic Thrombolysis (Class I)** (or Surgical/Catheter Embolectomy if lytics contraindicated)
Intermediate-High Risk	No	**YES**	**YES (Both Present)**	**YES (Both Present)**	**Parenteral/Oral Anticoagulation + ICU/Telemetry Monitoring**; **Rescue Reperfusion / CDT** if deterioration (**PEITHO**)
Intermediate-Low Risk	No	**YES**	**Either One Positive (or Both Negative)**	**Either One Positive (or Both Negative)**	**Inpatient Anticoagulation (LMWH/Fondaparinux -> DOAC)**

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Low-Risk PE (~1% mortality)	No	**NO** (PESI I–II / sPESI = 0)	**NO**	**NO**	**Direct Oral Anticoagulant (DOAC) + Early Discharge (<24–48 h) / Home Treatment (Class IIa — HoT-PE)**

IV OBJECTIVE ECHOCARDIOGRAPHIC AND CTPA SIGNS OF RV DYSFUNCTION

- **Bedside Transthoracic Echocardiography (Mandatory First Test in Unstable Suspected PE):**
  - **RV/LV Basal End-Diastolic Diameter Ratio >= 1.0** with interventricular septal flattening (D-sign).
  - **McConnell Sign: Akinesia of the mid-free wall of the RV with preserved (normokinetic/hyperkinetic) apical contractility** (high specificity >94% for acute PE, though also seen in RV infarction).
  - **The "60/60 Sign":** Coexistence of a shortened **Pulmonary Acceleration Time (PAT) <60 ms** (with mid-systolic notching of the RVOT pulsed-wave Doppler envelope) and a **Tricuspid Regurgitation Peak Systolic Gradient <60 mmHg** (confirming acute pressure load on an unconditioned RV).
  - **Decreased TAPSE (<16 mm):** Independently predicts PE-related mortality.
  - **Right Heart Thrombus-in-Transit:** Mobile serpentine thrombus in the RA/RV or straddling a PFO (present in 4%; carries >20% mortality).
  - **CT Pulmonary Angiography (CTPA — Diagnostic Gold Standard):** Direct intraluminal filling defect ("saddle" or lobar/segmental embolus) with an **RV/LV diameter ratio >= 0.9 to 1.0** on 4-chamber view and contrast reflux into the IVC/hepatic veins.

V EVIDENCE-BASED MANAGEMENT AND LANDMARK CLINICAL TRIALS

- **Hemodynamic Support in RV Obstructive Shock:**
  - **Judicious Fluid Challenge (<=500 mL Only):** Give **no more than 500 mL of isotonic crystalloid over 15 to 30 minutes** only in patients with low central venous pressure; aggressive volume loading **over-distends the RV, shifts the septum further into the LV, increases RV wall stress/ischemia, and worsens shock**.
  - **Vasopressors and Inotropes: Norepinephrine (0.1 to 1.0 mcg/kg/min)** is the first-line vasopressor (restores aortic root RCA perfusion pressure and improves systemic RV-LV interaction), supplemented with **Dobutamine (2 to 10 mcg/kg/min)** or **Inhaled Nitric Oxide** if cardiac output remains low; **VA-ECMO** serves as a bridge to surgical or mechanical embolectomy in refractory cardiac arrest/shock.
  - **Anticoagulation Regimens (Class I):**
  - **Parenteral: LMWH (Enoxaparin 1 mg/kg SC q12h)** or **Fondaparinux** is preferred over **Unfractionated Heparin (UFH: 80 U/kg bolus + 18 U/kg/h)** except in **High-Risk PE with shock, severe renal failure (CrCl <30 mL/min), or severe obesity**.
  - **First-Line Single-Drug DOAC Regimens (AMPLIFY & EINSTEIN-PE Trials): Apixaban (10 mg BD for 7 days, then 5 mg BD)** or **Rivaroxaban (15 mg BD for 21 days with food, then 20 mg OD)** (whereas **Dabigatran 150 mg BD** and **Edoxaban 60 mg OD** require 5 days of initial parenteral heparin). (DOACs are **contraindicated in pregnancy, severe renal failure, and triple-positive Antiphospholipid Syndrome**.)
  - **Extended Secondary Prevention (>6 Months — AMPLIFY-EXT & EINSTEIN CHOICE Trials):** After 6 months of treatment for unprovoked PE, reduced-dose **Apixaban 2.5 mg BD** or **Rivaroxaban 10 mg OD** reduces recurrent VTE by ~80 percent without increasing major bleeding.
  - **Systemic Thrombolysis and Catheter-Directed Therapies (CDT):**
  - **High-Risk PE (Class I): Alteplase (rt-PA) 100 mg IV over 2 hours** (or **0.6 mg/kg [max 50 mg] over 15 minutes / 50 mg IV bolus in cardiac arrest**).
  - **PEITHO Trial (*NEJM* 2014 — Why Routine Lytics are Class III in Intermediate-High Risk PE):** In 1,005 normotensive Intermediate-High Risk PE patients, weight-based **Tenecteplase** reduced 7-day death or hemodynamic collapse (**2.6% vs. 5.6%; p = 0.02**), but caused a **5-fold increase in major extracranial bleeding (6.3% vs. 1.2%)** and a **10-fold increase in hemorrhagic/ischemic stroke (2.4% vs. 0.2%)** with zero difference in 30-day mortality or late CTEPH—restricting systemic thrombolysis in intermediate-risk PE strictly to **rescue therapy** if hemodynamic decompensation occurs.
  - **Catheter-Directed Therapies (ULTIMA, OPTALYSE-PE, FLARE/FLASH, and PEERLESS Trials): Ultrasound-Facilitated Catheter-Directed Thrombolysis (USCDT / EKOS: 4 to 12 mg total Alteplase per lung)** (**ULTIMA, OPTALYSE-PE**) and **Large-Bore Mechanical Aspiration Thrombectomy (FlowTriever / Indigo)** (**FLARE, FLASH**) rapidly reverse RV/LV dilation with <1.5% major bleeding. In the head-to-head randomized **PEERLESS Trial** (*Circulation* 2024, n = 550 intermediate-high risk PE), **Large-Bore Mechanical Thrombectomy (FlowTriever)** proved **superior to Catheter-Directed Thrombolysis** for the primary hierarchical win-ratio endpoint (driven by significantly **fewer clinical deteriorations/bailouts [1.8% vs. 5.4%]** and **less ICU admission/length of stay**, with similar mortality and intracranial bleeding).
  - **Post-PE Syndrome and CTEPH Screening (Class I):** Every acute PE survivor must be evaluated at **3 to 6 months** post-PE; persistent dyspnea or functional limitation warrants **Transthoracic Echocardiography** and a **Ventilation/Perfusion (V/Q) lung scan** (not CTPA alone) to rule out **Chronic Thromboembolic Pulmonary Hypertension (CTEPH)**.

KEY REFERENCES

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