Massive Pulmonary Embolism

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KEYWORDS

• Pulmonary embolism • Thrombolysis • Pulmonary embolectomy • Anticoagulation
• Right ventricular dysfunction

KEY POINTS

- The presentation of pulmonary embolism (PE) is frequently nonspecific and scoring systems may aid the diagnosis and risk stratification of patients.
- The main cause of mortality is obstructive shock and associated right ventricular (RV) failure.
- Systemic thrombolysis (unless contraindicated) is recommended as the first-line treatment of patients with massive PE to decrease the thromboembolic burden on the RV and increase pulmonary perfusion.
- Surgical pulmonary embolectomy or catheter-directed thrombectomy should be considered in those with contraindications to fibrinolysis, or those who have persistent hemodynamic compromise or RV dysfunction despite fibrinolytic therapy.
- Critical care management predominantly involves supporting the right ventricle, by optimizing preload, RV contractility, and coronary perfusion pressure and minimizing afterload.

INTRODUCTION

Acute pulmonary embolism (PE) represents the sudden obstruction of part of the pulmonary arterial vasculature, which is usually caused by embolization of thrombus from the deep veins within the lower limbs and pelvis. It may also be caused by air, fat, or amniotic fluid. PE is the third commonest cause of cardiovascular death (after coronary artery disease and stroke) and more than 600,000 cases are believed to occur in the United States annually.[1] PE was found in 18% of autopsies and in most (70%) of these was considered to be the main or a contributory cause of death.[2] The incidence increases exponentially with age, with the mean age at presentation of 62 years,[2,3] affecting men and women equally.[4]

Although no predisposing factors are identified in approximately 20% of patients (idiopathic or unprovoked PE),[5] most patients have either patient-related or setting-related attributable risk factors (secondary or provoked PE). Patient-related factors include advanced age, previous venous thromboembolism, active cancer, underlying coagulopathy (including factor V Leiden and prothrombin mutations), smoking, hormone replacement therapy, and the oral contraceptive pill.[6,7] Medical conditions associated with an increased risk of PE include heart failure, stroke, respiratory failure, sepsis, and inflammatory bowel disease.[8] Setting-related risk factors include protracted immobility secondary to major general/orthopedic surgery, major fracture, air travel, pregnancy, chemotherapy, or the presence of a central venous line.[9] Commonly, more than 1 risk factor is present.

Historically, PE was classified according to the anatomic burden of the thrombus in the pulmonary vasculature.[10] However, the outcome of these patients is more dependent on the hemodynamic compromise induced by the PE, such as the presence of circulatory arrest, hypotension, or right

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ventricular (RV) dysfunction.[5] PE has therefore been reclassified into 3 different prognostic categories by the European Society of Cardiology and American Heart Association (**Box 1**).[11,12]

Data from the International Cooperative Pulmonary Embolism Registry (ICOPER) reported 90-day mortality for patients with massive PE of 52% compared with 15% for those with submassive and nonmassive PE.[5] Similarly, data from the Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) reported 65% in-hospital mortality for patients with acute PE requiring cardiopulmonary resuscitation, compared with 25% for those presenting with cardiogenic shock, and 8% for hemodynamically stable patients.[13] The presence of RV dysfunction is associated with a 2-fold increase in 90-day mortality.[14]

Box 1
Classification of PE into prognostic categories by the European Society of Cardiology and American Heart Association

1. High-risk (massive) PE (20%), which is a life-threatening condition and defined as PE in the presence of
   a. Arterial hypotension (systolic blood pressure <90 mm Hg or a decrease of >40 mm Hg) for more than 15 minutes or requiring inotropic support, which is not caused by a new-onset arrhythmia
   b. Cardiogenic shock (oliguria, lactic acidosis, cool extremities, or altered level of consciousness)
   c. Circulatory collapse, in patients with syncope or undergoing cardiopulmonary resuscitation
2. Intermediate-risk (submassive) PE (32%), which is defined as PE with a systolic blood pressure greater than 90 mm Hg but echocardiographic evidence of RV dysfunction or pulmonary hypertension, or the presence of increased markers of myocardial injury (such as troponin)
3. Low-risk (nonmassive) PE (48%), which is defined as PE with a systolic blood pressure greater than 90 mm Hg and no evidence of RV dysfunction, pulmonary hypertension, or increased markers of myocardial injury.

Data from Torbicki A, Perrier A, Konstantinides S, et al. ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008;29(18):2282; and Jaff MR, McMurtry MS, Archer SL, et al, American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, American Heart Association Council on Peripheral Vascular Disease, American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123(16):1789–93.

PATHOPHYSIOLOGY

Obstruction of flow through the main pulmonary arteries results in increased afterload on the RV. In addition to mechanical obstruction of the RV, release of vasoactive mediators, such as thromboxane A_2 and serotonin, result in pulmonary vasoconstriction and increased pulmonary vascular resistance.[15] The resultant increase in RV wall tension results in displacement of the interventricular septum to the left and impaired left ventricular (LV) filling.[16] If untreated, the RV outflow obstruction also results in reduced preload on the LV, reduced cardiac output, and circulatory collapse and shock.[17] Younger patients with otherwise normal underlying cardiac function may tolerate the hemodynamic stress placed by a large PE without developing RV dysfunction or shock. However, in patients with compromised cardiac function, the onset of RV failure and circulatory collapse may be more rapid. In addition, hypoxia may result from the low cardiac output entering the pulmonary circulation, ventilation-perfusion mismatch, and the presence of a right-to-left shunt (through a patent foramen ovale, opened by the increased right-sided pressure).[18]

CLINICAL PRESENTATION

The clinical presentation of PE varies widely. Patients with massive PE may present with severe dyspnea at rest, syncope, or even cardiac arrest, whereas those with nonmassive PE may be asymptomatic or have limited symptoms. Their past medical history may include some of the risk factors for venous thromboembolism. Physical signs include tachycardia, tachypnea, systemic hypotension, and cyanosis. Evidence of RV dysfunction includes distended neck veins, parasternal heave, accentuated pulmonary component of the second heart sound, and a systolic murmur consistent with tricuspid regurgitation. An RV gallop rhythm may also be heard. The presence of a pleural rub, in association with pleuritic chest pain, may be secondary to pleural irritation caused by pulmonary infarction. Use of a scoring system, such as the Wells criteria or Geneva score, may aid

the clinical diagnosis and risk stratification of the patient.[19,20]

DIAGNOSIS AND RISK STRATIFICATION

The combination of clinical features and predisposing risk factors has been incorporated into clinical scoring systems that are used to predict the likelihood of PE and determining which investigations to perform. These investigations include the Wells score, simplified Geneva score and Pulmonary Embolism Severity Index (PESI) (**Tables 1–3**).[19–21] The most extensively validated and widely used clinical scoring system is the Wells score.[22]

The chest radiograph is usually abnormal in patients with acute PE.[23,24] Although the features are mainly nonspecific, such as atelectasis or pleural effusion, it can be used to exclude other causes of dyspnea or chest pain, such as pneumonia or pleural effusion. Arterial blood gas analysis usually shows hypoxemia (Pa_{O_2} <80 mm Hg), with hypocapnia and respiratory alkalosis.[25] In up to 20% of patients, a normal Pa_{O_2} and alveolar-arterial gradient may be found. Alternatively, hypercapnia with respiratory and metabolic acidosis may be seen in patients with massive PE requiring cardiopulmonary resuscitation. After assessment of the clinical and hemodynamic status of the patient using a clinical scoring system, the patients are subdivided into different probabilities of PE.

If the patient has a high clinical probability of PE, as determined by the clinical scoring systems, then multidetector computed tomography pulmonary angiography (CTPA) is required to determine the presence of thrombus within the pulmonary arterial vasculature.[11] CTPA has become the imaging of choice in patients with suspected PE, because of its speed of scanning, widespread availability, and high sensitivity and specificity (>90%).[26] It provides excellent visualization of the pulmonary arterial vasculature, including the main, lobar, and segmental pulmonary arteries, evidence of RV strain, characterization of extravascular structures, and for the detection of venous thrombosis (**Fig. 1**). However, in hemodynamically unstable patients, who cannot be transferred for CTPA, echocardiography may be required. An alternative imaging modality, such as VQ scintigraphy, may also be required in

Table 1
Wells score

Variable	Points
Predisposing factors	
Previous DVT or PE	1.5
Recent surgery or immobilization	1.5
Cancer	1
Symptoms	
Hemoptysis	1
Clinical signs	
Heart rate >100 bpm	1.5
Clinical signs of DVT	3
Clinical judgment	
Alternative diagnosis less likely than PE	3
	Total
Clinical probability (3 levels)	
Low	0–1
Intermediate	2–6
High	≥7
Clinical probability (2 levels)	
PE unlikely	0–4
PE likely	>4

Abbreviation: DVT, deep venous thrombosis.

Data from Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost 2000;83(3):418.

Table 2
Simplified Geneva score

Variable	Points
Predisposing factors	
Age >65 y	1
Previous DVT or PE	1
Surgery or fracture within 1 mo	1
Active malignancy	1
Symptoms	
Unilateral lower limb pain	1
Hemoptysis	1
Clinical signs	
Pain on deep palpation of lower limb and unilateral edema	1
Heart rate 75–94 bpm	1
Heart rate >94 bpm	2
Clinical Probability	**Total**
PE unlikely	0–2
PE likely	>2

Abbreviation: DVT, deep venous thrombosis.

Data from Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med 2006;144:165–71.

Table 3
PESI

Variable	Points
Age	1 per y
Male gender	10
Cancer (active or past history)	30
Heart failure	10
Chronic lung disease	10
Heart rate >110 bpm	20
Systolic blood pressure <100 mm Hg	30
Respiratory rate >30 bpm	20
Temperature <36°C	20
Altered mental status (disorientation, lethargy, stupor, or coma)	60
Oxygen saturation <90% on room air	20
Clinical Interpretation (Mortality at 30 d)	
Class 1: very low mortality risk (0%–1.6%)	<66
Class 2: low mortality risk (1.7%–3.5%)	<86
Class 3: moderate mortality risk (3.2%–7.1%)	<106
Class 4: high mortality risk (4.0%–11.4%)	<126
Class 5: very high mortality risk (10.0%–24.5%)	>126

Data from Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172(8):1041–6.

patients with a contraindication to CTPA, such as those with renal failure or contrast allergy.[27]

If the patient has been classified as a low or intermediate clinical probability of PE, a D-dimer enzyme-linked immunosorbent assay (ELISA) should be performed as the first-line investigation (sensitivity 96% and specificity 39%).[28] Serum D-dimer is a degradation product of cross-linked fibrin and acts as an indirect marker for coagulation and subsequent fibrinolysis. Because the D-dimer ELISA has a high negative predictive value, its absence effectively rules out acute PE, and an alternative diagnosis should be sought.[29] However, the positive predictive value of increased serum D-dimer levels is low, because although D-dimer is specific for fibrin, fibrin can be produced in a wide variety of conditions, including aortic dissection, cancer, inflammation, and infection.[30,31] Hence, if the D-dimer ELISA is positive, the patient should undergo CTPA.[11]

Once the diagnosis of acute PE has been made, the patients are stratified into low-risk (nonmassive), intermediate-risk (submassive) and high-risk (massive) groups, according to the presence of hypotension, shock, or RV dysfunction. The clinical status of the patient differentiates the high-risk (massive) PE from patients with non–high-risk PE. Echocardiography can then be used to further delineate patients with non–high-risk PE into intermediate-risk PE (with evidence of RV dysfunction) or low-risk PE (with no RV dysfunction) groups.[32] Surrogate markers of RV dysfunction include RV dilatation (RV end diastolic dimension >30 mm), interventricular septal flattening with paradoxic motion, increased RV/LV

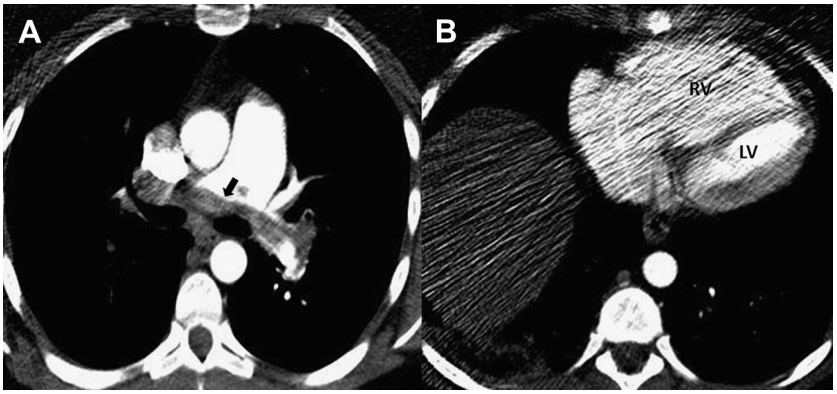

Fig. 1. Contrast-enhanced CTPA axial images showing (*A*) a large saddle embolus at the pulmonary artery bifurcation (*arrow*) with extension into both the left and right pulmonary arteries, and (*B*) evidence of right heart strain shown by enlarged right heart chambers, an RV/LV ratio greater than 1.5, and displacement of the interventricular septum. (*Courtesy of* Dr Deepa Gopalan, Cambridge, United Kingdom.)

ratio (>0.9), RV hypokinesis, pulmonary hypertension (pulmonary artery systolic pressure >30 mm Hg), and increased tricuspid regurgitation jet velocity (>2.6 m/s), which are found in approximately 25% of patients with acute PE (**Fig. 2**).[33,34] Echocardiography can also be used to exclude other important causes of acute circulatory collapse, including acute myocardial infarction, pericardial tamponade, or type A aortic dissection. The absence of RV dysfunction on echocardiography in a patient with shock or hypotension virtually rules out acute PE as a cause of the hemodynamic instability.[32] Transesophageal echocardiography can provide excellent imaging of the RV and proximal pulmonary vasculature to identify thrombus, as well as assessing RV function and size.[35] In patients with suspected PE with evidence of RV dysfunction, it has a sensitivity of 80% and specificity of 97%.[35]

Biomarkers, including serum troponin I or T and brain natriuretic peptide (BNP), may also be useful in detecting evidence of RV dysfunction in patients with acute PE.[36] Troponin levels, including troponin I and troponin T, are increased in the presence of PE, secondary to increased RV wall tension and end-diastolic pressure, reduced right coronary artery flow, increased RV myocardial oxygen demand, RV myocardial ischemia (even in the presence of normal coronary arteries) and subsequent leakage of the enzymes from the RV myocytes into the bloodstream.[37] They can be used to risk stratify patients with non–high-risk PE into intermediate-risk PE (with increased troponin levels) or low-risk PE (normal troponin levels), because increased troponin levels are used as a surrogate of RV dysfunction.[38] Similarly, plasma B-type natriuretic peptide (BNP) is released from the RV in response to increased pressure and stretch and has been shown to correlate with the presence of RV dysfunction.[39] Increased levels of both troponin and BNP have been shown to be associated with adverse prognosis and short-term outcomes in patients with acute PE.[40,41] However, increased levels of both troponin and BNP are not specific to PE.

Electrocardiography (ECG) is normal in up to 30% of patients[42] but often shows nonspecific changes, such as sinus tachycardia, atrial fibrillation, or ST/T wave changes.[43,44] Despite having a low sensitivity and specificity, the ECG may be useful in showing evidence of right heart strain, such as T-wave inversion in V_{1-4}, P pulmonale, right axis deviation, incomplete or complete right bundle branch block, or the combination of a prominent S wave in lead I, Q wave in lead III, and T-wave inversion in lead III (classic $S_1Q_3T_3$ pattern, which is present in only 2%–15% of patients with PE).[45]

Because massive PE has a high mortality in the first 6 hours after the onset of symptoms, early diagnosis is paramount in order to instigate timely management. The diagnosis is frequently first made at autopsy.[46,47]

MANAGEMENT

The primary cause of death in patients with massive PE is low cardiac output. Massive PE should be suspected in patients with major hemodynamic instability accompanied by an increased central venous pressure, which is not otherwise explained by pericardial tamponade, acute myocardial infarction, or tension pneumothorax. Because the short-term mortality increases depending on the degree of hemodynamic insult caused by the obstruction to RV outflow, the choice of initial therapy also depends on the severity of the hemodynamic insult.

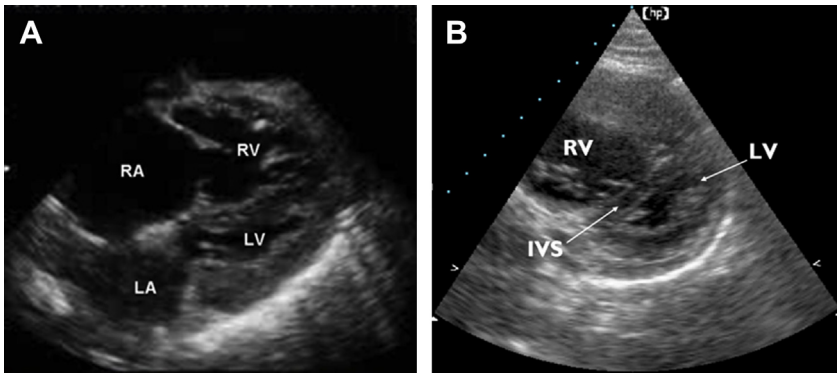

Fig. 2. Transthoracic echocardiography images in a patient with massive PE, with (*A*) subcostal long axis view showing acute right heart dilatation, with the RV larger than the LV and (*B*) parasternal short axis view showing a small compressed LV, which is D-shaped with a flattened IVS, and a dilated RV. IVS, interventricular septum; LA, left atrium; RA, right atrium.

ANTICOAGULATION

Unless there is a strong contraindication, parenteral anticoagulation should be commenced immediately in all patients in whom acute PE is believed to be the diagnosis.[12] Options include low-molecular-weight heparin (LMWH), intravenous unfractionated heparin (UFH), or subcutaneous fondaparinux (a selective factor Xa inhibitor). Subcutaneous LMWH or fondaparinux are preferred for most patients, because they are associated with a lower incidence of thromboembolic events, heparin-induced thrombocytopenia, and major bleeding (LMWH 1.3% vs UFH 2.1%) and do not require monitoring.[48,49] Fondaparinux can be given in weight-adjusted doses without monitoring as a once-daily subcutaneous injection, because it has a half-life of 15 to 20 hours.[50] UFH is indicated in patients with an increased risk of bleeding or in those in whom thrombolysis is being considered, because its short-acting effects can be directly reversed with protamine.[51] Intravenous UFH should also be used in patients with high-risk (massive) PE, because the effectiveness of LMWH and fondaparinux has not been investigated in this patient population.[48] UFH is also preferred in patients with severe renal impairment (because LMWH and fondaparinux are excreted by the kidney) and in patients with extreme obesity (in whom dosing of LMWH is unpredictable).[11] It is administered intravenously with a bolus of 80 U/kg followed by a continuous infusion of 18 U/kg per hour, which is subsequently adjusted to achieve an activated partial thromboplastin time ratio (aPTTR) between 2.0 and 2.5. The aPTTR is measured 4 to 6 hours after the initial dose, 3 hours after each dose adjustment, and then once daily when the therapeutic aPTTR has been achieved. Anticoagulation with heparin (UFH, LMWH, or fondaparinux) should be continued for at least 5 days.[52] For patients with heparin-induced thrombocytopenia, an alternative non–heparin-based anticoagulant, such as lepirudin, argatroban, or bivalirudin, can be used.[53]

FIBRINOLYSIS

In contrast to the passive action of heparin, fibrinolytic drugs (including urokinase, streptokinase, tenecteplase, and tissue plasminogen activator) actively promote thrombus lysis by hydrolysis of fibrin molecules. These drugs are enzymes that convert circulating inactive plasminogen into its active analogue plasmin. Plasmin is a serine protease enzyme that cleaves fibrin, releasing fibrin degradation products, including D-dimer molecules.[54] These agents are therefore able to induce a more rapid regression of the obstructive thrombotic burden to RV outflow compared with heparin alone.[55,56] However, the benefits of adding fibrinolytic therapy to heparin need to be balanced by the potential side effects, including the increased risk of major hemorrhage and increased blood transfusion requirement.[57]

Fibrinolytic therapy should ideally be initiated within 48 hours of symptoms onset for the greatest benefit but has been shown to have some efficacy up to 14 days.[58,59] Absolute contraindications to thrombolysis include recent major surgery, bleeding, trauma (within 2 weeks), intracranial hemorrhage, recent stroke (within 2 months), any hemorrhagic stroke, or significant coagulopathy. Relative contraindications include pregnancy, thrombocytopenia, and prolonged cardiopulmonary resuscitation.[12] Of the 478 patients who received fibrinolysis in MAPPET, over 40% (n = 193) had at least 1 relative contraindication.[13] These patients require high-dependency or intensive care monitoring for observation of the complications of acute PE and identification of the hemorrhagic complications of thrombolytic therapy.

The role of thrombolytic therapy for patients with intermediate-risk (submassive) PE remains controversial. The effects of thrombolysis in this patient group have been examined in 2 prospective randomized, placebo-controlled trials.[55,60] The Management Strategies and Prognosis of Pulmonary Embolism-3 Trial randomly assigned 256 patients with acute PE and RV dysfunction but without arterial hypotension or shock to heparin plus 100 mg of alteplase (n = 118) or heparin plus placebo (n = 138).[60] The primary end point, which was defined as in-hospital death or clinical deterioration requiring an escalation of treatment (including catecholamine infusion, secondary thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, emergency surgical embolectomy, or thrombus fragmentation by catheter), was significantly higher in the placebo group compared with the alteplase group, especially the need for emergency escalation of treatment (24.6% vs 10.2%, $P = .004$). However, there was no difference in mortality between the 2 groups (placebo 2.2% vs alteplase 3.4%, $P = .71$). There were no episodes of fatal bleeding or cerebral bleeding in patients receiving heparin plus alteplase. In the second study, 200 patients were randomly allocated intravenous tissue plasminogen activator plus heparin or heparin alone to determine the incidence of pulmonary hypertension after intermediate-risk (submassive) PE.[55] Patients treated with tissue plasminogen activator had a significant reduction in median pulmonary artery systolic

pressure compared with those treated with heparin alone (22 vs 2 mm Hg, $P<.05$). At 6 months, 27% of the patients treated with heparin alone developed increased pulmonary artery systolic pressure, suggesting an increased risk of developing long-term chronic thromboembolic pulmonary hypertension.

In a meta-analysis assessing patients with intermediate-risk PE,[61] there was no difference in mortality between those receiving heparin plus thrombolysis compared with heparin alone. The potential benefits of thrombolysis in patients with intermediate-risk PE needs to be balanced with the risk of bleeding, especially in patients with absolute and relative contraindications to systemic fibrinolysis. Even in carefully selected patients without absolute contraindications to thrombolysis, the rate of major hemorrhage and hemorrhagic stroke approaches 20% and 3%, respectively.[5] Hence, the clinical benefit of thrombolysis may be present only in a subgroup of patients with intermediate-risk PE, especially in those patients without an increased risk of bleeding. To further risk stratify patients in this group, the prospective, international, multicenter, randomized, double-blind PIETHO (Pulmonary Embolism Thrombolysis) trial has been initiated.[62] The trial will compare thrombolysis with tenecteplase plus heparin versus placebo plus heparin in 1000 normotensive patients with confirmed PE, RV dysfunction, and increased troponin levels. Until the results of this trial are available, the current guidelines suggest managing stable patients with intermediate-risk (submassive) PE using therapeutic heparin alone, in a similar manner to low-risk (nonmassive) patients.[12]

However, in hemodynamically unstable patients (high-risk PE), systemic thrombolysis (unless contraindicated) is recommended as the first-line treatment to decrease the thromboembolic burden on the RV and increase pulmonary perfusion.[51] This recommendation is supported by evidence from a prospective randomized controlled trial, in which patients with cardiogenic shock, RV dysfunction, and acute PE were randomized to either streptokinase (1,500,000 IU) followed by intravenous UFH or intravenous UFH alone.[63] The study was stopped early, because the 4 patients randomized to streptokinase improved in the first hour after treatment, survived and at 2-year follow-up were all without pulmonary arterial hypertension, whereas the 4 patients in the heparin-alone group all died within 1 to 3 hours of arrival in the emergency room. These results were confirmed in a meta-analysis of 5 trials with 254 patients[57] that investigated the effectiveness of thrombolysis in patients with high-risk (massive) PE and cardiogenic shock. It showed a significant reduction in recurrent PE or death (9.4% vs 19.0%; odds ratio 0.45, 95% confidence interval [CI] 0.22–0.92) with the number needed to treat being 10. However, retrospective data from ICOPER showed that thrombolytic therapy did not significantly reduce 90-day mortality (46.3% vs 55.1%; hazard ratio 0.79; 95% CI, 0.44–1.43) in patients with acute PE and cardiogenic shock (n = 108).[5]

Systemic thrombolysis has also been shown to improve hemodynamic parameters in patients with high-risk PE, compared with heparin alone, including a 12% decrease in vascular obstruction, 30% reduction in mean pulmonary arterial pressure, 15% increase in cardiac index, faster improvement in pulmonary blood flow, and improved reduction in the total perfusion defect.[55,64,65] The potential therapeutic benefit of thrombolysis in these patients needs to be balanced with the risk of bleeding. The risk of nonmajor bleeding is significantly increased and major bleeding nonsignificantly increased in patients receiving thrombolysis compared with heparin. Of the 304 patients who received fibrinolysis in ICOPER, 22% had major bleeding complications and 3% had intracranial bleeding.[5,66]

The guidelines suggest that thrombolytic therapy should be considered for patients with high-risk (massive) PE and an acceptable risk of bleeding complications.[12] 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. However, this strategy needs to be balanced with the increasing the risk of bleeding. Thrombolytic therapy should be not used in patients with low-risk (nonmassive) PE or stable patients with intermediate-risk (submassive) PE.

PULMONARY EMBOLECTOMY

Current indications for surgical embolectomy include patients with massive central PE with contraindications to fibrinolysis or those who have persistent hemodynamic compromise or RV dysfunction despite fibrinolytic therapy.[12] In addition, patients with free-floating thrombus within the right atrium or RV or with impending paradoxic embolism through a patent foramen ovale should also undergo surgical intervention.[18,67] Before embarking on surgical embolectomy, it is important to radiologically show a centrally accessible PE, within the main pulmonary trunk, or left or right main pulmonary artery, because patients with

most thrombus burden located peripherally do not benefit from surgery.

Standard surgical technique involves a median sternotomy and institution of cardiopulmonary bypass (CPB), usually with bicaval venous cannulation. This technique allows careful inspection of the right atrium, interatrial septum, and the RV. In cases in which thrombus is visible in the right atrium on echocardiography, cannulation of the femoral vein and superior vena cava can be used. To minimize myocardial ischemia, the procedure may be performed using normothermic CPB on a beating heart without cross-clamping the aorta. Access to the thrombus is gained via a curved incision in the main pulmonary artery extending into the left pulmonary artery. An additional incision in the right pulmonary artery (between the ascending aorta and superior vena cava) may also be required. Adequate exposure is gained using CPB suction and short episodes of reduced CPB flow. In some patients, cardioplegic arrest with or without systemic hypothermia is required, for greater periods of circulatory arrest and better visualization during removal of the thrombus; if a patent foramen ovale is present; or if intracardiac thrombi are present.[68,69] A combination of curved forceps, Fogarty catheter, suction catheter, and manual compression of the lungs is used to extract the thrombus from the pulmonary arteries. It is important to extract only visible thrombus, which can be achieved up to the level of the segmental pulmonary arteries, and to avoid blind instrumentation of the fragile pulmonary arteries. Intraoperative transesophageal echocardiography can be used to aid thrombus location and extraction.[70] In these patients, protracted weaning of CPB may be necessary, especially in patients with RV dysfunction. Bleeding may also be a problem, especially in those who have had preoperative thrombolysis. Heparin is started 6 hours after surgery and continued until warfarin is therapeutic. In patients with persistent RV failure after embolectomy, temporary mechanical support using an RV assist device or extracorporeal membrane oxygenation (ECMO) may also be required.[71]

Compared with medical therapy, surgical embolectomy has been shown to have improved outcomes in patients with massive PE. In a nonrandomized study comparing pulmonary embolectomy versus thrombolysis and best medical therapy, patients in the surgical group had reduced mortality and recurrence of PE.[72] In view of this finding, some centers have taken a more aggressive approach and extended the indications to also include patients with anatomically extensive PE with RV dysfunction but in the absence of circulatory shock (intermediate-risk PE).[73]

Previously, outcomes after surgical embolectomy were associated with high in-hospital mortality.[74] With improved surgical techniques and early intervention, current mortality is reported as low as 3.6%.[75] Predictors of early mortality after pulmonary embolectomy include patients with cardiac arrest or undergoing cardiopulmonary resuscitation and those with clot extending peripherally into and beyond the subsegmental arteries.[76] Hemodynamically stable patients who undergo surgical intervention have excellent long-term results, with a recent study reporting 83% 3-year survival.[71] The recurrence rate of PE after surgical embolectomy can be as high as 5%.[77]

Surgical embolectomy provides an excellent therapeutic option for patients with high-risk (massive) PE, with comparable early mortality and significantly fewer bleeding complications than thrombolysis.[72] However, results are worse for those who undergo surgical intervention after cardiopulmonary resuscitation or failed thrombolysis.[75]

CATHETER-DIRECTED THROMBECTOMY

Catheter-directed thrombectomy is an alternative therapeutic strategy that can be used for the treatment of acute PE. It is usually performed in patients with acute high-risk (massive) PE, in whom thrombolysis is contraindicated or has failed, and in whom surgical intervention is not available or contraindicated.[11] However, catheter-directed thrombectomy is not recommended for patients with low-risk PE or patients with intermediate-risk PE, in the absence of hemodynamic instability.[12]

The principal aim of catheter-directed thrombectomy is to achieve rapid debulking of a large central occlusive thrombus to reduce the afterload and strain on the RV, thereby increasing pulmonary and systemic perfusion. However, the fragmentation process redistributes the thrombus into multiple smaller branches further downstream. The hemodynamic consequence of multiple smaller thrombi in a large volume of the peripheral arterial tree is believed to be less significant than that of a central thrombus in the main PA.[78] Furthermore, by breaking up the large central thrombus into smaller fragments, it increases the surface area for exposure of the fibrinolytic agent or intrinsic thrombolytic enzymes to cause thrombus dissolution.[79] Using access via the femoral vein, catheter-directed thrombectomy involves either rheolytic or rotational techniques to disrupt the thrombus, in combination with aspiration of the thrombus fragments. Rheolytic techniques use a high-pressured jet system infusing saline to mechanically disrupt the thrombus.[80] In combination, ultrasound energy can be used to

dissociate the fibrin bonds within the thrombus to increase clot permeability and increase the number of plasminogen activation receptor sites for fibrinolysis.[81,82] Rotational techniques involve using a specifically designed thrombectomy catheter, with a covered, high-speed spiral fragmentation tip that rotates at up to 40,000 rpm and also aspirates thrombus fragments.[83]

Complications include distal thrombus embolization, perforation or dissection of the pulmonary artery, injury to the RV, arrhythmia, pulmonary hemorrhage, pericardial tamponade, and femoral venous injury. To reduce the risk of perforation, only pulmonary artery branches greater than 6 mm should be treated, and the procedure should be stopped once the hemodynamic status of the patient improves, irrespective of the angiographic result.[84]

Catheter-directed thrombolysis can be used as an adjunct to catheter-directed thrombectomy.[79] It involves delivering the fibrinolytic agent directly into the pulmonary embolus via a catheter with multiple side holes under fluoroscopic guidance. In combination with catheter-directed thrombectomy, local administration of fibrinolytic agents allows lower doses to be used, because it is delivered directly and the mechanical thrombectomy has increased the surface area of the thrombus available to the drug. The fibrinolytic agent should be injected directly into the thrombus, because any drug injected proximal to the obstructing thrombus is washed out by the local eddy currents into the nonobstructed pulmonary arteries, thereby reducing its therapeutic efficacy.[85] Results of catheter-directed thrombolysis in patients with acute high-risk (massive) PE were examined in a meta-analysis, which described the procedural success of hemodynamic improvement in 86% of patients.[86] However, a prospective, randomized trial failed to show any improvement in PA flow or pressures after local administration of the fibrinolytic agent, compared with systemic administration.[87] In view of this finding, catheter-directed thrombolysis is not recommended in the current guidelines.[12] Although no studies have compared the therapeutic efficacy of surgery and catheter-directed techniques, the PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy and Catheter Thrombolysis) registry has been set up to identify the role of catheter-directed therapies in patients with acute PE.

ICU MANAGEMENT

The main cause of death in patients with massive PE is cardiogenic shock related to RV dysfunction.[14] Thus, in addition to standard treatment of the critically ill patient, intensive care management in PE demands consideration of the physiologic role of the RV, knowledge of the mechanisms of RV failure, and the pharmacologic and mechanical options available to the intensivist.

The principal roles of the RV are to act as a conduit for blood flow between the systemic venous return and the lungs; to provide adequate pulmonary flow at an appropriate pressure to allow gas exchange; to maintain low filling pressures and avoid venous congestion and maintain cardiac output; to interact with the pericardium and left heart; and neurohormonal control of the circulation.[88] The right heart has important physiologic differences when compared with the left, which become increasingly important when there is an increase in afterload. It has a lower oxygen requirement (lower myocardial mass, preload, and afterload), greater extraction reserve, and receives perfusion in both systole and diastole.[89] Thus, as afterload increases, there is a high risk of ischemia with perfusion limited to diastole, and more chronically, an increase in myocardial mass. The principles of management of RV failure in the context of increased afterload therefore include ensuring optimal preload, maximizing RV contractility, reducing the pulmonary vascular resistance, and achieving adequate aortic root pressure to maintain right coronary artery perfusion.[90]

OPTIMIZATION OF RV PRELOAD

Although stroke volume from the RV is highly preload-dependent under normal circumstances, in pulmonary hypertension both underfilling and overfilling of the right heart may be deleterious.[91] Measured cardiac output may not be an accurate indicator of potential organ damage caused by RV failure, because the combination of venous hypertension with only a modest reduction in output may be associated with significant organ dysfunction.[92] Fluid studies in animal models of PE are controversial, with some showing volume loading increasing cardiac index but others showing worsening of shock by induction of RV ischemia or reduction in LV filling.[93–95] In the context of massive PE with acute RV failure, a volume challenge may initially increase cardiac output, but continued fluid challenges without careful monitoring may result in RV volume overload, venous hypertension, and a progressive decrease in cardiac output.[96] This situation should be suspected if there is an increase in serum lactate, increase in hepatic enzymes, an abnormal prothrombin time, oliguria, or gastrointestinal dysfunction. Hemodynamic parameters include an increasing V wave on the central venous pressure trace from

increasing tricuspid regurgitation and progressive RV dilatation. In such circumstances, reduction in afterload, removal of volume, and escalation of RV support are indicated, including the use of inotropy and mechanical circulatory support.

RV CONTRACTILITY

RV systolic function can be increased with the use of positive inotropic agents or inodilators. Several studies have been conducted in patients with pulmonary hypertension, but no high-quality evidence supports the use of any single vasoactive drug in the context of PE.[97] The most extensively studied inotropic agent is dobutamine.[98] Although low-dose dobutamine (up to 10 μg/kg/min) improves RV contractility in patients with pulmonary vascular dysfunction, it may demand coadministration of pressor agents. Phosphodiesterase 3 inhibitors increase RV contractility and in addition reduce pulmonary vascular resistance, but, again, their effects on the systemic vascular resistance generally require concomitant administration of pressor agents.[99] The novel agent levosimendan has been shown to reduce pulmonary vascular resistance and increase RV contractility in patients with biventricular dysfunction.[100] Although it has been proposed to improve RV-pulmonary artery coupling in patients with PE, evidence for its use is limited. The proarrhythmogenic effects of dopamine significantly limit its use in these patients.

RV AFTERLOAD

The RV is exquisitely sensitive to increases in afterload. Thus, in addition to the pharmacologic, catheter-based, and surgical techniques described to reduce thrombus burden, manipulation of the pulmonary circulation, modification of ventilatory strategies, maintenance of normocarbia, and avoidance of hypoxia may also improve RV function.

Systemic administration of pulmonary vasodilators frequently results in a decrease in systemic blood pressure, with the potential to exacerbate RV ischemia and reduce preload. Administration of inhaled pulmonary vasodilators, including nitric oxide, adenosine, prostanoids, phosphodiesterase 5 inhibitors, milrinone, nigoglycerin, and nitroprusside, may avoid these systemic effects and act to reduce hypoxic vasoconstriction and improve ventilation-perfusion mismatch.[101] There have been reports of inhaled nitric oxide (iNO) effectively reducing pulmonary vascular resistance and increasing cardiac output in patients with PE, most commonly after surgical embolectomy.[102–104] A recent case series reported rapid and dramatic improvement in hemodynamic parameters and oxygenation in patients with massive PE treated with iNO, suggesting that it should be considered as a temporizing agent pending initiation of definitive treatment (thrombolysis, surgery, or catheter-directed thrombectomy) until pulmonary dynamics have normalized.[105]

Positive pressure ventilation increases RV afterload, and in adult respiratory distress syndrome, high ventilatory pressures have been associated with increased acute cor pulmonale and increased mortality.[106] This potentially adverse effect has to be balanced against the effects of hypoxia and hypercarbia on the pulmonary circulation, when they act to increase pulmonary vascular resistance and hence RV afterload. When ventilation is unavoidable in the context of RV dysfunction, pressures (in particular positive end expiratory and plateau pressures) should be limited as far as possible, and the inspiratory time should be minimized, in particular in patients with restrictive RV physiology.[107]

CORONARY PERFUSION PRESSURE

In the context of pulmonary hypertension, when pulmonary vascular resistance exceeds systemic vascular resistance, right coronary artery filling occurs only in diastole. In this scenario, it is therefore essential to maintain aortic diastolic pressure, to enable coronary perfusion and avoid ischemia. Although augmentation of aortic root pressure with vasopressors is well established, the beneficial effects must be balanced against potentially detrimental pulmonary vasoconstriction. Sympathomimetic agents include the catecholaminergic pressor norepinephrine and the noncatecholaminergic pressor phenylephrine. The effects on the pulmonary vasculature are complex, relating to the dose-dependent α-adrenoreceptor and β-adrenoreceptor stimulation plus the severity of RV dysfunction.[17] Although arginine vasopressin, acting via the V_1 receptor, is a pulmonary vasodilator at low dose, it may cause bradycardia and dose-related myocardial dysfunction at higher doses. However, there is some evidence that low-dose arginine vasopressin may be of use in cases that are resistant to the usual treatments.[108]

MECHANICAL SUPPORT

A range of devices may be considered to maintain cardiac output on the ICU, including optimization of pacing, ventricular assist devices (VAD) and ECMO. In the critically ill patient with RV dysfunction, atrial arrhythmias are poorly tolerated. Therapeutic options should be to restore and maintain

sinus rhythm, optimization of fluid and electrolyte balance, treatment of potential triggers (including sepsis), and institution of pharmacotherapy (amiodarone or digoxin).[109] Ensuring optimal electromechanical activity of the heart can be important but complex and must be individualized to each patient.[110] A restrictive right heart that is failing may have a limited stroke volume, requiring a relatively high heart rate to maintain cardiac output. However, patients with pulmonary hypertension may have a long duration of systole (indicated by the duration of tricuspid regurgitation on echocardiography), which limits cardiac filling if the heart rate is excessive. Echocardiography can be used to optimize the heart rate and atrioventricular delay in these patients. When cardiogenic shock is present despite all interventions, patients may be considered for advanced mechanical circulatory support. Several case series have been published using venoarterial ECMO (VA-ECMO), as a bridge to treatment or recovery in patients with massive PE.[111] Potential advantages over VAD include speed of initiation of therapy, normalization of blood oxygen levels, and bypassing the pulmonary bed, thereby avoiding the potential further increase of pulmonary pressures.[112] For patients in cardiogenic shock as a result of massive PE, VA-ECMO can be successful if extracorporeal support is initiated early. Over 48 to 72 hours, emboli generally either resolve or migrate more distally, allowing patients to be weaned from the mechanical support. VA-ECMO and VAD have in addition been reported as a successful bridge to recovery in patients who have undergone pulmonary thrombectomy with CPB support.[113]

INFERIOR VENA CAVA FILTER

An inferior vena cava (IVC) filter should be considered in patients with a contraindication to anticoagulation, major bleeding complication during anticoagulation, recurrent embolism while receiving therapeutic anticoagulation, and usually in patients who have required ECMO after PE.[11,114] The filters are usually placed in the infrarenal IVC (**Fig. 3**) but can be placed in a suprarenal position if thrombus exists just below the renal veins. The filters can be permanent, or retrievable if the patient no longer requires caval interruption.[115] Early complications of IVC filter deployment include device malposition, pneumothorax, hematoma, air embolism, inadvertent carotid artery puncture, and arteriovenous fistula.[116]

The PREPIC trial (Prevention du Risque d'embolie Pulmonaire par Interruption Cave), which randomized 400 patients with proximal deep venous thrombosis at high risk for PE, showed that placement of an IVC filter significantly reduced the incidence of recurrent PE at 12 days (1.1% vs 4.8%, $P = .03$) and at 8 years (6.2% vs 15.1%, $P = .008$).[117] However, IVC filters were associated with an increased incidence of recurrent deep venous thrombosis (DVT) at 2 years (20.8% vs 11.6%, $P = .02$) and postthrombotic syndrome (40%). Because the beneficial effects of implanting an IVC filter in reducing the risk of recurrent PE are accompanied by an increased incidence of recurrent DVT with no effect on overall mortality, the use of an IVC filter in patients with acute PE is not routinely recommended.[12]

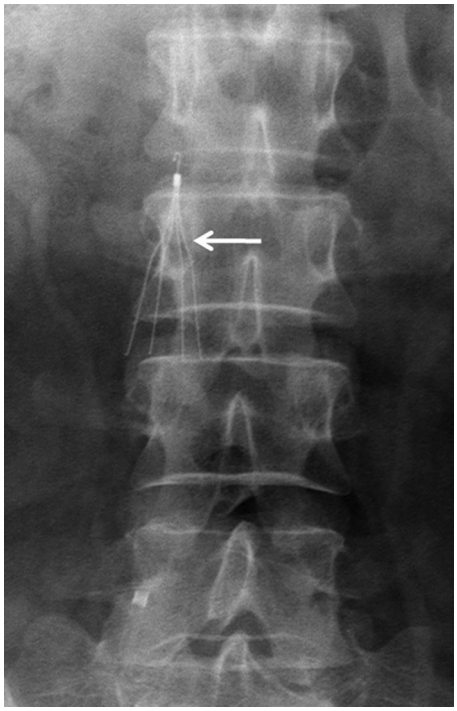

Fig. 3. Fluoroscopic image of a temporary caval filter (*arrow*) positioned in the infrarenal vena cava. (*Courtesy of* Dr Deepa Gopalan, Cambridge, United Kingdom.)

LONG-TERM ANTICOAGULATION

The long-term treatment of patients after PE is aimed at preventing extension of the thrombus and recurrent venous thromboembolism.[118] This goal is achieved with oral anticoagulation using a vitamin K analogue, such as warfarin, aiming for a target international normalized ratio of 2.5 (range 2.0–3.0). The treatment duration is determined by a balance between the risk of recurrence and risk of anticoagulation-related major bleeding. Anticoagulation is recommended for 3 months after a provoked PE, 6 months for an unprovoked PE, and

as long as the cancer is active for patients with malignancy.[119] Newer oral anticoagulants, such as dabigatran (factor IIa inhibitor) and rivaroxaban (factor Xa inhibitor), have been introduced, with the advantage that neither requires dose titration or monitoring.[51] Both have been shown to be non-inferior to warfarin, with respect to the incidence of recurrent venous thromboembolism or major bleeding, in the RECOVER and EINSTEIN trials, respectively.[120,121]

OUTCOMES

Despite the improvement in diagnostic and therapeutic modalities, contemporary in-hospital mortality for patients with PE is still approximately 7%.[5,122] For patients with high-risk (massive) PE, the mortality ranges between 25% and 50%, whereas patients with non–high-risk PE have a lower mortality of 3% to 15%. The presence of RV dysfunction and hemodynamic instability are the most significant predictors of a poor early outcome. Long-term predictors of mortality include age and the presence of comorbid conditions, such as congestive heart failure, malignancy, or chronic lung disease. Long-term follow-up of patients after acute PE is required to monitor for the development of chronic thromboembolic pulmonary hypertension.[123]

SUMMARY

PE is common and potentially lethal, with death usually caused by cardiogenic shock from RV failure. Challenges in diagnosis provided by the often nonspecific symptoms and signs may lead to delay in institution of definitive treatment. Despite the availability of pharmacologic, catheter-based, and surgical interventions, mortality remains high. Strategies to avoid DVT and PE in patients judged to be at risk remain pivotal in reducing PE-associated mortality.

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