Chapter 9
Pulmonary Embolism in the ER

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9.1 Scope of the Problem

Pulmonary embolism (PE) is the third cause of cardiovascular mortality after myocardial infarction and stroke, the leading cause of pregnancy-related maternal death in developed countries and the second cause of mortality in cancer patients [1]. PE is the third most common cause of death in patients surviving the first 24 h after traumatic injury [2]. Unfortunately, PE diagnosis can be a challenge due to a broad clinical presentation. The significant morbidity and mortality associated with this condition warrants prompt and accurate diagnosis evaluation and optimal treatment. The right ventricular function and the clinical condition drive the risk stratification, treatment, and in-hospital prognosis [3].

9.2 Prevalence

The epidemiology of PE is uncertain because it may remain asymptomatic, or its diagnosis may be an incidental finding. Among 900,000 annual venous thromboembolism (VTE) events occurring in the United States, it is estimated that more than 250,000 are diagnosed with PE in the emergency room (ER) [4]. The incidence of VTE rises sharply after age 60 for both, male and female, and PE accounts for most of this increase [5]. Of the lethal cases, 34% presented with sudden fatal PE, and 59% were deaths resulting from PE that remained undiagnosed during life [6]. The growing epidemic of obesity is another important contributor to the increasing incidence of PE.

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9.3 Thrombosis Mechanisms

Venous thrombosis is included among thrombosis models of low-pressure segment circulation. Currently, multiple clinical and molecular lines of evidence suggest a close link between the coagulation system, inflammation, and immunothrombosis [1]. Current evidence establishes a relationship among atherothrombotic risk factors, venous thrombosis, and inflammation as a trigger of thrombosis events [1] (Table 9.1).

9.4 High-Clinical Suspicion in the ER

The relevance of categorizing a patient in a high-clinical suspicion level attempt to accurate testing and is based on at least one transitory or permanent risk factors (Table 9.2), clinical findings, and expertise (Fig. 9.1) (Table 9.3).

Table 9.1 Mechanisms of venous thrombosis

Initiation	The process of coagulation starts on intravascular tissue factor (ITF)-exposing cells and on the surface of activated platelets. In the beginning, ITF-exposing cells and microparticles are exposed to coagulation factors in the vessels lumen. Platelets activated by vascular injury are recruited and adhere to the site of injury. The ITF/FVIIa complex activates coagulation factors IX to IXa and X to Xa, generating trace amounts of thrombin
Amplification	The small amount of thrombin acts as a signal for further platelet activation and aggregation. On the surface of platelets, thrombin activates FV, FVIII, and FXI
Propagation	FVIIIa forms a complex with FIXa (Xase), and FVa forms a complex with FXa (prothrombinase) on the platelet surface, accelerating the generation of FXa and thrombin, respectively. When FXa is associated with FVa, it is protected from ITF pathway inhibitor and antithrombin. In the propagation phase, a burst of thrombin is generated, which is sufficient for the clotting of soluble fibrinogen into a fibrin meshwork.
Inflammation	Interleukin-6 induces the expression of intravascular tissue factor, fibrinogen, factor VIII, and von Willebrand factor. Interleukins-6 and -8 enhancements of cytokine and chemokine levels inducing endothelial activation, endothelial cell damage, increased platelet aggregation, increased sensitivity to thrombin, and recruitment and activation of leukocytes at the vascular wall. An increased interleukin-6 level lowers the concentration of antithrombin, protein S, and thrombomodulin
Immunothrombosis	Includes innate immune mechanisms, the neutrophil extracellular genetic traps (NETs), and the immunothrombosis dysregulation. The relationship among pathogen-associated molecular patterns or damage-associated molecular patterns, monocytes, and their microvesicles express and deliver activated intravascular tissue factor to sites of pathogen exposure, which initiates the extrinsic pathway of coagulation

Transitory risk factors separate provoked from unprovoked PE. The risk of PE increases in patients older than 40 years, with double risk each subsequent decade [6]. Atherosclerotic risk factors are frequently present in unprovoked PE outpatients. Possibly, chronic or acute infections triggering immunothrombosis and inflammation are the main mechanisms in unprovoked PE older outpatients [1].

9.5 Clinical Presentation

PE presents with rapid onset and ensuing precipitous decline. The capital symptom is dyspnea at rest or induced by exertion. Clinical and physical findings are highly variable, often depending on the presence of burden thrombus, pulmonary hypertension, right ventricular dysfunction (RVD), and previous cardiopulmonary state (Table 9.3). Transitory dyspnea or tachycardia is often the clinical expression in segmental or subsegmental PE patients. In some cases, near syncope or syncope is the

Table 9.2 Major risk factors for pulmonary embolism [1, 6, 7]

Odds ratios	Molecular bases
Odds ratios >10 Fracture of lower limb (previous 3 months) Hip or knee replacement Major trauma Myocardial infarction (within previous 3 months) Previous venous thromboembolism Spinal cord injury	*Inflammation* Smoking, obesity, dysglycemia, diabetes mellitus, metabolic syndrome, dyslipidemia, ischemic heart disease, acute coronary syndromes, stroke, peripheral artery disease, hypertension, COPD, acute or chronic heart failure, respiratory failure, atrial fibrillation, connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, etc.) renal chronic failure, nephrotic syndrome, Behcet's disease, chemotherapy, active cancer
Odds ratios 2–9 Arthroscopic knee surgery Autoimmune diseases Blood transfusion Central venous lines Chemotherapy Congestive heart or respiratory failure Erythropoiesis-stimulating agents Hormone replacement therapy (depends on formulation) In vitro fertilization Cancer (highest risk in metastatic disease) Oral contraceptive therapy Paralytic stroke Postpartum period Thrombophilia	*Secondary thrombophilia* *Coagulation cascade and platelet activation* Fracture, hip or knee replacement, major or minor surgery, major trauma, spinal cord injury, arthroscopic knee surgery, fracture, hip or knee replacement, major or minor surgery, major trauma, spinal cord injury, arthroscopic knee surgery, and cesarean section

(continued)

Table 9.2 (continued)

Odds ratios	Molecular bases
Odds ratios <2 Bed rest >3 days Diabetes mellitus Hypertension Immobility due to sitting (e.g., prolonged car or air travel) Increasing age Laparoscopic surgery (e.g., cholecystectomy) Obesity Pregnancy Varicose veins	*Molecular thrombophilia* *Acquired* Lupus anticoagulant, antiphospholipid antibody syndrome, hyperhomocysteinemia (less commonly inherited secondary to a mutation in methylenetetrahydrofolate reductase), deficiency of dysfibrinogenemia, myeloproliferative disorders such as polycythemia rubra vera, elevated levels of lipoprotein (a) Hereditary Deficiency of antithrombin III, protein C or protein S, factor V Leiden mutation, prothrombin gene mutation, primary thrombocytopenia, hypercoagulability syndromes, deficit or abnormalities of plasminogen, dysplasminogenemia, hyperprothrombinemia, deficiency of factor XII, factor VIII increase, deficiency or abnormalities of plasminogen, increase plasminogen activator inhibitor type-1, paroxysmal nocturnal hemoglobinuria
	Miscellaneous mechanisms Hypercoagulable state: age >40 years, aging, pregnancy, postpartum, secondary polycythemia Therapeutic action: hormone replacement and oral contraceptive therapy, pacemaker or implantable cardiac defibrillator leads and indwelling venous catheters Heparin-induce thrombocytopenia
	Triggers *Stasis*: prolonged car or air travel, bed-bound, computer work, or immobility related to the home or nursing home: frail elder, convalescence secondary to chronic heart failure, pulmonary or neurological diseases, cancer, degenerative osteoarthropathy, obesity *Chronic or acute infections*: periodontitis, upper or lower respiratory tract, gastrointestinal, urinary, prostate, etc.

only clinical expression in elderly low-risk or submassive PE [8]. Also, physicians should be in warning in unexplained acute exacerbation of COPD [9], in-hospital patients with community-acquired pneumonia [10], and unexplained worsening of dyspnea in chronic atrial fibrillation patients [11].

Dyspnea plus ischemic-like chest pain, near syncope or syncope, with or without hypotension are highly suggestive of submassive or massive PE. Concomitant neurologic symptoms or signs and/or back or abdominal pain suggest a paradoxical embolism secondary to patent foramen ovale in submassive PE patients. Physicians in charge should be in warning to identify subclinical strokes in the intent to avoid hemorrhagic transformation [12].

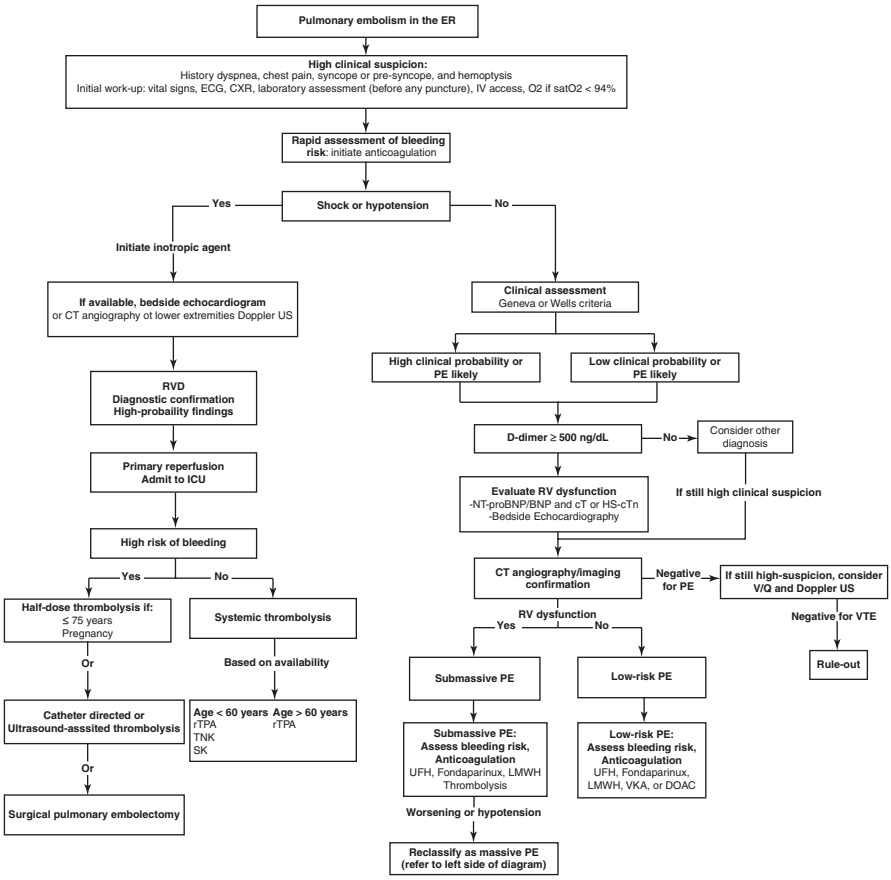

Fig. 9.1 Diagnostic algorithm for low-probability, submassive, and massive PE

Table 9.3 Main clinical characteristics of acute pulmonary embolism

Low risk	Submassive or massive
Persistent or transitory dyspnea at rest or exertion	Dyspnea at rest or exertion
Tachycardia	Ischemic-like chest pain
Tachypnea	Near syncope or syncope
Pleuritic chest pain	Tachycardia
Cough without hemoptysis	Respiratory distress
Dizziness	Hypotension
Near syncope or syncope	Oxygen desaturation
Transitory oxygen desaturation or normal	Cardiogenic shock
Normal blood pressure	Cardiac arrest

9.6 Assessment of Clinical Probability

Despite the limited sensitivity and specificity of individual symptoms, signs, and common tests, the combination of each of these findings, using clinical judgment or prediction rules, allows to classify patients with suspected PE into distinct categories of clinical or pretest probability and severity that correspond to an increasing actual prevalence of confirmed PE [6]. The pretest probability must be assessed based on validated scores, Wells or revised Geneva (Tables 9.4 and 9.5), in patients with high-clinical suspicion of low-risk PE. Both tests are simple and based on information easy to obtain [6].

Table 9.4 Wells rules

Clinical prediction rules	Original version	Simplified version
Previous PE or DVT	1.5	1
Heart rate ≥ 100 b.p.m	1.5	1
Surgery or immobilization last 4 weeks	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely PE	2	1
The clinical probability of PE		
Three-level score		
Low	0–1	NA
Intermediate	2–6	NA
High	≥7	NA
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

PE pulmonary embolism, *DVT* deep venous thrombosis, *BPM* beats per minute, *NA* not available

Table 9.5 Revised Geneva score

Clinical prediction rules	Original version	Simplified version
Previous PE or DVT	3	1
Heart rate	NA	NA
75–94 bpm	3	1
>95 bpm	5	2
Surgery or fracture in the last month	2	1
Hemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower deep venous palpation and unilateral edema	4	1
Age >65 years	1	1
The clinical probability of PE		
Three-level score		
Low	0–3	0–1

Table 9.5 (continued)

Clinical prediction rules	Original version	Simplified version
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE unlikely	0–5	0–2
PE likely	≥6	≥3

PE pulmonary embolism, *BPM* beats per minute, *NA* not applicable

9.7 D-Dimer

This biomarker reflects the coagulation system and endogenous fibrinolysis activation. D-Dimer testing should be considered in the context of clinical probability, in patients with or without clinical stability. D-Dimer is a highly sensitive test (91–97% for enzyme-linked immunofluorescence) to exclude PE (<500 ng/dL) (Fig. 9.1) [6]. A positive D-dimer (>500 ng/dL) may be useful in high-clinically suspected PE as it indicates that venous thrombosis is possible. In the setting of high-clinical suspicion and normal value D-dimer (<500 ng/dL), diagnosis tests are mandatory [6].

D-Dimer has a low to moderate specificity (43–50%) since abnormal values may be found in several clinical conditions such as cancer, trauma, inflammatory disease, and infections [6]. However, D-dimer increased in a lower proportion of community-acquired pneumonia patients and had higher levels associated with PE [10]. D-Dimer must be obtained from the first venous or puncture. We recommended the same cutoff level for the young and elderly population.

9.8 Initial Risk Stratification

A fast-track approach is the cornerstone of the initial workup. The history and physical examination can provide important clues for risk stratification. The Pulmonary Embolism Severity Index (PESI) score and its simplified (sPESI) (Table 9.6) version offer clinicians' similar prognostic accuracy with greater ease. Patients are considered candidates for the outpatient treatment of PE if their PESI score is <85 points or have sPESI 0 points. Considering that several reports have shown sPESI failure, in the setting of submassive PE [13, 14], biomarkers and/or echocardiogram is an important complement before making a decision, especially in those considered to outpatient treatment.

Clinically defining an acute PE will depend if we use the American Heart Association [15] classification or European Society of Cardiology [6] classification. However, in both RVD (Table 9.7), the hemodynamic impact on systemic and pulmonary pressure constitutes the cornerstone of risk stratification.

Pulmonary vascular obstruction >25% is frequently associated with pulmonary arterial hypertension, RVD (Table 9.7), and clinical instability, whereas pulmonary vascular obstruction <25% is often associated with clinical stability and normal right ventricular function [16].

Table 9.6 Pulmonary Embolism Severity Index

PESI score		Simplified PESI score	
Age	Age in years	Age >80 years	1
Male sex	10	History of cancer	1
History of cancer	30	History of cardiopulmonary disease	1
History of heart failure	10	Heart rate >110 bpm	1
History of chronic lung disease	10	SBP <110 mmHg	1
Heart rate >110 bpm	20	Oxygen saturation <90%	1
SBP <100 mmHg	30		
Oxygen saturation <90%	20		
Respiratory rate ≥30/min	20		
Temperature <36 °C	20		
Altered mental status	60		
Class I very low risk ≤65 II low risk 66–85 III intermediate risk 86–105 IV high risk 106–125 V very high risk >125		*Class* Low risk 0 High risk >1	

PESI pulmonary embolism severity index, *BPM* beats per minute, *SBP* systolic blood pressure

Table 9.7 Classifications of pulmonary embolism [6, 15]

American Heart Association	European Society of Cardiology
Massive: clinical instability by sustained hypotension (systolic blood pressure <90 mmHg) for at least 15 min or requiring inotropic support, not due to a cause other than PE and RVD	*High risk*: shock of hypotension, PESI class III–V or sPESI >1, signs of RV dysfunction on an imaging test and cardiac laboratory biomarkers (both positives)
Submassive: clinical stability without systemic hypotension (systolic blood pressure >90 mmHg) but either RVD or myocardial necrosis	*Intermediate* *High risk*: normal blood pressure, PESI class III–V or sPESI ≥1, signs of RV dysfunction on an imaging test and cardiac laboratory biomarkers (both positives)
Low risk: clinical stability, the absence of RVD and normal biomarkers	*Low risk*: normal blood pressure, PESI class III–V or sPESI >1, signs of RV dysfunction on an imaging test and cardiac laboratory biomarkers (either one or none positive)
	Low risk: normal blood pressure, PESI class I–II or sPESI 0, assessment of RV dysfunction and cardiac laboratory biomarkers optional, if assessed both negative

PESI pulmonary embolism severity index, *sPESI* simplified PESI, *PE* pulmonary embolism, *RVD* right ventricular dysfunction, *RV* right ventricle

Table 9.8 Physical examination findings

Low risk	Massive or submassive
Cardiac examination Normal heart sounds Tachycardia	*Cardiac examination* Tachycardia Right ventricular lift Increased P2 Third and fourth heart sound suggesting pulmonary hypertension and right ventricular dysfunction Low P2 it is a confounder and has been related with severe right ventricular dysfunction
Respiratory examination Normal lung sounds	*Respiratory examination* Normal lung sounds
Deep venous system Leg pain Warmth Swelling Homans' sign Ollow' sign	*Deep venous system* Leg pain Warmth Swelling Homans' sign Ollow' sign

9.9 Physical Examination

A careful clinical examination should be performed, with attention being paid to identify clinical stability, pulmonary hypertension, RVD, as well as deep venous thrombosis (Table 9.8). In most of the low-risk patients, the cardiopulmonary examination is normal, and it is possible to identify symptoms and signs of deep venous thrombosis. In addition, normal oxygen saturation is observed in 21% of low-risk PE patients [17].

Listening to an attenuated and low S_2 could be considered as an early sign of severe RVD. Jugular venous distension and cyanosis are infrequent specifically in patients with early onset of symptoms and early arrival to the ER. Cyanosis must be related to severe RVD and cardiogenic shock or another clinical situation (COPD, congenic heart disease) [7]. Normal blood pressure cannot exclude impending clinical instability and in-hospital poor outcome in submassive PE [18]. Deep venous thrombosis complicated with severe edema, warm, swelling, and pain is infrequent in submassive and massive PE patients.

9.10 Work up

9.10.1 Chest X-Ray

The analysis must focus on the pulmonary artery circulation. The study could be normal in low-risk PE (segmental or subsegmental) and, however, always is abnormal in lobar, submassive, and massive PE (Fig. 9.2) (Table 9.9). Main pulmonary

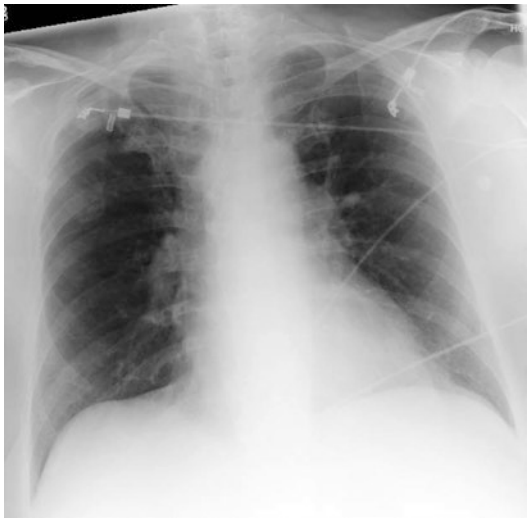

Fig. 9.2 A female patient with submassive pulmonary embolism. Chest X-Ray showing bilateral Westermark sign and right main artery dilatation with cutoff

Table 9.9 Chest X-ray in pulmonary embolism

Findings	Low risk	Submassive	Massive
Normal heart size and pulmonary arterial circulation[a]	✓		
Hampton sign	✓		
Fleischner lines			
Significative or small right or left pleural effusion	✓		
Westermark sign	✓	✓	✓
Left or right or both pulmonary artery cutoff	✓	✓	✓
Left or right or both pulmonary artery dilatation	✓	✓	✓
Main pulmonary artery dilatation		✓	✓
Right ventricular dilatation		✓	✓
Elevated right diaphragm		✓	✓

[a]Segmental or subsegmental thrombus

artery dilatation and right ventricular dilatation is infrequent, mainly in those who early arrival after onset symptoms. Bedside chest X-ray is a challenge to identify classic signs in clinical instability PE patients, however, allows to excluding other clinical situations mimicking PE (acute pulmonary edema, COPD exacerbation, cardiac tamponade, extensive pneumothorax, etc.)

9.10.2 Right Ventricular Dysfunction Multimodal Risk Stratification

We suggest a multimodal approach to identify RVD (Fig. 9.1) through clinical findings, ECG, biomarkers, and echocardiogram at the time of screening (Table 9.10).

The best stratification approach will be depending on experience, expertise, and available technology in each center.

9.10.3 Electrocardiogram

In the stratification approach, this accessible tool provides important findings to identify severe right ventricular pressure overload, ischemia, or infarction (Table 9.11). A normal electrocardiogram (ECG) is unlikely in submassive or massive PE. ECG is not a test to rule out PE. However, it is helpful in predicting

Table 9.10 Biomarkers of right ventricle dysfunction

Modality	Findings
Clinical	Dyspnea plus ischemic-like chest pain or near syncope or syncope, transitory or sustained hypotension, increased P2, third and fourth right heart sound, oxygen saturation <90%
ECG	Right axis deviation, S1Q3T3, aVR ST elevation, V1 qR and ST elevation, anteroseptal ST elevation or depression or anteroseptal T-wave inversion, new complete or incomplete right bundle-branch block, new-onset atrial fibrillation or flutter
Biomarkers	Elevation of BNP >100 pg/mL or elevation of N-terminal pro-BNP >300 pg/mL and elevation of high-sensitive troponin assays with a coefficient of variance of <10% at the 99th percentile value
Echocardiography	RV dilation (apical four-chamber RV diameter divided by LV diameter >0.9) RV systolic dysfunction RV dilation (four-chamber RV diameter divided by LV diameter >0.9), RV hypokinesis
CT scan	RV dilatation, RV/LV dimension ratios, ventricular and atrial septum shifting to the left side

BNP B-type natriuretic peptide, *RV* right ventricle, *LV* left ventricle

Table 9.11 Electrocardiogram in pulmonary embolism

Findings	Low risk	Submassive	Massive
Normal	✓		
ST unspecific changes	✓		
Normal axis	✓		
QRS axis deviation >90° or indeterminate axis		✓	✓
S1Q3T3		✓	✓
Q wave and T inversion (III and aVF) but not in II		✓	✓
aVR ST elevation		✓	✓
V1 qR and ST elevation		✓	✓
ST elevation inferior or anteroseptal		✓	✓
ST depression inferior or anteroseptal		✓	✓
V1 to V4 anteroseptal T-wave inversion		✓	✓
Complete or incomplete right bundle-branch block		✓	✓
Atrial fibrillation or flutter		✓	✓
Low-voltage in the limbs leads			✓

Table 9.12 Electrocardiogram related to in-hospital adverse events

Outcomes	ECG findings	OR	95% CI	p-value
In-hospital mortality	qR in V1	4.72	2.54–8.78	<0.001
	ST elevation in V1	4.27	2.73–6.66	<0.001
	Right ventricular strain	4.13	1.22–14.0	0.023
	Complete right bundle-branch block	3.90	2.46–6.29	<0.001
	S1Q3T3	3.38	2.46–4–66	<0.001
	QRS axis deviation >90°	3.24	1.86–5.64	<0.001
	ST elevation in DIII	3.08	1.65–5.81	<0.001
	ST depression in V1–V6	2.50	1.43–4.36	
Adjusted in-hospital mortality	Advanced right bundle-branch block	5.790	2.47–13.6	<0.001
30 days mortality	T peak – Tend interval	12.9	3.05–54.7	0.001
	RV transmural ischemic pattern	4.22	1.14–15.6	0.031
	RV subendocardial ischemia plus RV transmural ischemia	4.02	1.13–14.3	0.032
	ST elevation in V1	3.23	1.71–6.11	<0.001
	ST depression DI and DIII or V4–V6	2.52	1.30–4.90	0.006
	Atrial fibrillation	2.47	1.18–5.17	0.01
	St elevation DI and DIII or V4–V6	2.03	1.06–3.90	0.03
	Negative T waves	6.1	1.3–29.1	NR

ECG electrocardiogram, *OR* odds ratio, *CI* confidence interval, *RV*, right ventricle

adverse clinical outcomes in confirmed PE (Table 9.12) [19]. Although tachycardia is a classical electrocardiogram finding, bradycardia could be identified in patients with primary or secondary conduction system disease [20]. The dynamic ST abnormalities on ECG mimicking an acute coronary syndrome (Fig. 9.3).

9.10.4 Transthoracic and Transesophageal Echocardiogram

In the setting of clinical instability, transthoracic echocardiography (TTE) can be performed to establish or excluded rapidly bedside RVD (Figs. 9.4 and 9.5). In addition, excluded alternative diagnosis mimicking PE as acute myocardial infarction, aortic dissection, pericardial tamponade, etc. In those with poor acoustic window, transesophageal echocardiography (TEE) allows a better right ventricular examination, and eventually thrombus in the main pulmonary artery, and proximal branches can be found. Table 9.13 shows the echocardiographic findings in the broad clinical spectrum of PE.

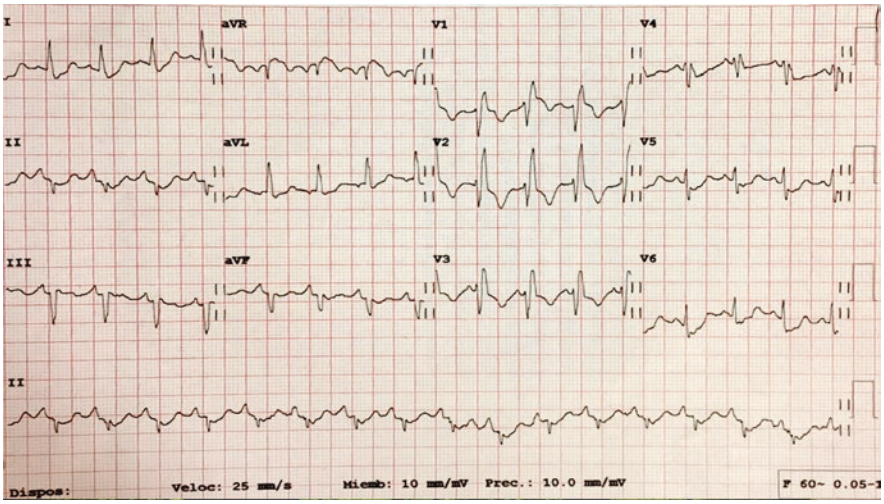

Fig. 9.3 A female patient with massive PE. ECG showing QRS axis deviation <30°, aVR ST elevation, incomplete right bundle-branch block, and V1 ST elevation, as well as ST depression

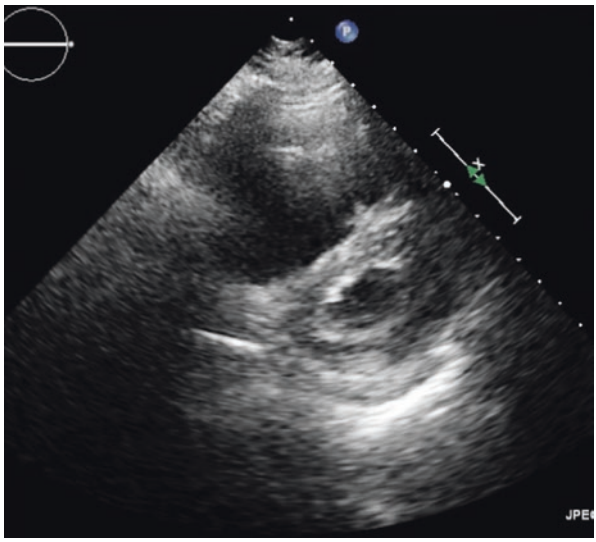

Fig. 9.4 A female patient with massive PE. Transthoracic echocardiogram showing right ventricular dilatation

TTE has more sensitivity to identify patent foramen ovale in submassive PE patients [12]. TTE/TEE findings plus clinical and plasmatic measurement biomarkers of RVD are enough to start thrombolysis in severe massive PE. Systolic pulmonary artery pressure >60 mmHg suggests chronic pulmonary hypertension.

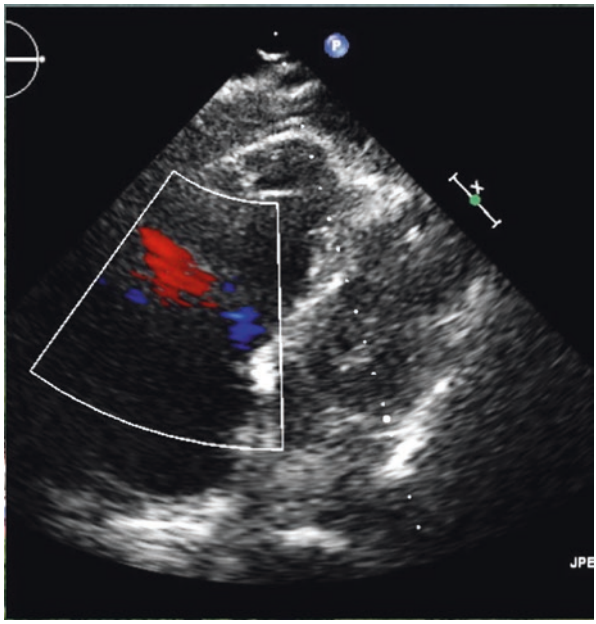

Fig. 9.5 A female patient with massive PE. Transthoracic echocardiogram showing right ventricular dilatation and McConnell's sign

Table 9.13 Echocardiographic findings in pulmonary embolism

Qualitative evaluation	**Low risk**	**Submassive**	**Massive**
Normal right ventricle	✓		
Right ventricular wall	5 mm	5 mm	5 mm
Paradoxical interventricular systolic septum motion		✓	✓
Flattened interventricular septum		✓	✓
Right atrium dilatation		✓	✓
Right ventricular dilatation		✓	✓
Four-apical chamber view RV/LV change ratio	<1:1	2:1	>2:1
Regional right ventricular hypokinesis		✓	✓
McConnell's sign		✓	✓
Patent foramen oval		✓	✓
Thrombus in-transit		✓	✓
Global right ventricular hypokinesis			✓
Quantitative evaluation			
RV/LV end-diastolic dimension ratio		✓	✓
Parasternal long axis view	<0.6	>0.6	>0.6
Four-chamber view	<0.9	>0.9	>0.9
Tricuspid regurgitation jet velocity	<2.6 m/s	>2.6 m/s	>2.6 m/s
Systolic pulmonary artery pressure	<50 mmHg	>50 mmHg	>50 mmHg
TAPSE	>17 mm	<17 mm	<17 mm

RV right ventricle, *LV* left ventricle, *TAPSE* tricuspid annular plane systolic excursion

9.10.5 Limitations of Transthoracic and Transesophageal Echocardiography

9.10.5.1 Transthoracic Echocardiogram

- Poor acoustic window
- Not available in the ER

9.10.5.2 Transesophageal Echocardiogram

- Expertise in the setting of severe clinical instability is mandatory
- Not available in the ER

9.10.6 Cardiac Computed Tomography

This imaging test has prognostic utility to establish signs of RVD, such as RV dilatation. RV/LV dimension ratios, ventricular and atrial septum shifting to the left side, and inferior vena cava diameter. In addition, it is possible identify severe right ventricular dilatation and septal deviation, also detect thrombus occluding right or left main, segmental or subsegmental pulmonary arteries.

9.10.7 Biomarkers

Bedside cardiac biomarkers establish RVD, ischemia, or type 2 myocardial infarction (Table 9.14). B-type natriuretic peptide (BNP) plasma measurements >600 pg/dL are observed in the setting of massive PE complicated with cardiogenic shock or in the late stage of RVD. Amounts around 400 pg/dL are frequent in the early stage of submassive or massive PE.

Considering that the half-life of BNP is 23 min, therefore approximately 2 h are required to reflect changes in the setting of the acute left of RVD. Physicians in charge should be aware of this 2-hour lag period before the onset of BNP to avoid underdiagnosing ventricular dysfunction [21].

Abnormal values of high-sensitive troponin assays establish right ventricular ischemia or necrosis. Troponin T concentrations >14 pg/mL had a negative predictive value of 98% about a complicated clinical course [22]. Also, abnormal measurements of BNP and high-sensitive troponin assays are closely related with an increase rate of in-hospital mortality and adverse events.

9.11 Diagnosis Approach

9.11.1 Chest Computed Tomography

Contrast-enhanced chest CT is the predominant diagnostic imaging technique to establish PE diagnosis by a thrombus in the pulmonary circulation (Fig. 9.6) (Table 9.15). The enhanced resolution of newer multi-detector CT scanners has increased the detection rate of subsegmental PE [23]. Negative chest CT has a high (99.1–99.4%) negative predict value to exclude PE in the assessment of high-clinical suspicion patients (Fig. 9.1). In the setting of high-clinical suspicion and negative chest CT, a multimodal approach including ventilation-perfusion lung scan and/or venous ultrasound increase facilitates making a clinical decision. Chest CT appears to be at least as accurate as invasive contrast pulmonary angiography.

Table 9.14 B-type natriuretic peptide and high-sensitivity troponin assays

Findings	Low risk	Submassive	Massive
BNP	<100 pg/dL	>100 pg/dL	>100 pg/dL
N-terminal pro-BNP	<300 pg/dL	>300 pg/dL	>300 pg/dL
High-sensitive troponin assays	At least one value above the 99th percentile upper reference limit		

BNP B-type natriuretic peptide

Table 9.15 Chest CT and ventilation-perfusion lung scan findings

Chest CT	**Low risk**	**Submassive**	**Massive**
Subsegmental or segmental artery	✓		
Lobar artery	✓		
Right or left artery		✓	✓
Both right and left artery		✓	✓
Main pulmonary artery			✓
Saddle thrombus			✓
V/Q lung scan			
Two subsegmental defects	✓		
<segmental defects	✓		
<8 segmental defects	✓	✓	
≥8 segmental defects		✓	✓
Vascular pulmonary obstruction <25%	✓		
Vascular pulmonary obstruction >25%	✓	✓	✓

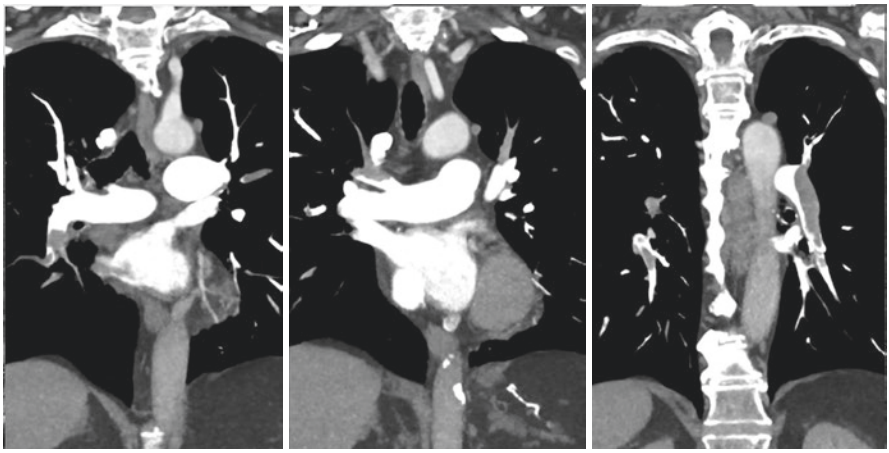

Fig. 9.6 A female patient with massive PE. Chest computed tomography showing bilateral thrombus in the pulmonary circulation

9.11.2 Ventilation-Perfusion Lung Scanning

The diagnostic requires at least one segmental or two subsegmental defects (Table 9.15). The purpose of the ventilation-perfusion scan is to increase specificity. In acute PE, ventilation is expected to be normal in hypoperfused segments, the so-called mismatch. Should be used in outpatients with low clinical probability and a normal chest X-ray is an important option in special populations as children, female, young, pregnant, history of contrast medium-induced anaphylaxis, severe renal failure, and history of with myeloma or paraproteinemia [7].

9.11.3 Laboratory Evaluation

In high-clinical suspicion, PE patients should focus on the use of D-dimer, BNP, and high-sensitive troponin. However, basal creatinine clearance, hemoglobin, and platelet count measurements identify high-risk patients to bleeding complications and a potential heparin-induced thrombocytopenia. Hyperglycemia and leukocytosis are linked to poor in-hospital outcome.

9.12 Treatment in the ER

The clinical condition, RVD, and risk for major bleeding complications drive the treatment choice [3]. There is an association between early anticoagulation and reduced mortality for patients with acute PE [24].

There is no bleeding risk score validated in PE. Variables related to major bleeding complications are elderly, female gender, low body mass index, and short size [25]. Parenteral or oral anticoagulation is the foundation of the treatment in low-risk PE patients (Table 9.16) and systemic thrombolysis in massive PE.

Non-vitamin K antagonist oral anticoagulants facilitated outpatient treatment; however, current evidence suggesting caution in PE associated with RVD [13].

Unfractionated heparin is recommended in >75 years with high risk of bleeding complication, renal failure, and morbid obesity low-risk PE patients (Table 9.17). Weight-adjusted unfractionated heparin regimen is recommended in impeding clinical instability submassive PE and as adjunctive treatment in massive PE [26] (Table 9.17).

Thrombolysis is recommended (without major risk bleeding) in clinical suspicion of impending instability, increased respiratory rate [27], and normal blood pressure in lower limits [18] submassive PE patients. If physicians in charge decide to use the "wait-and-see approach" [6], in the event that thrombolysis is needed, unfractionated heparin is the option to avoid crossover heparins. Tenecteplase and alteplase are an option in <65 years and half-dose alteplase in >65 years PE patients [3, 28]. The major and relative contraindications to use systemic thrombolysis are shown in Table 9.18. Low-dose alteplase is safety and efficacy in the catheter- or ultrasound-directed thrombolysis [29] (Table 9.19). The European Society of Cardiology, American Heart Association, and American College of Cardiology recommendations for anticoagulation and thrombolysis are shown in Tables 9.20 and 9.21.

Table 9.16 Parenteral and oral anticoagulation in low-risk pulmonary embolism

Drug	Dosage	Interval
Enoxaparin	1.0 mg/kg or 1.5 mg/kg	BID or OD
Tinzaparin	175 U/kg	OD
Dalteparin	100 IU/kg or 200 IU/kg (cancer patients)	OD or BID
Nadroparin	86 IU/kg or 171 IU/kg	OD or BID
Fondaparinux	5 mg (body weight <50 kg) 7.5 mg (body weight 50–100 kg) 10 mg (body weight >100 kg)	OD
Apixaban	10 mg 5 mg or 2.5 mg	BID for 7 days BID
Rivaroxaban	15 mg 20 mg or 15 mg	BID for 21 days OD

Table 9.17 aPTT- and weight-adjusted unfractionated heparin regimens

aPTT adjusted	**Regimens**
<35 s (<1.2 times control)	80 U/kg bolus increase infusion rate by 4 UI/kg/h
35–45 s (1.2–1.5 times control)	40 U/kg bolus increase infusion rate by 2 U/kg/h
46–70 s (1.5–2.3 times control)	No change
71–90 s (2.3–3.0 times control)	Reduce infusion rate by 2 U/kg/h
>90 s (>3.0 times control)	Stop infusion for 1 h, and then reduce infusion rate by 3 U/kg/h
Weight adjusted A bolus of 60 U/kg (maximum 4000 U)	Constant heparin infusion (12 U/kg/h, maximum 1000 U/h) adjusted to maintain an aPTT of 50–70 s for 24–48 h

aPTT activated partial thromboplastin time, *U* units

Table 9.18 Major and relative contraindications to use systemic thrombolysis [6]

Relative	Major
The transient ischemic attack in the preceding 6 months Oral anticoagulant therapy Pregnancy or within 1 week postpartum Non-compressible puncture site Traumatic resuscitation Refractory hypertension (systolic blood pressure >180 mmHg) Advanced liver disease Infective endocarditis Active peptide ulcer	Hemorrhagic stroke or stroke of unknown origin at any time Ischemic stroke in the preceding 6 months Central nervous system damage or neoplasms Recent major trauma/surgery/head injury in the preceding 3 weeks Gastrointestinal bleeding within the last month Known bleeding risk

Table 9.19 Thrombolytic regimens

Medication	Regimens	
FDA approved		
Alteplase	100 mg in 2-hour infusion	
FDA not approved		
Streptokinase	1,500,000 IU in 1 or 2 hours infusion	
Alteplase	20 mg bolus followed 80 mg in 1-hour infusion	
Alteplase	10 mg as a loading dose over 10 min followed by 40 mg over 2 h or 50 mg over 1 h infusion	
Tenecteplase	*Weight (kg)*	*Dose (mg)*
	<60	30
	60–70	35
	70–80	40
	80–90	45
	>90	50
Catheter-directed thrombolysis with alteplase	20 mg	
Ultrasound-directed thrombolysis with alteplase	17.2 mg to 35.1 mg in 14 h to 33.2 h infusion or 4 mg in 2 or 4 h	

FDA Food and Drug Administration, *IU* international units

Table 9.20 European Society of Cardiology recommendations [6]

High-risk PE	COR	LOE
It is recommended that intravenous anticoagulation with UFH be initiated without delay in patients with high-risk PE	I	C
Thrombolytic therapy is recommended	I	B
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed	I	C
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed	IIa	C
Intermediate or low risk		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic workup is in progress	I	C
LMWH or fondaparinux is the recommended form of acute-phase parenteral anticoagulation for most patients	I	A
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0–3.0)	I	B
As an alternative to the combination of parenteral anticoagulation with VKA, anticoagulation with rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily is recommended	I	B
As an alternative to the combination of parenteral anticoagulation with VKA, anticoagulation with apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily is recommended	I	B
As an alternative to VKA treatment, administration of dabigatran 150 mg twice daily or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment is recommended following acute-phase parenteral anticoagulation	I	B
As an alternative to VKA treatment, administration of edoxaban is recommended following acute-phase parenteral anticoagulation	I	B
New oral anticoagulants are not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min for rivaroxaban, dabigatran, and edoxaban and < 25 mL/min for apixaban)	III	A
Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients not suffering from shock or hypotension	III	B
Close monitoring is recommended in patients with intermediate-high-risk PE to permit early detection of hemodynamic decompensation and timely initiation of rescue reperfusion therapy	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of hemodynamic decompensation	IIa	B
Surgical pulmonary embolectomy may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high	IIb	C
Percutaneous catheter-directed treatment may be considered in intermediate-high-risk patients if the anticipated risk of bleeding under thrombolytic treatment is high	IIb	B

PE pulmonary embolism, *COR* class of recommendation, *LOE* level of evidence, *UFH* unfractioned heparin, *LMWH* low molecular weight heparin, *VKA* vitamin K antagonists

Table 9.21 American Heart Association and American College of Cardiology recommendations [15]

Initial anticoagulation	COR	LOE
Therapeutic anticoagulation with subcutaneous LMWH, intravenous or subcutaneous UFH with monitoring, unmonitored weight-based subcutaneous UFH, or subcutaneous fondaparinux should be given to patients with objectively confirmed PE and no contraindications to anticoagulation	I	A
Therapeutic anticoagulation during the diagnostic workup should be given to patients with intermediate or high clinical probability of PE and no contraindications to anticoagulation	I	C
Fibrinolysis		
Fibrinolysis is reasonable for patients with massive acute PE and an acceptable risk of bleeding complications	IIa	B
Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications	IIb	C
Fibrinolysis is not recommended for patients with low-risk PE	III	B
Fibrinolysis is not recommended for patients with submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening	III	B
Fibrinolysis is not recommended for undifferentiated cardiac arrest	III	B
Catheter embolectomy		
Depending on local expertise, either catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE and contraindications to fibrinolysis	IIa	C
Catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE who remain unstable after receiving fibrinolysis	IIa	C
For patients with massive PE who cannot receive fibrinolysis or who remain unstable after fibrinolysis, it is reasonable to consider a transfer to an institution experienced in either catheter embolectomy or surgical embolectomy if these procedures are not available locally and safe transfer can be achieved	IIa	C
Either catheter embolectomy or surgical embolectomy may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis)	IIb	C
Catheter embolectomy and surgical thrombectomy are not recommended for patients with low-risk PE or submassive acute PE with minor RV dysfunction, minor myocardial necrosis, and no clinical worsening	III	C
Endovascular thrombolysis and surgical venous thrombectomy		
CDT or PCDT should be given to patients with IFDVT associated with limb-threatening circulatory compromise (i.e., phlegmasia cerulea dolens)	I	C
Patients with IFDVT at centers that lack endovascular thrombolysis should be considered for transfer to a center with this expertise if indications for endovascular thrombolysis are present	I	C
CDT or PCDT is reasonable for patients with IFDVT associated with rapid thrombus extension despite anticoagulation and/or symptomatic deterioration from the IFDVT despite anticoagulation	IIa	B

(continued)

Table 9.21 (continued)

Initial anticoagulation	COR	LOE
CDT or PCDT is reasonable as first-line treatment of patients with acute IFDVT to prevent PTS in selected patients at low risk of bleeding complications	IIa	B
Surgical venous thrombectomy by experienced surgeons may be considered in patients with IFDVT	IIb	B
Systemic fibrinolysis should not be given routinely to patients with IFDVT	III	A
CDT or PCDT should not be given to most patients with chronic DVT symptoms (>21 days) or patients who are at high risk for bleeding complications	III	B

COR a class of recommendation, *LOE* level of evidence, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin, *PE* pulmonary embolism, *RV* right ventricle, *CDT* catheter-directed thrombolysis, *PCDT* pharmaco-mechanical catheter-directed thrombolysis, *IFDVT* iliofemoral deep venous thrombosis

Table 9.22 Differential diagnosis

Diseases	Low risk	Submassive	Massive
Physical deconditioning	✓		
Anxiety	✓		
Hyperreactivity	✓		
Asthma	✓		
Bronchial acute infection	✓		
Pneumonia	✓		
Pulmonary fibrosis	✓	✓	
COPD exacerbation	✓	✓	
Non-cardiogenic pulmonary edema		✓	✓
Heart failure	✓	✓	✓
Cardiac prosthetic valvular dysfunction	✓	✓	✓
Acute coronary syndromes	✓	✓	✓
Pericardial effusion	✓	✓	
Cardiac tamponade		✓	✓
New onset atrial fibrillation or flutter		✓	✓
Acute aortic syndromes		✓	✓

COPD chronic obstructive pulmonary disease

9.13 Differential Diagnosis

In the setting of high-clinical suspicion PE, the differential diagnosis depends on clinical stability or instability (Table 9.22). PE must be excluded through diagnostic workup. However, we need to considerer other cardiovascular and pulmonary frequent clinical conditions.

9.14 Additional Clinical Practice Takeaway

- PE is frequently seen in unexplained acute exacerbation of COPD [9], in patients with community-acquired pneumonia [10], and in those with unexplained worsening of dyspnea and chronic atrial fibrillation [11].
- In new-onset paroxysmal atrial fibrillation and right ventricular strain on ECG, PE must be suspected.
- PE must be excluded in patients older than 70 years and in patients presenting syncope with or without an alternative explanation [8].
- PE should be considered, in patients with a previous history of heart failure with or without preserved ejection fraction or chronic lung diseases and unexplained acute exacerbation.
- There is an increased in mortality in ER patients who did not receive heparin until after hospital admission compared with patients who received heparin in the ER [30].
- Patients who suffer unprovoked PE have an increased risk of future recurrence.
- Central venous access must be guided by echocardiography, to avoid multiple punctures increasing potential bleeding complications.
- Unfractionated heparin is preferred over LMWH in patients with a high probability for surgical interventions and in unstable patients. This avoids the increase of risk if the patient requires thrombolysis thereafter.
- Avoid fluid overload in hypotensive patients, since it could precipitate or worsen RVD.
- Streptokinase could induce severe hypotension, typically at the 30-minute mark or after 30 min of ongoing infusion, monitor accordingly.

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