Acute pulmonary embolism

Definition:

Pulmonary embolism is an acute, serious condition that can be directly life threatening. It happens when an artery in the lungs is blocked by a substance that has traveled from elsewhere in the body through the bloodstream. This substance usually results from a blood clot in the legs or pelvis. The blockage of an artery that supplies the lungs, causes severe damage, interrupts their smooth operation and may, depending on the importance of the blocked artery, directly lead to death ***(Lambrini et al., 2018).***

The most common form of emboli that causes pulmonary embolism is the blood clot described above. But there are also other situations that may occur, such as amniotic emboli during childbirth, scatter tumor emboli from a malignant disease or even traumatic fat emboli originating from the bone or bone marrow in patients with sustained blunt trauma and multiple fractures ***(Girtovitis 2014).***

Classification:

PE can be broadly classified as either massive or non-massive. Patients with massive PE usually present with hemodynamic instability and are treated with either thrombolytic therapy or pulmonary embolectomy, while patients with non-massive PE are generally hemodynamically stable and can be treated with anticoagulation alone ***(Jae et al., 2014).***

Non-massive PE: it is acute PE without systemic hypotension (systolic blood pressure >90 mm Hg) but with either RV dysfunction or

myocardial necrosis. Massive PE: it is acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction, pulselessness, or persistent profound bradycardia (heart rate <40 bpm with signs or symptoms of shock) ***(Jaff et al., 2011).***

Epidemiology:

Venous thromboembolism (VTE), clinically presenting as DVT or PE, is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke ***(Raskob et al., 2014).***

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 ***(Keller et al., 2020).***

Cross-sectional data show that the incidence of VTE is almost eight times higher in individuals aged ≥80 years than in the fifth decade of life ***(Wendelboe & Raskob 2016).***In parallel, longitudinal studies have revealed a rising tendency in annual PE incidence rates over time ***(Keller et al., 2020).***

PE may cause ≤300 000 deaths per year in the US, ranking high among the causes of cardiovascular mortality ***(Wendelboe & Raskob 2016).***

Predisposing factors:

Venous thromboembolism (VTE) is considered to be a consequence of the interaction between patient-related usually permanent risk factors and setting-related usually temporary risk factors. Since categorization of

temporary and permanent risk factors for VTE is important for assessing the risk of recurrence, and consequently for decision-making on chronic anticoagulation ***(Konstantinides et al., 2020).***

There is an extensive collection of predisposing environmental and genetic factors for VTE; a list of predisposing (risk) factors is shown in **(Table1)**.

Table 1: predisposing factors for venous thromboembolism.

Strong risk factors	• 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	• 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

Week risk factors	• 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

(Rogers et al., 2012).

Pathophysiology:

Acute PE interferes with both the circulation and gas exchange. Right ventricular (RV) failure due to pressure overload is considered the primary cause of death in severe PE ***(Konstantinides et al., 2020).***Occlusion greater than 30–50% cross-sectional area of an arterial bed slowly increases pulmonary artery pressure by release of thromboxane and other vasoactive metabolites in response to endothelial cell stress ***(Burrowes,Clark&Tawhai 2011).***

PE-induced vasoconstriction, mediated by the release of thromboxane A2 and serotonin, contributes to the initial increase in pulmonary vascular resistance (PVR) after PE ***(Smulders 2000).*** Anatomical obstruction and hypoxic vasoconstriction in the affected lung area lead to an increase in PVR, and a proportional decrease in arterial compliance ***(Lankhaar, et al., 2006).***

The abrupt increase in PVR results in RV dilation, which alters the contractile properties of the RV myocardium via the Frank Starling mechanism. The increase in RV pressure and volume leads to an increase in wall tension and myocyte stretch. The contraction time of the RV is

prolonged, while neurohumoral activation leads to inotropic and chronotropic stimulation. Together with systemic vasoconstriction, these compensatory mechanisms increase pulmonary artery pressure (PAP), improving flow through the obstructed pulmonary vascular bed and thus temporarily stabilizing systemic blood pressure (BP). However, the extent of immediate adaptation is limited, as a non-preconditioned, thin-walled RV is unable to generate a mean PAP >40 mmHg ***(Konstantinides et al., 2020).***

Presentation is highly variable and results from complete or partial obstruction of the pulmonary vasculature causing increased pulmonary pressures and ventilation perfusion (V/Q) mismatches. It is important to note that the degree of obstruction can range from minimal disturbance to completely obstructed arteries. As such, patients may be asymptomatic in some instances and severely compromised in others. As vascular obstruction increases, supply to downstream lung parenchyma decreases, leading to poor perfusion of alveoli capillary beds. This can result in a mismatch between ventilation and perfusion, causing type 1 respiratory failure ***(Hepburn et al., 2019).***

In the acute setting there may not be a rise in pulmonary artery pressure. Instead, RV function may be impaired due to increased afterload and myocardial ischemia as the coronary perfusion gradient declines from low systemic blood pressure and increased chronotropic activity ***(Konstantinides et al., 2014).***

Prolongation of RV contraction time into early diastole in the left ventricle (LV) leads to leftward bowing of the inter-ventricular septum ***(Marcus et al., 2008).*** The de-synchronization of the ventricles may be exacerbated by the development of right bundle branch block. As a result,

LV filling is impeded in early diastole, and this may lead to a reduction in the cardiac output (CO), and contribute to systemic hypotension and hemodynamic instability***(Mauritz et al., 2011).***

The detrimental effects of acute PE on the RV myocardium and the circulation are summarized in **(*Figure 1).***

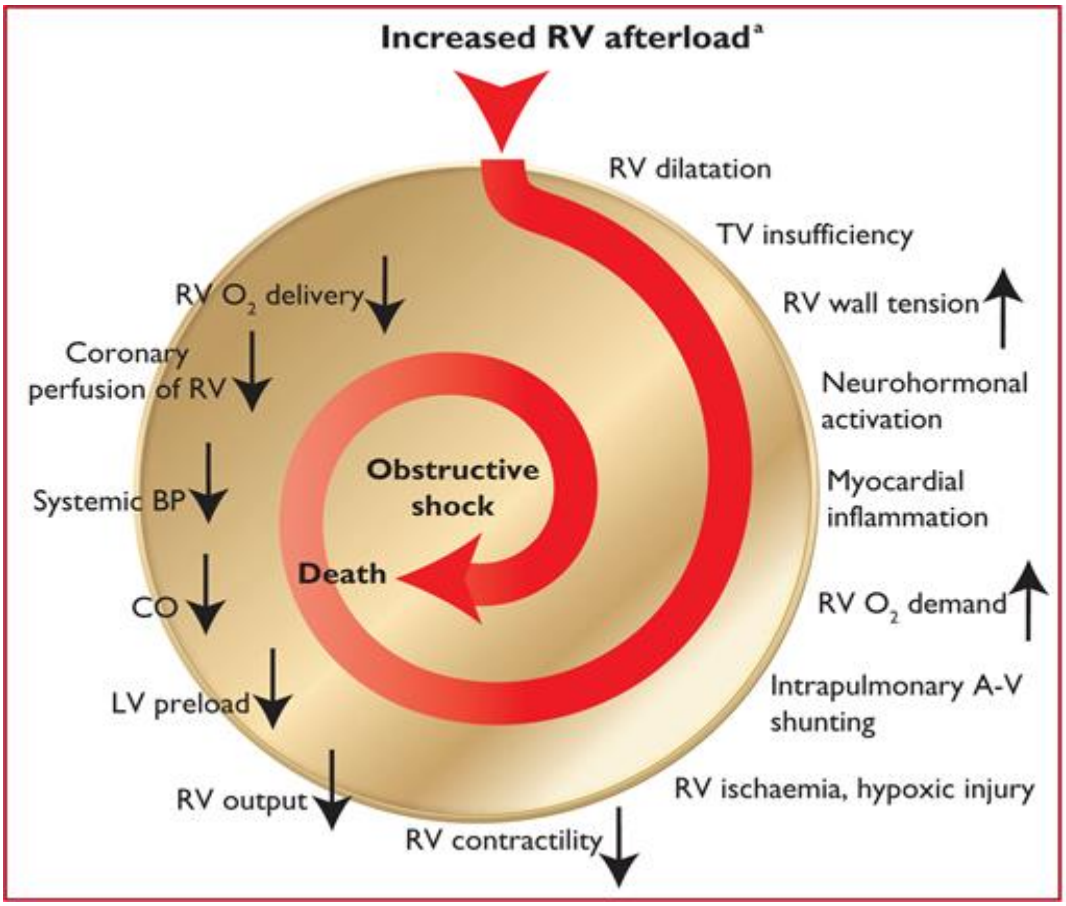

Figure (1): Key factors contributing to hemodynamic collapse and death in acute pulmonary embolism.

(Konstantinides et al., 2020).

Respiratory failure in PE is predominantly a consequence of hemodynamic disturbances***(Burrowes et al., 2011).*** Low CO results in desaturation of the mixed venous blood. Zones of reduced flow in obstructed pulmonary arteries, combined with zones of overflow in the

capillary bed served by non-obstructed pulmonary vessels, result in ventilation/perfusion mismatch, which contributes to hypoxemia***(Konstantinides et al., 2020).***

Small distal emboli may create areas of alveolar hemorrhage resulting in hemoptysis, pleuritis, and pleural effusion, which is usually mild. This clinical presentation is known as 'pulmonary infarction'. Its effect on gas exchange is normally mild, except in patients with pre-existing cardiorespiratory disease ***(Konstantinides et al., 2020).***

Clinical symptoms and signs of overt RV failure and hemodynamic instability, indicate a high risk of early (in-hospital or 30 day) mortality. High-risk PE is defined by hemodynamic instability and encompasses the forms of clinical presentation shown in **(*Table 2)***.

Table 2: Definition of hemodynamic instability which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation).

1- Cardiac arrest	Need for cardiopulmonary resuscitation
2-Obstructive shock	Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status And End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate
3-Persistent hypotension	Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis

(Konstantinides et al., 2020).

However, the absence of hemodynamic instability does not exclude beginning (and possibly progressing) RV dysfunction, and thus an elevated PE-related early risk. In this large population, further assessment is necessary to determine the level of risk and adjust management decisions accordingly ***(Konstantinides et al., 2020)***

Diagnosis:

The increased awareness of venous thromboembolic disease and the ever-increasing availability of non-invasive imaging tests, mainly computed tomography (CT) pulmonary angiography (CTPA), have generated a tendency for clinicians to suspect and initiate a diagnostic workup for PE more frequently than in the past ***(Konstantinides et al., 2020).***

(1) clinical presentation

The clinical signs and symptoms of acute PE are non-specific. In most cases, PE is suspected in a patient with dyspnea, chest pain, pre-syncope or syncope, or hemoptysis***(Pollack et al., 2011).*** Hemodynamic instability is a rare but important form of clinical presentation, as it indicates central or extensive PE with severely reduced hemodynamic reserve. Syncope may occur, and is associated with a higher prevalence of hemodynamic instability and RV dysfunction***(Barco et al., 2018).*** Conversely, and according to the results of a recent study, acute PE may be a frequent finding in patients presenting with syncope (17%), even in the presence of an alternative explanation***(Prandoni et al., 2016).***

In some cases, PE may be asymptomatic or discovered incidentally during diagnostic workup for another disease***(Konstantinides et al., 2020).***

Dyspnea may be acute and severe in central PE; in small peripheral PE, it is often mild and may be transient. In patients with pre-existing heart failure or pulmonary disease, worsening dyspnea may be the only symptom indicative of PE. Chest pain is a frequent symptom of PE and is usually caused by pleural irritation due to distal emboli causing pulmonary infarction***(Stein & Henry 1997).*** In central PE, chest pain may have a typical angina character, possibly reflecting RV ischemia, and requiring differential diagnosis from an acute coronary syndrome or aortic dissection***(Konstantinides et al., 2020).***

Assessment of clinical probability:

The combination of symptoms and clinical findings with the presence of predisposing factors for VTE allows the classification of patients with suspected PE into distinct categories of clinical or pre-test probability, which correspond to an increasing actual prevalence of confirmed PE. This pre-test assessment can be done either by empirical clinical judgement or by using prediction rules. As the post-test (i.e. after an imaging test) probability of PE depends not only on the characteristics of the diagnostic test itself but also on the pre-test probability, this is a key step in all diagnostic algorithms for PE ***(Konstantinides et al., 2020)***.

The most frequently used prediction rules are the revised Geneva rule **(*Table 3*)** and the Wells rule **(*Table 4*)*(Wells et al., 2000)***. Both prediction rules have been simplified in an attempt to increase their adoption into clinical practice; the simplified versions have been externally validated***(Douma et al., 2009)***.

Regardless of the score used, the proportion of patients with confirmed PE can be expected to be ~10% in the low-probability category, 30% in the moderate-probability category, and 65% in the high-

probability category. When the two-level classification is used, the proportion of patients with confirmed PE is ~12% in the PE-unlikely category and 30% in the PE-likely category***(Ceriani et al., 2010)***.

Table 3: The revised Geneva clinical prediction rule for pulmonary embolism.

Items	Clinical decision rule points (original version) ***(Le Gal et al., 2006)***.	Clinical decision rule points (simplified version) ***(Klok et al., 2008)***.
Previous PE or DVT	3	1
Heart rate 75-94 b.p.m	3	1
Heart rate 95 b.p.m or more	5	2
Surgery or fracture within the past month	2	1
Hemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral edema	4	1
Age > 65 years	1	1
Clinical probability		
Three level score		
Low	0-3	0-1
Intermediate	4-10	2-4
High	11 or more	5 or more
Two level score		
PE unlikely	0-5	0-2
PE likely	6 or more	3 or more

Table 4: The Wells clinical prediction rule for pulmonary embolism.

Items	Clinical decision rule points (original version) ***(Wells et al., 2000)***.	Clinical decision rule points (simplified version) ***(Gibson et al., 2008)***.
Previous PE or DVT	1.5	1
Heart rate >100 b.p.m	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three level score		
Low	0-1	Not applicable
Intermediate	2-6	Not applicable
High	7 or more	Not applicable
Two level score		
PE unlikely	0-4	0-1
PE likely	5 or more	2 or more

Searching for PE in every patient with dyspnea or chest pain may lead to high costs and complications of unnecessary tests. The Pulmonary Embolism Rule-out Criteria (PERC) were developed for emergency department patients with the purpose of selecting, on clinical grounds, patients whose likelihood of having PE is so low that diagnostic workup should not even be initiated***(Kline et al., 2004)***. They comprise eight clinical variables significantly associated with an *absence* of PE: age < 50 years; pulse < 100 beats per minute; SaO_2 >94%; no unilateral leg swelling; no hemoptysis; no recent trauma or surgery; no history of VTE; and no oral hormone use. The results of a prospective validation

study***(Penaloza et al., 2017)*** and those of a randomized non-inferiority management study suggested safe exclusion of PE in patients with low clinical probability who, in addition, met all criteria of the PERC rule***(Freund et al., 2018)***.

Investigations

1) Chest X-ray:

A chest X-ray is frequently abnormal and, although its findings are usually non-specific in PE, it may be useful for excluding other causes of dyspnea or chest pain ***(Elliott et al., 2000)***.

2) Electrocardiography:

Electrocardiographic changes indicative of RV strain—such as inversion of T waves in leads V1–V4, a QR pattern in V1, a S1Q3T3 pattern, and incomplete or complete right bundle branch block—are usually found in more severe cases of PE ***(Shopp et al., 2015)***. in milder cases, the only abnormality may be sinus tachycardia, present in 40% of patients. Finally, atrial arrhythmias, most frequently atrial fibrillation, may be associated with acute PE ***(Konstantinides et al., 2020).***

3) D-dimer:

D-dimer levels are elevated in plasma in the presence of acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. The negative predictive value of D-dimer testing is high, and a normal D-dimer level renders acute PE or DVT unlikely. On the other hand, the positive predictive value of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE ***(Konstantinides et al., 2020).*** D-dimer is also more frequently elevated in patients with

cancer***(Righini et al., 2006)***, in hospitalized patients***(Douma et al., 2011)***, in severe infection or inflammatory disease, and during pregnancy***(Chabloze al., 2001)***.

The specificity of D-dimer in suspected PE decreases steadily with age to ~10% in patients >80 years of age***(Righini et al., 2000)***. The use of age-adjusted cut-offs may improve the performance of D-dimer testing in the elderly. As an alternative to the fixed D-dimer cut-off, a negative D-dimer test using an age adjusted cut-off (age x 10 ng/ml, in patients aged >50 years) should be considered for excluding PE in patients with low or intermediate clinical probability or those that are PE unlikely.106. Use of the age-adjusted (instead of the 'standard' 500 µg/L) D-dimer cut-off increased the number of patients in whom PE could be excluded from 6.4 to 30%, without additional false-negative findings***(Righini et al., 2014).*** As an alternative to the fixed or age adjusted D-dimer cut-off, D-dimer levels adapted to clinical probability should be considered to exclude PE. D-dimer cut-off levels adapted to clinical probability according to YEARS model (sign of DVT, hemoptysis and whether an alternative diagnosis is less likely than PE) may be used. According to this model. PE is excluded in patients without clinical items and D-dimer level<1000 ng /ml or in patients with one or more clinical items and D-dimer level <500ng /ml***(van der Hulle et al., 2017).***

4) Echocardiography:

Acute PE may lead to RV pressure overload and dysfunction, which can be detected by echocardiography. Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function. This is why echocardiographic criteria for the diagnosis of PE have differed between

studies***(Konstantinides et al., 2020).***Because of the reported negative predictive value of 40–50%, a negative result cannot exclude PE ***(Roy et al., 2005).*** On the other hand, signs of RV overload or dysfunction may also be found in the absence of acute PE, and may be due to concomitant cardiac or respiratory disease ***(Bova et al., 2003).***

Echocardiographic findings of RV overload and/or dysfunction are graphically presented in Figure 2. RV dilation is found in ≥25% of patients with PE on transthoracic echocardiography (TTE) and is useful for risk stratification of the disease***(Kurnicka et al., 2016)***.the combination of a pulmonary ejection acceleration time (measured in the RV outflow tract) <60 ms with a peak systolic tricuspid valve gradient <60 mmHg ('60/60' sign), or with depressed contractility of the RV free wall compared to the 'echocardiographic' RV apex (McConnell sign), is suggestive of PE***(Kurzyna et al., 2002).***Decreased tricuspid annular plane systolic excursion (TAPSE) may also be present in PE patients**(Lobo et al., 2014).** Echocardiographic parameters of RV function derived from Doppler tissue imaging and wall strain assessment may also be affected by the presence of acute PE **(Figure 2).** The recent introduction of speckle tracking echocardiography (STE) has provided an objective means for quantifying the electro-mechanical delay between the RV and LV with improved accuracy and greater reproducibility than can be achieved with conventional two-dimensional echocardiogram **(Meris et al., 2010).**

Echocardiographic examination is not mandatory as part of the routine diagnostic workup in haemodynamically stable patients with suspected PE ***(Roy et al., 2005),*** although it may be useful in the differential diagnosis of acute dyspnoea. This is in contrast to suspected high-risk PE, in which the absence of echocardiographic signs of RV

overload or dysfunction practically excludes PE as the cause of haemodynamic instability. In the latter case, echocardiography may be of further help in the differential diagnosis of the cause of shock, by detecting pericardial tamponade, acute valvular dysfunction, severe global or regional LV dysfunction, aortic dissection, or hypovolaemia ***(Dresden et al., 2014).*** Conversely, in a haemodynamically compromised patient with suspected PE, unequivocal signs of RV pressure overload, especially with more specific echocardiographic findings (60/60 sign, McConnell sign, or right-heart thrombi), justify emergency reperfusion treatment for PE if immediate CT angiography is not feasible in a patient with high clinical probability and no other obvious causes for RV pressure overload ***(Dresden et al., 2014).***

Mobile right-heart thrombi are detected by TTE or transoesophageal echocardiography (TOE), or by CT angiography, in <4% of unselected patients with PE (***Casazza et al., 2014).*** Their prevalence may reach 18% among PE patients in the intensive care setting(***Casazza et al., 1997).*** Mobile right-heart thrombi essentially confirm the diagnosis of PE and are associated with high early mortality, especially in patients with RV dysfunction(***Barrios et al., 2017).***

In some patients with suspected acute PE, echocardiography may detect increased RV wall thickness or tricuspid insufficiency jet velocity beyond values compatible with acute RV pressure overload (>3.8 m/s or a tricuspid valve peak systolic gradient >60 mmHg) (***Guérin et al., 2014).*** In these cases, chronic thromboembolic (or other) pulmonary hypertension (PH) should be included in the differential diagnosis.

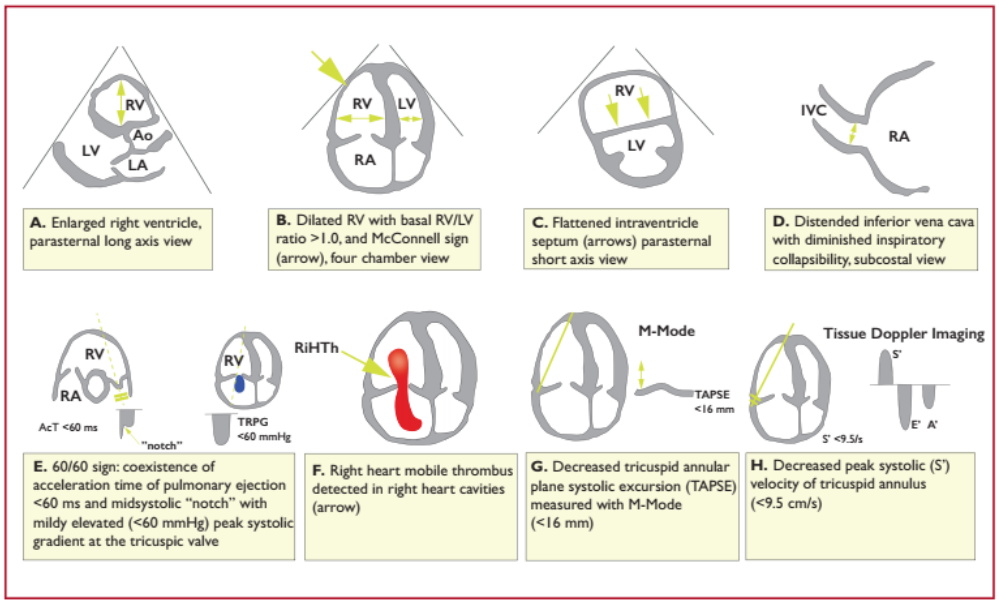

Figure (2): Graphic representation of transthoracic echocardiographic parameters in the assessment of right ventricular pressure overload.

(Konstantinides et al., 2020).

5) Computed tomographic pulmonary angiography:

Multidetector CTPA is the method of choice for imaging the pulmonary vasculature in patients with suspected PE. It allows adequate visualization of the pulmonary arteries down to the subsegmental level ***(Carrier et al.,2010).***

In patients with a low or intermediate clinical probability of PE, a negative CTPA had a high negative predictive value for PE (96 and 89%, respectively), but its negative predictive value was only 60% if the pre-test probability was high. Conversely, the positive predictive value of a positive CTPA was high (92–96%) in patients with an intermediate or high clinical probability, but much lower (58%) in patients with a low pre-test likelihood of PE ***(Stein et al.,2006).*** Therefore, clinicians should consider further testing in case of discordance between clinical judgement and the CTPA result ***(Konstantinides et al., 2020).***

6) Lung scintigraphy:

The planar ventilation/perfusion [V/Q (lung scintigraphy)] scan is an established diagnostic test for suspected PE. Perfusion scans are combined with ventilation studies, for which multiple tracers such as xenon-133 gas, krypton-81 gas, technetium-99m-labelled aerosols, or technetium-99m-labelled carbon microparticles (Technegas) can be used. The purpose of the ventilation scan is to increase specificity: in acute PE, ventilation is expected to be normal in hypoperfused segments (mismatched). Being a lower-radiation and contrast medium-sparing procedure, the V/Q scan may preferentially be applied in outpatients with a low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnant women, in patients with history of contrast medium-induced anaphylaxis, and patients with severe renal failure***(Reid et al., 2009).***

To facilitate communication with clinicians, a three-tier classification is preferable: normal scan (excluding PE), high-probability scan (considered diagnostic of PE in most patients), and non-diagnostic scan***(Glaser et al., 2011).***

Performing only a perfusion scan might be acceptable in patients with a normal chest X-ray; any perfusion defect in this situation would be considered a mismatch. The high frequency of non-diagnostic scans is a limitation because they indicate the necessity for further diagnostic testing***(Konstantinides et al., 2020).***

Several studies suggest that data acquisition in single-photon emission CT (SPECT) imaging, with or without low-dose CT, may decrease the proportion of non-diagnostic scans to as low as 0–5%***(Gutte et al., 2009).*** However, most studies reporting on the accuracy of SPECT

are limited by their retrospective design***(Kumar et al., 2015)*** or the inclusion of SPECT itself in the reference standard***(Reinartz et al., 2004),*** and only one study used a validated diagnostic algorithm ***(Le Duc-Pennec et al., 2012).*** The diagnostic criteria for SPECT also varied; most studies defined PE as one or two subsegmental perfusion defects without ventilation defects, but these criteria are infrequently used in clinical practice. In addition, the optimal scanning technique (perfusion SPECT, V/Q SPECT, perfusion SPECT with non-enhanced CT, or V/Q SPECT with non-enhanced CT) remains to be defined. Finally, few outcome studies are available, and with incomplete follow-up***(Simanek& Koranda et al., 2016).*** Large-scale prospective studies are needed to validate SPECT techniques.

7) Pulmonary angiography:

For several decades, pulmonary angiography was the 'gold standard' for the diagnosis or exclusion of acute PE, but it is now rarely performed as less-invasive CTPA offers similar diagnostic accuracy***(Qanadli et al., 2000).*** The diagnosis of acute PE is based on direct evidence of a thrombus in two projections, either as a filling defect or as amputation of a pulmonary arterial branch. Thrombi as small as 1–2 mm within the subsegmental arteries can be visualized by digital subtraction angiography, but there is substantial interobserver variability at this level***(Stein et al., 1999).***

The major strengths & weaknesses/limitations related to the use of pulmonary angiography in the diagnosis of PE in comparison with other imaging tests used for diagnosis PE are summarized in ***(Table 5).***

Table 5: Imaging tests for diagnosis of pulmonary embolism.

Imaging test	Strengths	Weakness/limitations
CTPA	Readily available around the clock in most centers Excellent accuracy Strong validation in prospective management outcome studies Low rate of inconclusive results (3–5%) May provide alternative diagnosis if PE excluded Short acquisition time	Radiation exposure Exposure to iodine contrast: Exposure to iodine contrast: ○limited use in iodine allergy and hyperthyroidism ○risks in pregnant and breastfeeding women ○contraindicated in severe renal failure Tendency to overuse because of easy accessibility Clinical relevance of CTPA diagnosis of subsegmental PE unknown
Planar V/Q scan	Almost no contraindications Relatively inexpensive Strong validation in prospective management outcome studies	Not readily available in all centers Interobserver variability in interpretation Results reported as likelihood ratios Inconclusive in 50% of cases Cannot provide alternative diagnosis if PE excluded

V/Q SPECT	Almost no contraindications Lowest rate of non-diagnostic tests (<3%) High accuracy according to available data Binary interpretation ('PE' vs. 'no PE')	Variability of techniques Variability of diagnostic criteria Cannot provide alternative diagnosis if PE excluded No validation in prospective management outcome studies
Pulmonary angiography	Historical gold standard	Invasive procedure Not readily available in all centers

(Konstantinides et al., 2020).

8) Magnetic resonance angiography:

Magnetic resonance angiography (MRA) has been evaluated for several years regarding suspected PE. However, the results of large-scale studies show that this technique, although promising, is not yet ready for clinical practice due to its low sensitivity, the high proportion of inconclusive MRA scans, and its low availability in most emergency settings***(Revel et al., 2012).***

9) Compression ultrasonography:

In the majority of cases, PE originates from DVT in a lower limb, and only rarely from upper-limb DVT (mostly following venous catheterization). In a study using venography, DVT was found in 70% of patients with proven PE***(HULL et al., 1983).*** Nowadays, lower-limb CUS has largely replaced venography for diagnosing DVT. CUS has a sensitivity >90% and a specificity of ~95% for proximal symptomatic DVT***(Kearon et al., 1998).*** CUS shows a DVT in 30–50% of patients with PE ***(Righini et al., 2008)***, and finding a proximal DVT in patients

suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing ***(Le Gal et al., 2006)***. However, patients in whom PE is indirectly confirmed by the presence of a proximal DVT should undergo risk assessment for PE severity and the risk of early death.

The only validated diagnostic criterion for DVT is incomplete compressibility of the vein, which indicates the presence of a clot, whereas flow measurements are unreliable***(Da Costa et al., 2016).***

In patients admitted to the emergency department with hemodynamic instability and suspicion of PE, a combination of venous ultrasound with cardiac ultrasound may further increase specificity. Conversely, an echocardiogram without signs of RV dysfunction and a normal venous ultrasound excluded PE with a high (96%) negative predictive value in one study***(Nazerian et al., 2018).***

10) Computed tomography venography:

When using CTPA, it is possible to image the deep veins of the legs during the same acquisition***(Stein et al., 2006).*** However, this approach has not been widely validated and the added value of venous imaging is limited***(Righini et al., 2008)***.Moreover, using CT venography is associated with increased radiation doses***(Rademaker et al., 2001)***.

Assessment of pulmonary embolism severity and the risk of early death:

Risk stratification of patients with acute PE is mandatory for determining the appropriate therapeutic management approach. initial risk

stratification is based on clinical symptoms and signs of hemodynamic instability **(Table 2)**, which indicate a high risk of early death. In the large remaining group of patients with PE who present without hemodynamic instability, further (advanced) risk stratification requires the assessment of two sets of prognostic criteria: (I) clinical, imaging, and laboratory indicators of PE severity, mostly related to the presence of RV dysfunction; and (II) presence of comorbidity and any other aggravating conditions that may adversely affect early prognosis***(Konstantinides et al., 2020).***

1)Clinical parameters of pulmonary embolism severity:

Acute RV failure, defined as a rapidly progressive syndrome with systemic congestion resulting from impaired RV filling and/or reduced RV flow output, is a critical determinant of outcome in acute PE. Tachycardia, low systolic BP, respiratory insufficiency (tachypnoea and/or low SaO_2), and syncope, alone or in combination, have been associated with an unfavorable short-term prognosis in acute PE***(Harjola et al., 2016).***

2)Imaging of right ventricular size and function:

- **Echocardiography:**

Echocardiographic parameters used to stratify the early risk of patients with PE are graphically presented in *Figure* 2. Systematic reviews and meta-analyses have suggested that RV dysfunction on echocardiography is associated with an elevated risk of short-term mortality in patients who appear hemodynamically stable at presentation, but its overall positive predictive value for PE-related death was low (<10%) in a meta-analysis***(Coutance et al., 2011).***This weakness is partly

related to the fact that echocardiographic parameters have proved difficult to standardize***(Pruszczyk et al., 2014)***.Nevertheless, echocardiographic assessment of the morphology and function of the RV is widely recognized as a valuable tool for the prognostic assessment of normotensive patients with acute PE in clinical practice.

- **Computed tomographic pulmonary angiography:**

CTPA parameters used to stratify the early risk of patients with PE. Four-chamber views of the heart by CT angiography can detect RV enlargement (RV end-diastolic diameter and RV/LV ratio measured in the transverse or four-chamber view) as an indicator of RV dysfunction***(Konstantinides et al., 2020)*.**

Mild RV dilation (RV/LV slightly above 0.9) on CT is a frequent finding (>50% of hemodynamically stable PE patients), but it probably has minor prognostic significance***(Côté et al., 2017).*** However, increasing RV/LV diameter ratios are associated with rising prognostic specificity***(Etesamifard et al., 2016)***,even in patients considered to be at 'low' risk on the basis of clinical criteria***(Côté et al., 2017)***.Thus, RV/LV ratios ≥ 1.0 (instead of 0.9) on CT angiography may be more appropriate to indicate poor prognosis.

Apart from RV size and the RV/LV ratio, CT may provide further prognostic information based on volumetric analysis of the heart chambers***(Aviram et al., 2016)*** and assessment of contrast reflux to the inferior vena cava (IVC) ***(Aviram et al., 2012)***.

3)Laboratory biomarkers:

- **Markers of myocardial injury:**

Elevated plasma troponin concentrations on admission may be associated with a worse prognosis in the acute phase of PE. A meta-analysis showed that elevated troponin concentrations were associated with an increased risk of mortality, both in unselected patients and in those who were hemodynamically stable at presentation***(Konstantinides et al., 2020).***

Increased circulating levels of cardiac troponins have relatively low specificity and positive predictive value for early mortality in normotensive patients with acute PE. However, when interpreted in combination with clinical and imaging findings, they may improve the identification of an elevated PE-related risk and the further prognostic stratification of such patients. At the other end of the severity spectrum, high-sensitivity troponin assays possess a high negative predictive value in the setting of acute PE***(Lankeit et al., 2010).***

Heart-type fatty acid-binding protein (H-FABP), an early and sensitive marker of myocardial injury, provides prognostic information in acute PE, both in unselected***(Boscheri et al., 2010)*** and normotensive patients***(Dellas et al., 2018)***. In a meta-analysis investigating 1680 patients with PE, H-FABP concentrations ≥6 ng/mL were associated with an adverse short-term outcome and all-cause mortality***(Bajaj et al., 2015)***.

- **Markers of right ventricular dysfunction**

RV pressure overload due to acute PE is associated with increased myocardial stretch, which leads to the release of B-type natriuretic

peptide (BNP) and N-terminal (NT)-proBNP. Thus, the plasma levels of natriuretic peptides reflect the severity of RV dysfunction and hemodynamic compromise in acute PE***(Henzler et al., 2012)***.

Similar to cardiac troponins, elevated BNP or NT-proBNP concentrations possess low specificity and positive predictive value (for early mortality) in normotensive patients with PE***(Kucher et al., 2003)***, but low levels of BNP or NT-proBNP are capable of excluding an unfavorable early clinical outcome, with high sensitivity and a negative predictive value***(Coutance et al., 2011)***. In this regard, an NT-proBNP cut-off value <500 pg/mL was used to select patients for home treatment in a multicenter management study***(Agterof et al., 2010)***. If emphasis is placed on increasing the prognostic specificity for an adverse early outcome, higher cut-off values ≥600 pg/mL might be more appropriate ***(Lankeit et al., 2014).***

- **Other laboratory biomarkers**

Lactate is a marker of imbalance between tissue oxygen supply and demand, and consequently of severe PE with overt or imminent hemodynamic compromise. Elevated arterial plasma levels ≥2 mmol/L predict PE-related complications, both in unselected***(Vanni et al., 2013)*** and in initially normotensive PE patients***(Vanni et al., 2017)***.

Elevated serum creatinine levels and a decreased (calculated) glomerular filtration rate are related to 30-day all-cause mortality in acute PE ***(Kostrubiec et al., 2019).*** Elevated neutrophil gelatinase-associated lipocalin and cystatin C, both indicating acute kidney injury, are also of prognostic value ***(Kostrubiec et al., 2012).***

A recent meta-analysis investigating patients with acute PE found that hyponatremia predicted in-hospital mortality ***(Zhou et al., 2017).***

Vasopressin is released upon endogenous stress, hypotension, and low CO. Its surrogate marker, copeptin, has been reported to be useful for risk stratification of patients with acute PE ***(Vuilleumier et al., 2016).*** In a single-center derivation study investigating 268 normotensive PE patients, copeptin levels ≥24 pmol/L were associated with a 5.4-fold increased risk of an adverse outcome (***Hellenkamp et al., 2015).***

4)Integration of aggravating conditions and comorbidity into risk assessment of acute pulmonary embolism:

In addition to the clinical, imaging, and laboratory findings, which are directly linked to PE severity and PE-related early death, baseline parameters related to aggravating conditions and comorbidity are necessary to assess a patient's overall mortality risk and early outcome. Of the clinical scores integrating PE severity and comorbidity, the Pulmonary Embolism Severity Index (PESI) **(*Table 6*)** is the one that has been most extensively validated to date (***Donzé et al., 2008).*** The principal strength of the PESI lies in the reliable identification of patients at low risk for 30-day mortality (PESI classes I and II). One randomized trial employed a low PESI as the principal inclusion criterion for home treatment of acute PE (***Aujesky et al., 2011).***

In view of the complexity of the original PESI, which includes 11 differently weighed variables, a simplified version (sPESI) has been developed and validated (***Righini et al., 2011).*** As with the original version of the PESI, the strength of the sPESI lies in the reliable identification of patients at low risk for 30 day mortality. The prognostic performance of the sPESI has been confirmed in observational cohort studies, although this index has not yet been prospectively used to guide therapeutic management of low-risk PE patients (***Elias et al., 2016).***

Table 6: Original and simplified Pulmonary Embolism Severity Index.

Parameter	Original version***(Aujesky et al., 2005)***.	Simplified version***(Jiménez et al., 2010)***.
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	---
Cancer	+30 points	1 point
Chronic heart failure	+10 points	---
Chronic pulmonary disease	+10 points	1 point
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 oxy-hemoglobin saturation <90%	+20 points	1 point
Risk stratification		
	• **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%
	• **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%

5) Prognostic assessment strategy:

The classification of PE severity and the risk of early (in-hospital or 30 day) death is summarized in *Table* 7. Risk assessment of acute PE begins upon suspicion of the disease and initiation of the diagnostic workup. At this early stage, it is critical to identify patients with (suspected) high-risk PE. This clinical setting necessitates an emergency diagnostic algorithm **(Figure 3,4)** and immediate referral for reperfusion treatment. Testing for laboratory biomarkers such as cardiac troponins or natriuretic peptides is not necessary for immediate therapeutic decisions in patients with high-risk PE. In the absence of hemodynamic instability at presentation, further risk stratification of PE is recommended, as it has implications for early discharge vs. hospitalization or monitoring of the patient. **(Table 7)** provides an overview of the clinical, imaging, and laboratory parameters used to distinguish intermediate- and low-risk PE. The PESI is—in its original or simplified form—the most extensively validated and most broadly used clinical score to date, as it integrates baseline indicators of the severity of the acute PE episode with aggravating conditions and the comorbidity of the patient. Overall, a PESI of class I–II or an sPESI of 0 is a reliable predictor of low-risk PE ***(Konstantinides et al., 2020).***

In addition to clinical parameters, patients in the intermediate-risk group who display evidence of both RV dysfunction (on echocardiography or CTPA) and elevated cardiac biomarker levels in the circulation (particularly a positive cardiac troponin test) are classified into the intermediate–high-risk category. close monitoring is recommended in these cases to permit the early detection of hemodynamic decompensation or collapse, and consequently the need for rescue

reperfusion therapy***(Meyer et al., 2014).*** Patients in whom the RV appears normal on echocardiography or CTPA, and/or who have normal cardiac biomarker levels, belong to the intermediate–low-risk category. As an alternative approach, use of further prognostic scores combining clinical, imaging, and laboratory parameters may be considered to semi-quantitatively assess the severity of the PE episode, and distinguish intermediate–high-risk and intermediate–low-risk PE***(Konstantinides et al., 2020).***

Table 7: Classification of pulmonary embolism severity and the risk of early (in-hospital or 30 day) death.

	Indicators of risk			
Early mortality risk	Hemodynamic instability	Clinical parameters of PE severity and/or comorbidity: PESI class III-V or sPESI ≥1	RV dysfunction on TTE or CTPA	Elevated cardiac troponin levels
High	+	+	+	+
Intermediate-high	-	+	+	+
Intermediate-low	-	+	One (or more) positive	
Low	-	-	-	Assessment optional; if assessed, negative

(Konstantinides et al., 2020)

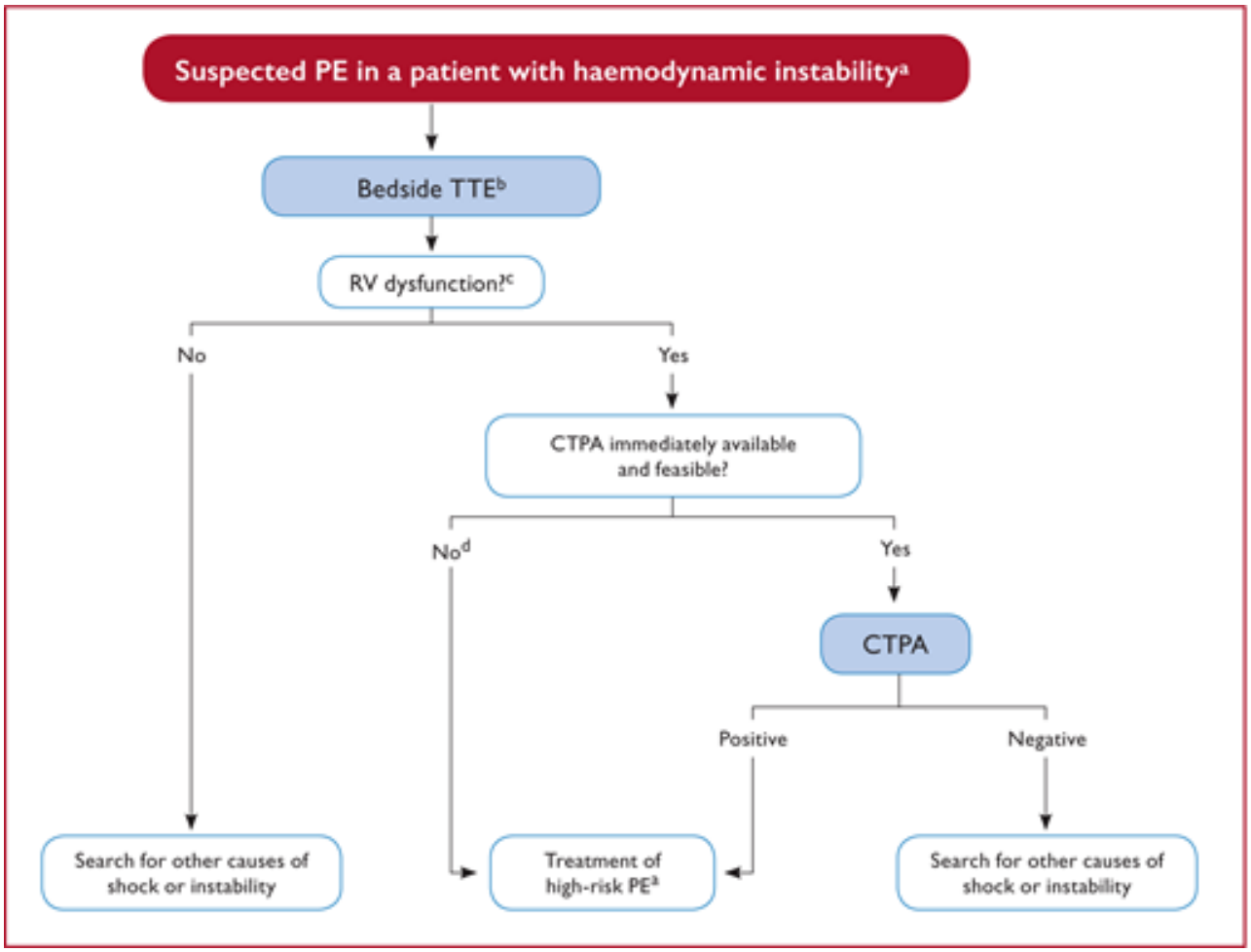

Figure (3): Diagnostic algorithm for patients with suspected high-risk pulmonary embolism presenting with hemodynamic instability.

(Konstantinides et al., 2020).

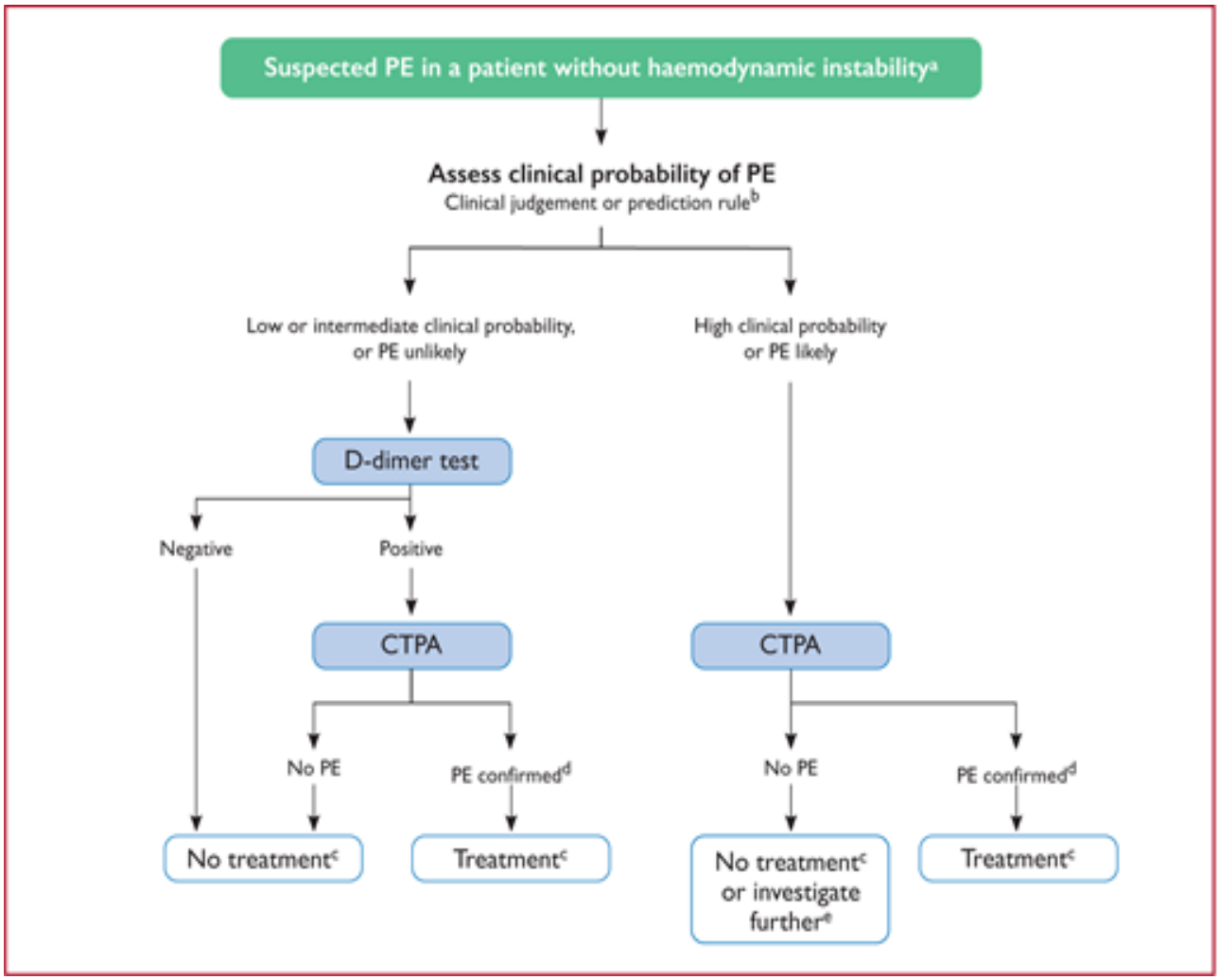

Figure (4): Diagnostic algorithm for patients with suspected pulmonary embolism without hemodynamic instability.

(Konstantinides et al., 2020).

Treatment:

1)Hemodynamic and respiratory support:

- **Oxygen therapy and ventilation:**

Hypoxemia is one of the features of severe PE, and is mostly due to the mismatch between ventilation and perfusion. Administration of

supplemental oxygen is indicated in patients with PE and SaO_2 <90%. Severe hypoxemia/respiratory failure that is refractory to conventional oxygen supplementation could be explained by right-to-left shunt through a patent foramen ovale or atrial septal defect***(Konstantinides et al., 1998).*** Further oxygenation techniques should also be considered, including high-flow oxygen (i.e. a high-flow nasal cannula) and mechanical ventilation (non-invasive or invasive) in cases of extreme instability (i.e. cardiac arrest), taking into consideration that correction of hypoxemia will not be possible without simultaneous pulmonary reperfusion***(Messika et al., 2017).***

Patients with RV failure are frequently hypotensive or are highly susceptible to the development of severe hypotension during induction of anesthesia, intubation, and positive-pressure ventilation. Consequently, intubation should be performed only if the patient is unable to tolerate or cope with non-invasive ventilation. When feasible, non-invasive ventilation or oxygenation through a high-flow nasal cannula should be preferred; if mechanical ventilation is used, care should be taken to limit its adverse hemodynamic effects. In particular, positive intrathoracic pressure induced by mechanical ventilation may reduce venous return and worsen low CO due to RV failure in patients with high-risk PE; therefore, positive end-expiratory pressure should be applied with caution***(Konstantinides et al., 2020)***

- **Pharmacological treatment of acute right ventricular failure:**

An overview of the current treatment options for acute RV failure is provided in **(Table 8).**

Table 8: Treatment of right ventricular failure in acute high-risk pulmonary embolism.

Strategy	Properties and use	Caveats
Volume optimization		
Cautious volume loading, saline, or Ringer's lactate, ≤500 mL over 15–30 min.	Consider in patients with normal–low central venous pressure (due, for example, to concomitant hypovolemia).	Volume loading can over-distend the RV, worsen ventricular interdependence, and reduce CO.
Vasopressors &inotropes		
Norepinephrine, 0.2–1.0 µg/kg/min.	Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient.	Excessive vasoconstriction may worsen tissue perfusion.
Dobutamine, 2–20 µg/kg/min.	Increases RV inotropy, lowers filling pressures.	May aggravate arterial hypotension if used alone, without a vasopressor; may trigger or aggravate arrhythmias.
Mechanical circulatory support		
Veno–arterial ECMO/extracorporeal life support.	Rapid short-term support combined with oxygenator.	Complications with use over longer periods (>5–10 days), including bleeding and infections; no clinical benefit unless combined with surgical embolectomy; requires an experienced team.

(Konstantinides et al., 2020)

If the central venous pressure is low, modest (≤500 mL) fluid challenge can be used as it may increase the cardiac index in patients with acute PE***(Mercat et al., 1999).***However, volume loading has the potential to over-distend the RV and ultimately cause a reduction in systemic CO***(Green & Givertz 2012).*** Experimental studies suggest that aggressive

volume expansion is of no benefit and may even worsen RV function***(Ghignone, Girling & Prewitt 1984).***Cautious volume loading may be appropriate if low arterial pressure is combined with an absence of elevated filling pressures. Assessment of central venous pressure by ultrasound imaging of the IVC (a small and/or collapsible IVC in the setting of acute high-risk PE indicates low volume status) or, alternatively, by central venous pressure monitoring may help guide volume loading. If signs of elevated central venous pressure are observed, further volume loading should be withheld***(Konstantinides et al., 2020).***

Use of vasopressors is often necessary, in parallel with (or while waiting for) pharmacological, surgical, or interventional reperfusion treatment. Norepinephrine can improve systemic hemodynamics by bringing about an improvement in ventricular systolic interaction and coronary perfusion, without causing a change in PVR***(Ghignone, Girling & Prewitt 1984).*** Its use should be limited to patients in cardiogenic shock. Based on the results of a small series, the use of dobutamine may be considered for patients with PE, a low cardiac index, and normal BP; however, raising the cardiac index may aggravate the ventilation/perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels***(Manier&Castaing 2012).***Although experimental data suggest that levosimendan may restore RV–pulmonary arterial coupling in acute PE by combining pulmonary vasodilation with an increase in RV contractility, no evidence of clinical benefit is available***(Kerbaul et al., 2007).***

Vasodilators decrease PAP and PVR, but may worsen hypotension and systemic hypoperfusion due to their lack of specificity for the pulmonary vasculature after systemic [intravenous (i.v.)] administration. Although small clinical studies have suggested that inhalation of nitric

oxide may improve the hemodynamic status and gas exchange of patients with PE***(Summerfield et al., 2012),*** no evidence for its clinical efficacy or safety is available to date***(Bhat et al., 2015).***

- **Mechanical circulatory support and oxygenation:**

The temporary use of mechanical cardiopulmonary support, mostly with veno–arterial extracorporeal membrane oxygenation (ECMO), may be helpful in patients with high-risk PE, and circulatory collapse or cardiac arrest. Survival of critically ill patients has been described in a number of case series***(Meneveau et al., 2018),*** but no RCTs testing the efficacy and safety of these devices in the setting of high-risk PE have been conducted to date. Use of ECMO is associated with a high incidence of complications, even when used for short periods, and the results depend on the experience of the center as well as patient selection. The increased risk of bleeding related to the need for vascular access should be considered, particularly in patients undergoing thrombolysis. At present, the use of ECMO as a stand-alone technique with anticoagulation is controversial and additional therapies, such as surgical embolectomy, have to be considered***(Meneveau et al., 2018).***

A few cases suggesting good outcomes with use of the Impella® catheter in patients in shock caused by acute PE have been reported***(Shokr et al., 2018).***

- **Advanced life support in cardiac arrest:**

Acute PE is part of the differential diagnosis of cardiac arrest with non-shockable rhythm against a background of pulseless electrical activity. In cardiac arrest presumably caused by acute PE, current guidelines for advanced life support should be followed***(Perkins et al.,***

2018). The decision to treat for acute PE must be taken early, when a good outcome is still possible. Thrombolytic therapy should be considered; once a thrombolytic drug is administered, cardiopulmonary resuscitation should be continued for at least 60–90 min before terminating resuscitation attempts***(Truhlář et al., 2015).***

3) Anticoagulation:

- **Parenteral anticoagulation:**

In patients with high or intermediate clinical probability of PE, anticoagulation should be initiated while awaiting the results of diagnostic tests. This is usually done with subcutaneous, weight-adjusted low-molecular weight heparin (LMWH) or fondaparinux, or i.v. unfractionated heparin (UFH) ***(Konstantinides et al., 2020).***

LMWH and fondaparinux are preferred over UFH for initial anticoagulation in PE, as they carry a lower risk of inducing major bleeding and heparin-induced thrombocytopenia***(Stein et al., 2009).*** Neither LMWH nor fondaparinux need routine monitoring of anti-Xa levels. Use of UFH is nowadays largely restricted to patients with overt hemodynamic instability or imminent hemodynamic decompensation in whom primary reperfusion treatment will be necessary. UFH is also recommended for patients with serious renal impairment [creatinine clearance (CrCl) ≤30 mL/min] or severe obesity. If LMWH is prescribed in patients with CrCl 15 − 30 mL/min, an adapted dosing scheme should be used. The dosing of UFH is adjusted based on the activated partial thromboplastin time***(Konstantinides et al., 2020).***

- **Non-vitamin K antagonist oral anticoagulants:**

NOACs are small molecules that directly inhibit one activated

coagulation factor, which is thrombin for dabigatran and factor Xa for apixaban, edoxaban, and rivaroxaban. Owing to their predictable bioavailability and pharmacokinetics, NOACs can be given at fixed doses without routine laboratory monitoring. Compared with vitamin K antagonists (VKAs), there are fewer interactions when NOACs are given concomitantly with other drugs***(Steffel et al., 2018).*** In the phase III VTE trials, the dosages of dabigatran, rivaroxaban, and apixaban were not reduced in patients with mild–moderate renal dysfunction (CrCl between 30–60 mL/min), whereas edoxaban was given at a 30 mg dose in these patients. Patients with CrCl <25 mL/min were excluded from the trials testing apixaban, whereas patients with CrCl <30 mL/min were excluded from those investigating rivaroxaban, edoxaban, and dabigatran***(Konstantinides et al., 2020).***

Phase III trials on the treatment of acute VTE as well as those on extended treatment beyond the first 6 months, demonstrated the non-inferiority of NOACs compared with the combination of LMWH with VKA for the prevention of symptomatic or lethal VTE recurrence, along with significantly reduced rates of major bleeding***(van Es et al., 2014).***

Compared with VKA-treated patients, critical site major bleeding occurred less frequently in NOAC-treated patients; in particular, there was a significant reduction in intracranial bleeding and in fatal bleeding with NOACs compare with VKAs***(Van der Hulle et al., 2014)***

- **Vitamin K antagonist oral anticoagulants:**

VKAs have been the gold standard in oral anticoagulation for more than 50 years. When VKAs are used, anticoagulation with UFH, LMWH, or fondaparinux should be continued in parallel with the oral anticoagulant for ≥5 days and until the international normalized ratio

(INR) value has been 2.0–3.0 for 2 consecutive days. Warfarin may be started at a dose of 10 mg in younger (e.g. aged <60 years) otherwise healthy patients and at a dose ≤5 mg in older patients***(Witt et al., 2016).*** The daily dose is adjusted according to the INR over the next 5–7 days, aiming for an INR level of 2.0–3.0. Pharmacogenetic testing may increase the precision of warfarin dosing***(Carlquist et al., 2011).*** When used in addition to clinical parameters, pharmacogenetic testing improves anticoagulation control and may be associated with a reduced risk of bleeding, but does not reduce the risk of thromboembolic events or mortality***(Kheiri et al., 2018).***

In patients who are selected and appropriately trained, self-monitoring of VKA is associated with fewer thrombo-embolic events and increased time in the therapeutic range compared with usual care***(Sharma et al., 2015).***

4) Reperfusion treatment:

• Systemic thrombolysis

Thrombolytic therapy leads to faster improvements in pulmonary obstruction, PAP, and PVR in patients with PE, compared with UFH alone; these improvements are accompanied by a reduction in RV dilation on echocardiography***(Kline et al., 2014).*** The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6–14 days***(Daniels et al., 1997).*** Unsuccessful thrombolysis, as judged by persistent clinical instability and unchanged RV dysfunction on echocardiography after 36 h, has been reported in 8% of high-risk PE patients***(Meneveauet al., 2006).***

A meta-analysis of thrombolysis trials that included (but were not confined to) patients with high-risk PE, defined mainly as the presence of cardiogenic shock, indicated a significant reduction in the combined outcome of mortality and recurrent PE. This was achieved with a 9.9% rate of severe bleeding and a 1.7% rate of intracranial hemorrhage***(Marti al., 2015).***

In normotensive patients with intermediate-risk PE, defined as the presence of RV dysfunction and elevated troponin levels, the impact of thrombolytic treatment was investigated in the Pulmonary Embolism Thrombolysis (PEITHO) trial***(Meyer al., 2014).*** Thrombolytic therapy was associated with a significant reduction in the risk of hemodynamic decompensation or collapse, but this was paralleled by an increased risk of severe extracranial and intracranial bleeding***(Meyer al., 2014).*** In the PEITHO trial, 30 day death rates were low in both treatment groups, although meta-analyses have suggested a reduction in PE-related and overall mortality of as much as 50–60% following thrombolytic treatment in the intermediate-risk category***(Chatterjee al., 2014).***

The approved regimens and doses of thrombolytic agents for PE, as well as the contraindications to this type of treatment, are shown in **(Table 9)**. Accelerated i.v. administration of recombinant tissue-type plasminogen activator (rtPA; 100 mg over 2 h) is preferable to prolonged infusions of first-generation thrombolytic agents (streptokinase and urokinase). UFH may be administered during continuous infusion of alteplase, but should be discontinued during infusion of streptokinase or urokinase***(Konstantinides et al., 2014).*** Reteplase***(Tebbe et al., 1999),*** desmoteplase***(Tebbe et al., 2009), ,***or tenecteplase***(Kline et al., 2014).*** have also been investigated; at present, none of these agents are approved for use in acute PE.

It remains unclear whether early thrombolysis for (intermediate- or high-risk) acute PE has an impact on clinical symptoms, functional limitation, or CTEPH at long-term follow-up. A small randomized trial of 83 patients suggested that thrombolysis might improve functional capacity at 3 months compared with anticoagulation alone***(Kline et al., 2014).***

Table 9: Thrombolytic regimens, doses, and contraindications.

Molecule	Regimen	Contraindications to fibrinolysis
RtPA	100 mg over 2 h. Accelerated regimen: 0.6 mg/kg over 15 min (maximum dose 50 mg).	• **Absolute** • History of hemorrhagic stroke or stroke of unknown origin • Ischemic 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 ischemic attack in previous 6 months • Oral anticoagulation • Pregnancy or first post-partum week • Non-compressible puncture sites • Traumatic resuscitation • Refractory hypertension (BP >180 mmHg) • Advanced liver disease • Infective endocarditis • Active peptic ulcer
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 over 2 h.	

(Konstantinides et al., 2020).

- **Percutaneous catheter directed treatment:**

Mechanical reperfusion is based on the insertion of a catheter into the pulmonary arteries via the femoral route. Different types of catheters are used for mechanical fragmentation, thrombus aspiration, or more commonly a pharmaco-mechanical approach combining mechanical or ultrasound fragmentation of the thrombus with *in situ* reduced-dose thrombolysis***(Konstantinides et al., 2020).***

Most knowledge about catheter-based embolectomy is derived from registries and pooled results from case series***(Kaymaz et al., 2018).*** The overall procedural success rates (defined as hemodynamic stabilization, correction of hypoxia, and survival to hospital discharge) of percutaneous catheter-based therapies reported in these studies have reached 87%***(Bajaj et al., 2016).*** however, these results may be subject to publication bias. One RCT compared conventional heparin-based treatment and a catheter-based therapy combining ultrasound-based clot fragmentation with low-dose *in situ* thrombolysis in 59 patients with intermediate-risk PE. In that study, ultrasound-assisted thrombolysis was associated with a larger decrease in the RV/LV diameter ratio at 24 h, without an increased risk of bleeding***(Kucheret al., 2014).*** Data from two prospective cohort studies***(Tapson al., 2018)***and a registry***(Kuo al., 2015),*** with a total of 352 patients, support the improvement in RV function, lung perfusion, and PAP in patients with intermediate- or high-risk PE using this technique. Intracranial hemorrhage was rare, although the rate of Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) severe and moderate bleeding complications was 10% in one of these cohorts***(Piazza al., 2015).***

- **Surgical embolectomy:**

Surgical embolectomy in acute PE is usually carried out with cardiopulmonary bypass, without aortic cross-clamping and cardioplegic cardiac arrest, followed by incision of the two main pulmonary arteries with the removal or suction of fresh clots. Recent reports have indicated favorable surgical results in high-risk PE, with or without cardiac arrest, and in selected cases of intermediate-risk PE***(Pasrija al., 2018).***Among 174 322 patients hospitalized between 1999 and 2013 with a diagnosis of PE in New York state, survival and recurrence rates were compared between patients who underwent thrombolysis (n = 1854) or surgical embolectomy (n = 257) as first-line therapy***(Lee al., 2018).***

Overall, there was no difference between the two types of reperfusion treatment regarding 30-day mortality (15 and 13%, respectively), but thrombolysis was associated with a higher risk of stroke and re-intervention at 30 days. No difference was found in terms of 5-year actuarial survival, but thrombolytic therapy was associated with a higher rate of recurrent PE requiring readmission compared with surgery (7.9 vs. 2.8%) ***(Konstantinides et al., 2020).***

Recent experience appears to support combining ECMO with surgical embolectomy, particularly in patients with high-risk PE with or without the need for cardiopulmonary resuscitation ***(Meneveau et al., 2018).***

5) Vena cava filters:

The aim of vena cava interruption is to mechanically prevent venous clots from reaching the pulmonary circulation. Most devices in current use are inserted percutaneously and can be retrieved after several weeks

or months, or left in place over the long-term, if needed. Potential indications include VTE and absolute contraindication to anticoagulant treatment, recurrent PE despite adequate anticoagulation, and primary prophylaxis in patients with a high risk of VTE. Other potential indications for filter placement, including free-floating thrombi, have not been confirmed in patients without contraindications to therapeutic anticoagulation***(Konstantinides et al., 2020).***

A systematic review and meta-analysis of published reports on the efficacy and safety of vena cava filters included 11 studies, with a total of 2055 patients who received a filter vs. 2149 controls. Vena cava filter placement was associated with a 50% decrease in the incidence of PE and an ~70% increase in the risk of DVT over time. Neither all-cause mortality nor PE-related mortality differed between patients with or without filter placement***(Bikdelis et al., 2017).***

Complications associated with vena cava filters are common and can be serious. A Lethal complications were rare, but 5% of the patients required major interventions such as surgical removal of the filter, endovascular stent placement or embolization, endovascular retrieval of the permanent filter***(Jia et al., 2015).***Further reported complications include filter fracture and/or embolization, and DVT occasionally extending up to the vena cava***(Angel et al., 2011).***