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Diagnosis and Management of Life-Threatening Pulmonary Embolism

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Abstract

Pulmonary embolus (PE) is estimated to cause 200 000 to 300 000 deaths annually. Many deaths occur in hemodynamically unstable patients and the estimated mortality for inpatients with hemodynamic instability is between 15% and 25%. The diagnosis of PE in the critically ill is often challenging because the presentation is nonspecific. Computed tomographic pulmonary angiography appears to be the most useful study for diagnosis of PE in the critically ill. For patients with renal insufficiency and contrast allergy, the ventilation perfusion scan provides an alternative. For patients too unstable to travel, echocardiography (especially transesophageal echocardiography) is another option. A positive result on lower extremity Doppler ultrasound can also aid in the decision to treat. The choice of treatment in PE depends on the estimated risk of poor outcome. The presence of hypotension is the most significant predictor of poor outcome and defines those with massive PE. Normotensive patients with evidence of right ventricular (RV) dysfunction, as assessed by echocardiography, comprise the sub-massive category and are at intermediate risk of poor outcomes. Clinically, those with sub-massive PE are difficult to distinguish from those with low-risk PE. Cardiac troponin, brain natriuretic peptide, and computed tomographic pulmonary angiography can raise the suspicion that a patient has sub-massive PE, but the echocardiogram remains the primary means of identifying RV dysfunction. The initial therapy for patients with PE is anticoagulation. Use of vasopressors, inotropes, pulmonary artery (PA) vasodilators and mechanical ventilation can stabilize critically ill patients. The recommended definitive treatment for patients with massive PE is thrombolysis (in addition to anticoagulation). In massive PE, thrombolytics reduce the risk of recurrent PE, cause rapid improvement in hemodynamics, and probably reduce mortality compared with anticoagulation alone. For patients with a contraindication to anticoagulation and thrombolytic therapy, surgical embolectomy and catheter-based therapies are options. Thrombolytic therapy in sub-massive PE results in improved pulmonary perfusion, reduced PA pressures, and a less complicated hospital course. No survival benefit has been documented, however. If one is considering the use of thrombolytic therapy in sub-massive PE, the limited documented benefit must be weighed against the increased risk of life-threatening hemorrhage. The role of surgical embolectomy and catheter-based therapies in this population is unclear. Evidence suggests that sub-massive PE is a heterogeneous group with respect to risk. It is possible that those at highest risk may benefit from thrombolysis, but existing studies do not identify subgroups within the sub-massive category. The role of inferior vena cava (IVC) filters, catheter-based interventions, and surgical embolectomy in life-threatening PE has yet to be completely defined.

Keywords

pulmonary embolism, diagnosis, risk stratification, thrombolysis, embolectomy, inferior vena caval filter, right ventricular dysfunction, therapy, echocardiography, biomarkers, critical care, intensive care

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Introduction

Venous thromboembolism (VTE) in critically ill patients is challenging to diagnose and treat. Prevalence and mortality are high,[1-3] but prompt diagnosis, risk stratification, and treatment can improve outcome.[4] The purpose of this review is to consider the special features related to the diagnosis of pulmonary embolism (PE) in the critically ill, to discuss risk stratification strategies, and to outline an approach to managing patients who are hemodynamically tenuous.

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Table 1. Risk Factors for VTE[a]

Acquired Risk Factors	Hereditary Risk Factors	Mixed/Unknown
Bed rest	Antithrombin deficiency	High levels of factor VIII
Travel	Protein C deficiency	High levels of factor IX
Immobilizer or cast	Protein S deficiency	High levels of factor XI
Trauma/spinal cord injury	Factor V leiden (FVL)	High levels of factor fibrinogen
Major surgery	Prothrombin gene mutation	Activated Protein C resistance in absence of FVL
Orthopedic surgery	Dysfibrinogenemia	Hyperhomocysteinemia
Malignancy	Factor XIII 34val	High levels of plasminogen activator
Oral contraceptives	Plasminogen deficiency	Elevated levels of lipoprotein (a)
Hormonal replacement therapy		Low levels of tissue factor pathway inhibitor
Antiphospholipid syndrome		
Myeloproliferative disorders		
Polycythemia vera		
Central venous catheters		
Age		
Obesity		
Chemotherapy		
Heparins		
Pregnancy/postpartum period		

[a] *N Engl J Med.* 2008;358(10):1037-1052[8]; *Hematology Am Soc Hematol Educ Program.* 2005[12].

Epidemiology

Approximately 600 000 PEs occur yearly in the United States, resulting in 200 000 to 300 000 deaths.[5,6] Only 150 000 of all patients with PE are actually diagnosed, indicating that thousands of PEs go undetected.[7] Many deaths due to PE are unrecognized and the diagnosis is often made at autopsy.[8] Many deaths occur in hemodynamically unstable patients mistakenly thought to have myocardial infarction or arrhythmias.[7]

The risk of VTE is especially high in the critically ill. Within the first week of intensive care unit (ICU) admission, more than 30% develop deep venous thrombosis (DVT) if they do not receive prophylaxis.[1] Of all patients in medical intensive care units, 29% to 33% develop DVT. Inpatient mortality is 42% higher for patients with VTE compared to those without.[1]

Estimates of the percentage of PE patients presenting with hemodynamic instability range from 4.2% in the International Cooperative PE Registry (ICOPER)[9] to as high as 22%.[3,10,11] In patients with hemodynamic instability, inpatient mortality is at least 15%; 25% for those with cardiogenic shock.[7] Several hereditary and acquired risk factors predispose individuals to VTE (Table 1). A detailed discussion of risk factors is beyond the scope of this article and the reader is referred to an excellent review for additional information.[12]

Definitions

It is helpful to divide PE into 3 categories: massive, submassive, and low risk. Those with massive PE are at highest risk for death (Table 2).[7,13] Key clinical features include hemodynamic compromise, shock, or need for cardiopulmonary resuscitation.[3] Hemodynamic compromise is defined by a systolic arterial pressure <90 mm Hg or a drop in systolic arterial pressure by at least 40 mm Hg.[7] Clinical evidence of shock may include tissue hypoperfusion, hypoxia, metabolic (lactic) acidosis, altered mental status, oliguria, or cool extremities.[7] Hemodynamic compromise must be caused by the PE not concomitant illness.

Patients with sub-massive PE have normal blood pressure and evidence of right ventricular (RV) dysfunction.[14] Evidence of acute RV strain on electrocardiogram (EKG) may also help define sub-massive PE. Right ventricular enlargement noted by computed tomographic pulmonary angiography (CTPA) can also indicate sub-massive PE. Elevated cardiac biomarkers (brain natriuretic peptide [BNP] and troponin I for example) raise the suspicion for sub-massive PE. Patients with submassive PE comprise 31% of PEs diagnosed[10] and have a 5.0% to 12.6% in-hospital mortality rate, compared to 0.9% in patients with low-risk PE who have no evidence of RV dysfunction (Table 2).[3,15,16]

Pathogenesis

Venous thromboembolism has long been considered one disease, comprising DVT and PE.[8] It was felt that PE most commonly arises from the deep veins of the legs. Among patients whose cause of death was due to PE by autopsy, approximately 83% had evidence of DVT in their legs.[17] In a retrospective review of hospitalized patients, 18% of all DVT presented in the upper extremities.[18] In all, 7% to 9% of upper extremity DVT may cause PE, mostly in those untreated.[18] Lower extremity thrombi originate predominantly in venous valve pockets and other sites of presumed venous stasis in the calves and propagate above the knee.[8] Once above the knee, thrombi are at greatest risk of migrating.

A study of trauma patients found that PE was not associated with DVT in the pelvic or lower extremity veins.[19] The authors concluded that some PE results from peripheral vein DVT but

Table 2. Categories of PE[a]

Category	RV dysfunction—TTE/TEE	Hypotension Shock	Cardiac Arrest	In-hospital Mortality
Massive[b]	Yes	Yes	Yes	57.4-71.4%
			No	11.6-33.7%
Sub-massive[c]	Yes	No	No	5.8-11.2%
Low risk	No	No	No	0.4-0.9%

Abbreviations: .RV, right ventricular; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram.

[a] *Chest.* 2002;121(3):877-905[3]; *Circulation.* 2005;112(2):28-32[7]; *Chest.* 2004; 125(4):1539-1545.[11]

[b] Hypotension—systolic blood pressure <90 mmHg or drop of at least 40 mm Hg for >15 minutes. Cardiogenic shock—hypotension and clinical signs of organ hypoperfusion and hypoxia, including an altered level of consciousness, urine output < 30 mL/h, or cold clammy extremities.

[c] Patients with normal blood pressures and evidence of shock should be placed in the sub-massive category.

also postulated that in situ clot formation within the pulmonary arteries may explain the lack of association between lower extremity DVT and PE in their report. Some have noted that the efforts to detect DVT in this study may have been suboptimal.[20]

Pathophysiology of Massive PE

Hemodynamics

Hemodynamic instability and shock are the most important factors contributing to PE-related death. The hemodynamic response to acute occlusion of the pulmonary vessels depends on several factors that increase pulmonary vascular resistance (PVR) and pressure overload, including clot size and the degree to which clot is centrally positioned.[3,8] Hypoxia further elevates PVR and pulmonary artery (PA) pressures as do mediators that include serotonin, platelet-activating factor, thrombin, vasoactive peptides (C3, C5a), and histamine.[21] The increase in PVR translates into an elevated PA pressure as long as cardiac output is sustained. As pressure loading worsens, RV stroke volume may drop.[22] Initial compensation by catecholamine-mediated tachycardia may delay the drop in cardiac output.[3]

Right ventricular dilation maintains cardiac output by preserving stroke volume, even if the ejection fraction falls. However, in the most severe cases, a combination of RV pressure overload, dilation, and ischemia eventually leads to a drop in stroke volume and cardiac output.[23] Increased RV size increases wall stress and tension. Wall stress reduces RV oxygen uptake and, combined with increased oxygen demand, sets the stage for ischemia.[3] Perfusion of the RV depends on the gradient between mean arterial pressure and subendocardial pressure. Elevated RV end-diastolic pressures impair subendocardial perfusion and oxygen supply.[3] The loss of subendocardial perfusion, increased RV wall tension, and increased oxygen demand result in RV ischemia and infarction.[23,24] Vasoconstrictors that increase aortic pressures and increase the coronary perfusion gradient may, in part, reverse RV ischemia by increasing mean arterial pressure.[24,25]

Pulmonary artery pressures increase with the PVR as long as cardiac output is maintained. As the RV fails, reduced cardiac output may reduce PA pressures if PVR remains fixed. For this reason, PA pressures do not reliably predict cardiac impairment.[3] A normal PA pressure may, in fact, signal severe RV impairment and pending circulatory collapse.

Left ventricular (LV) end-diastolic volume is reduced as a result of decreased RV output and dilation of the RV, which shifts the interventricular septum and impedes LV filling.[26,27] Reduced LV end-diastolic volume leads to decreased stroke volume, cardiac output, and systemic arterial pressures in patients with hemodynamically significant PE.

Impaired Gas Exchange

Hypoxemia (81%), increased A-a gradient (80%), and hypocapnia (74%) are the most frequently observed gas exchange abnormalities associated with PE.[28-30] As many as 12% of patients with sub-massive or massive PE have a $Pa_{O_2} \geq 80$ mm Hg.[31,32] Factors contributing to hypoxia include ventilation perfusion (VQ) mismatch, right to left shunt, impaired diffusing capacity and reduced mixed venous oxygen saturation (SvO_2).[3,23] Most hypoxia is due to VQ mismatch and reduced SvO_2.[3] Atelectasis is an important factor contributing to poor ventilation, the result of vascular obstruction, lung edema, hemorrhage, and loss of surfactant.[23,33]

Increased physiologic dead space may impair CO_2 exchange in sub-massive or massive PE. However, despite an increase in dead space ventilation, most patients present with hyperventilation and are typically hypocapneic.[34] In particularly large PEs or when the patient's ventilatory capacity is limited (for example due to underlying respiratory disease), hypercapnia may result.

Diagnosis

Signs and Symptoms

Pulmonary embolism can present with a wide range of nonspecific symptoms, vital sign irregularities, physical examination findings, and laboratory abnormalities.[29] Onset is generally acute. Common symptoms include dyspnea, chest pain (often pleuritic in nature), palpitations, cough, wheezing, and orthopnea. Asymmetric calf swelling or pain may occur with lower extremity DVT.

Massive PE can present with circulatory collapse, mental status changes, syncope, arrhythmias, seizures, and death.[35-37] Vital sign abnormalities include fever, tachycardia, hypotension, tachypnea, and/or hypoxemia. The physical examination can reveal accessory muscle use, decreased breath sounds, wheezing, rales, increased jugular venous distension, and an RV heave. Unfortunately, clinical signs and symptoms only raise suspicion for PE. Their sensitivity and specificity individually are insufficient for diagnosis.[38]

Differential Diagnosis and Pretest Probability

Clinical decision tools, like the Wells Score and the Revised Geneva Score, help determine the pretest probability for PE based on presenting signs and symptoms.[39,40] While these clinical decision tools help exclude PE in low prevalence populations, their utility in the critically ill is limited. The presentation associated with PE can mimic other life-threatening illnesses such as aortic dissection, pericardial tamponade, myocardial infarction, cor pulmonale, tricuspid regurgitation, chronic obstructive pulmonary disease exacerbation, pneumonia, and thyrotoxicosis.[41,42] For example, 25% of patients presenting with a severe chronic obstructive pulmonary disease (COPD) exacerbation of unknown origin were diagnosed with PE.[43] In addition, it may be difficult to detect PE in the context of concurrent critical illness, since many features such as hypotension, tachycardia, and hypoxia may already be present. Clinicians caring for critically ill patients with hemodynamic compromise or respiratory failure must have a low threshold for entertaining PE (especially in the setting of risk factors such as malignancy, recent surgery, central venous lines, or prior VTE) when the patient's clinical presentation cannot be explained satisfactorily by alternative diagnoses.

Laboratory Testing and Bedside Tools

The quantitative enzyme-linked immunosorbent assay (ELISA) test for D-dimer is 95% sensitive for VTE[44]; however, an elevated D-dimer is nonspecific and does not necessarily indicate the presence of clot. D-dimer is elevated in other conditions commonly seen in critically ill patients, including malignancy, infection, surgery, acute myocardial infarction, and pregnancy, in addition to VTE.[45] The utility of an elevated D-dimer to diagnose PE in the critically ill is therefore limited. Furthermore, as in ambulatory patients and inpatients, if the clinical suspicion is high despite a normal D-dimer, the diagnosis should still be pursued.[46]

Hypoxemia is highly sensitive but poorly specific since it occurs in the vast majority of illnesses associated with pulmonary dysfunction. An unexplained widened alveolar–arterial gradient can be highly suggestive of acute PE; however, a normal gradient or normal Pa_{O_2} cannot exclude PE.[32,47]

The EKG often shows sinus tachycardia but is neither sensitive nor specific for PE.[48] With a significant clot burden, more specific markers can manifest on the tracing, including an S1Q3T3 pattern, low-voltage, incomplete or complete right bundle-branch block, T wave inversions over the right precordial leads, pulmonary P wave, or rarely ST elevation.[49,50] These more severe EKG findings can prompt further diagnostic imaging to diagnose PE such as a CTPA or VQ scan.

Bedside volumetric capnography may be performed in mechanically ventilated patients, is noninvasive, and can estimate physiological dead space. A sudden reduction in end-tidal CO_2 and increase in physiological dead space to tidal volume ratio can raise the suspicion for PE in a critically ill patient.[51]

Diagnostic Imaging

Pulmonary angiogram. Angiography has traditionally been the gold standard method to diagnose PE. While highly sensitive and specific, the procedure is invasive, expensive, and has a morbidity and mortality rate of 3.5% to 6% and 0.2% to 0.5%, respectively.[52] The mortality risk is greater in the critically ill: 4% versus 1% in noncritical patients, according to the PIOPED II investigators.[53] Use of the pulmonary angiogram (PA gram) has declined during the last decade because of improvements in less invasive diagnostic methods, specifically CTPA[52,54]; it is now generally reserved for cases in which catheter-based treatment is an option[34] or for cases in which the CTPA (or VQ scan) cannot provide a definitive diagnosis.

Computed tomographic pulmonary angiography. The computed tomographic pulmonary angiography (CTPA) is minimally invasive and allows direct visualization of the pulmonary arteries. The accuracy of the CTPA is affected by the technology used. Current advanced multidetector devices can achieve sensitivity of 84% to 94% and specificity of 94% to 100%, after excluding studies with technical shortcomings.[52,54,55] In patients with a high clinical suspicion,[53] the positive predictive value is as high as 96%. Even if negative for PE, CT may identify other processes to explain the patient's condition (Table 3).

Computed tomographic pulmonary angiography is associated with a significant radiation exposure, the equivalent of 100 to 400 hundred chest X-rays, as well as an exposure to iodinated contrast material which can induce an allergic reaction or nephropathy.[53,56] Hazardous levels of radiation exposure may be relevant to the critically ill because of the need for serial imaging, but the importance of making a diagnosis generally outweighs the theoretical long-term sequelae from ionizing radiation, assuming PE is a realistic diagnostic possibility. In PIOPED II, patients with abnormal creatinine levels were excluded from CTPA investigation and the incidence of renal failure was only 0.1%.[53] In patients with abnormal creatinine levels, a positive lower extremity Doppler can prompt treatment.[53] If the lower extremity Doppler is negative, a VQ scan may be appropriate if CT is not an option.

For patients at risk of contrast-induced renal injury (diabetics, renal vascular disease, and chronic renal insufficiency) precautions should be taken. Prophylactic infusion of crystalloid solution (fluid containing bicarbonate may be more effective than saline), cessation of metformin, and cessation of nonsteroidal anti-inflammatory drugs may help prevent contrast-induced renal injury.[53] *N*-acetylcysteine has few harmful side effects. Despite inconclusive data regarding its effectiveness, it is often used to decrease the risk of renal injury.[57]

Patients with mild or moderate contrast allergy (rash or pruritis) may undergo CTPA at the discretion of the clinician with the use of steroids to prevent allergic reaction.[53] Those with severe allergy to iodinated contrast (anaphylaxis, dyspnea, airway compromise) should undergo lower extremity Doppler and follow a diagnostic pathway similar to those with elevated creatinine levels, for example, employing the VQ scan.[53]

Table 3. Imaging Modalities for the Diagnosis of PE in the Critically Ill Population

MODALITY	PROS	CONS
CT Pulmonary angiography (CTPA)[52,56,153]	Fast compared to VQ scan, TEE, PA gram Widely available Alternative or additional diagnoses offered Cost effective	Contrast exposure-risk of renal dysfunction or allergy Significant radiation exposure Requires transport
Lung scintigraphy (VQ Scan)[52,58,154]	Avoids contrast exposure	Indeterminate results in setting of other lung pathology Requires transport Delay in scheduling
Transthoracic echocardiography (TTE)[52,64]	Suggestive of cardiac side effects from PE Portable May suggest alternative explanation for shock	Unlikely to make definitive diagnosis alone
Transesophageal echocardiography (TEE)[68,69]	Portable May visualize RV dysfunction May offer direct visualization of clot in heart, both main and right lobar pulmonary arteries May suggest alternative explanation for shock	Invasive
Lower extremity ultrasound[52,65]	Fast Portable Identify venous thrombosis	Cannot make definitive diagnosis of PE Poor sensitivity for PE
MR angiography[72,73]	Imaging as far as segmental branches No exposure to iodinated contrast	Gadolinium exposure Requires transport Not widely available
Pulmonary angiography (PA gram)[52,155]	Opportunity to provide therapy at diagnosis (IVC filter, catheter directed therapy)	Invasive Contrast exposure-risk of renal dysfunction or allergy Significant radiation exposure Requires transport
Transthoracic ultrasonography[74]	Portable Noninvasive	Not well studied Not widely available

Abbreviations: CTPA, computed tomographic pulmonary angiography; VQ scan ventilation perfusion scan; MR, magnetic resonance.

Poor timing of intravenous contrast bolus, motion artifact, and flow artifact can undermine image quality. Patient cooperation is necessary to obtain high-quality images. Accurate diagnosis is difficult when image quality is poor. In one series, 21% of noncritically ill patients could not be given an initial diagnosis with CTPA.[55] It is unclear whether a similar rate of inconclusive studies applies to the critically ill. In summary, CTPA is the most useful way to diagnose PE, assuming the patient can travel to the scanner and there is no history of severe contrast allergy or significant renal disease.

Ventilation perfusion scan. The VQ scan has traditionally been a valuable diagnostic modality in the evaluation of PE, but much of the data on its performance does not include the critically ill. A comparison of VQ scans between critically ill and noncritically ill patients demonstrated similar sensitivity and specificity, as well as strong positive predictive value (89%) in the high pretest probability group for high probability scans.[58] The ventilation portion of the VQ scan is generally technically difficult to obtain when the patient is on a ventilator. An analysis of ventilated critically ill patients (with high pretest probability) receiving perfusion scans alone showed that the perfusion scan had similar positive predictive value (93% vs 94%) for high probability scans compared to the group with the ventilation scan included.[59]

Despite the comparable results obtained with scintigraphic scans in the critically ill, CTPA is the more commonly used modality.[60] The CTPA is more readily available in most institutions and a negative CTPA may still provide an alternative diagnosis. The significant proportion of nondiagnostic results (25.6% compared with 6.2% for CTPA) has also led to the decline in utilization of the VQ scan.[61,62] In patients with normal chest radiographs, the VQ scan (or perfusion scan) can serve as an accurate diagnostic tool for PE in the critically ill. In patients with an abnormal creatinine or severe allergy to iodinated contrast, the VQ scan remains a useful alternative.

Adjunct Imaging Modalities

Chest radiography. Radiographic abnormalities[63] seen in unselected patients with PE include cardiomegaly (27%), small pleural effusion (23%), elevated hemidiaphragm (20%), PA enlargement (19%), atelectasis (18%), and small infiltrates (17%). As many as 24% of chest radiographs are normal. Oligemia of the embolized lung has also been described.[23] The chest radiograph cannot be used alone to diagnose or exclude PE in the critically ill. It may be used to raise clinical suspicion or provide clues to alternate diagnoses.

Echocardiography. The transthoracic echocardiogram (TTE) may assist in the diagnosis of the unstable patient who cannot be transported or in whom timing is crucial for treatment decisions.[64] Diagnostic criteria for PE using TTE usually combine findings consistent with RV dysfunction/RV strain, in addition to visualizing clot. These findings[65] include RV hypokinesis, leftward displacement of the septum, elevated RV to LV diameter ratio, and a tricuspid regurgitant velocity >2.7 m/s. The presence of McConnell sign (RV hypokinesis with sparing of apical motion) has a reported specificity of 94% to 100% for PE.[64]

Transthoracic echocardiogram is rarely able to make a definitive PE diagnosis because intracardiac thrombus is seen in only 10%.[64] In a prospective study of 110 unselected patients with PE, TTE criteria (RV hypokinesis, RV end-diastolic diameter > 27 mm, and tricuspid regurgitation velocity > 2.7 m/s) failed to identify 50% of angiographically proven PE.[66] Any 2 echocardiographic findings (RV hypokinesis, RV end-diastolic diameter > 27 mm, and tricuspid regurgitant jet velocity greater than 27 m/s) coupled with a high pretest probability yielded a positive predictive value of 98%. The absence of RV dysfunction on TTE cannot exclude a PE, but TTE may raise clinical suspicion of PE. Transesophageal echocardiogram may also provide alternative explanations for the patient's presentation such as aortic dissection, pericardial tamponade, or acute myocardial infarction.[7]

Transesophageal echocardiogram can quickly diagnose and provide direct evidence to support the use of aggressive therapies in patients presenting with circulatory collapse from PE. Like the TTE it can reveal evidence of RV dysfunction and has even greater ability to visualize intracardiac thrombus. Transesophageal echocardiogram can also visualize the main pulmonary arteries, and right lobar pulmonary arteries.[67]

One study in the medical ICU found TEE to have 92% sensitivity and 100% specificity in detecting massive PE.[68] In another study in patients with RV dysfunction diagnosed by TTE, a follow-up TEE had a sensitivity of 76.1% and a specificity of 100% for diagnosing PE.[69] The authors reported no serious complications of TEE. The high specificity in these studies was due to the fact that visualization of thrombus was used to make a diagnosis,

Transesophageal echocardiogram can be used to make a bedside diagnosis in sedated/ventilated critically ill patients. Despite its apparent utility, TEE is not routinely used to diagnose PE. The requirement for an expert operator to perform the test is one possible explanation and its invasive nature compared to CTPA is another.

Lower extremity Doppler ultrasonography. Ultrasound is easy to use, noninvasive, and portable, making it a convenient adjunct imaging modality in the critically ill. Doppler ultrasonography has a high sensitivity (88%-100%) and specificity (92%-100%) for the detection of lower extremity DVT.[70] Among critically ill surgical patients, the sensitivity[71] of lower extremity ultrasound for the detection of PE was 44%. In a prospective study where unselected patients were referred for lower extremity ultrasound as the initial evaluation in suspected PE, patients with risk factors for VTE and symptoms of DVT had a 25% prevalence of DVT.[72] A negative lower extremity Doppler ultrasound should result in further testing for PE when suspicion is significant because the lower extremity ultrasound cannot exclude PE.

Ultrasound may be a useful alternative to the VQ scan in patients with renal dysfunction or severe contrast allergy. The detection of DVT by ultrasound can prompt anticoagulation (or placement of inferior vena cava [IVC] filter) in critically ill patients. If more aggressive therapies are considered, confirmatory studies such as CTPA, VQ scan, or TEE are advisable.

Other Modalities Under Investigation for Diagnosis of PE

Magnetic resonance angiography and thoracic ultrasonography are being investigated for use in the diagnosis of PE (Table 3).[73,74] The sensitivity and specificity of magnetic resonance angiography are 77% to 100% and 95% to 98%, respectively.[73] Those for thoracic ultrasonography are an estimated 80% to 94% and 84% to 92%.[74] Further investigation of both modalities is needed before either modality can be recommended in the critically ill.

Risk Assessment and Stratification

Estimating the risk of poor outcome for patients with PE is an important feature of management and is based largely on hemodynamic data. Distinguishing patients with sub-massive PE from those with low-risk PE is challenging, as patients with sub-massive PE may show no overt evidence of hemodynamic compromise.

Clinical Predictors of Poor Outcome

The strongest predictor of death at time of PE diagnosis is a low systolic arterial pressure. All-cause 3-month mortality is as high as 58.3% in patients with systolic blood pressure (SBP) < 90 mm Hg, compared with 15.1% in those with normal blood pressure.[9]

A simple, prospectively validated tool can be used to estimate mortality (PE-specific and all-cause) risk on the basis of a score derived from readily available clinical data.[36,75,76]

The score is based on factors such as age, respiratory rate, heart rate, SBP, temperature, oxygen saturation, chronic lung disease, heart failure, cancer, gender, and altered mental status. It is referred to as the PE severity index (PESI) and has been cited by other investigators.[76,77] Patients with higher scores may be triaged to higher levels of care (ie, monitored bed or critical care unit),[13] and benefit from further efforts at risk stratification such as assessment of cardiac function and measurement of cardiac biomarkers.

Assessment of Cardiac Function

Echocardiogram. Identification of RV dysfunction is crucial because it is associated with doubled all-cause mortality at 3 months.[9] The echocardiogram helps identify normotensive patients with RV dysfunction that might otherwise go undetected. Among patients with normal systemic arterial pressures,[78] RV hypokinesis is present in as many as 40%.

Findings on echocardiogram indicative of RV dysfunction include RV end-diastolic diameter to LV end-diastolic diameter ratio > 1 (Figure 1), RV end-diastolic diameter > 30 mm, septal dyskinesia, RV-Right atrial gradient > 30 mm Hg, pulmonary arterial flow acceleration <80 to 90 ms, RV hypokinesis, and tricuspid valve pressure gradient >30 mm Hg.[7,10,79-81] No single finding predicts the risk of death.[79] As a result, composite criteria, using 2 or more of the above findings, are often applied.

In one report, consecutive patients diagnosed with PE were evaluated by TTE.[82] Those with evidence of severe RV dysfunction had a higher mortality than those without (21.4% vs 7.1%, $P = .04$). In another study, normotensive patients with and without RV dysfunction were identified.[10] In all, 10% of the patients with RV dysfunction developed shock after admission and 4.6% died. In comparison, none of those without RV dysfunction developed shock or died. In another study, a meta-analysis was performed,[83] which included 5 studies in which normotensive patients were assessed with echocardiogram within 48 hours of presentation. The sensitivity and specificity of RV dysfunction for in-hospital mortality was 70% (95% CI 64%-86%) and 57% (95% CI 47%-66%), respectively. One should consider obtaining a TTE to determine whether normotensive patients with PE have RV dysfunction, given the increased mortality observed in patients with sub-massive PE. At this time, no guidelines exist to select which normotensive patients should have TTE performed, but cardiac biomarkers, CTPA, EKG, and clinical data may help with decisions in this regard.

Computed Tomography. In addition to diagnosing PE, CTPA can assist risk stratification. In one study, a CT angiographic score was devised based on the degree to which the pulmonary arteries were occluded.[84] The occlusion score correlated well with PA systolic pressures measured by echocardiogram, but the study was not designed to detect differences in clinical outcomes.

In a retrospective analysis of normotensive patients with PE, signs of RV dysfunction on CTPA correlated with

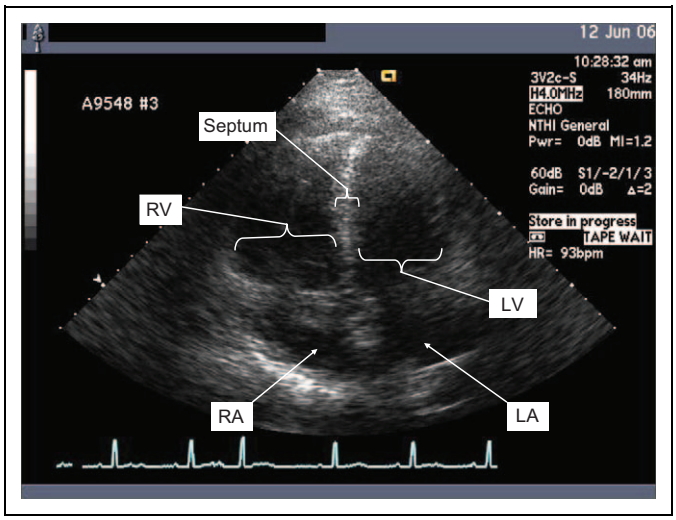

Figure 1. Transthoracic echocardiogram (TTE) with 4 chambers visualized demonstrates RV enlargement and flattening of interventricular septum in a patient with PE. RV indicates right ventricle; AV, atrioventricular; RA, right atrium; LV, left ventricle; LA, left atrium.

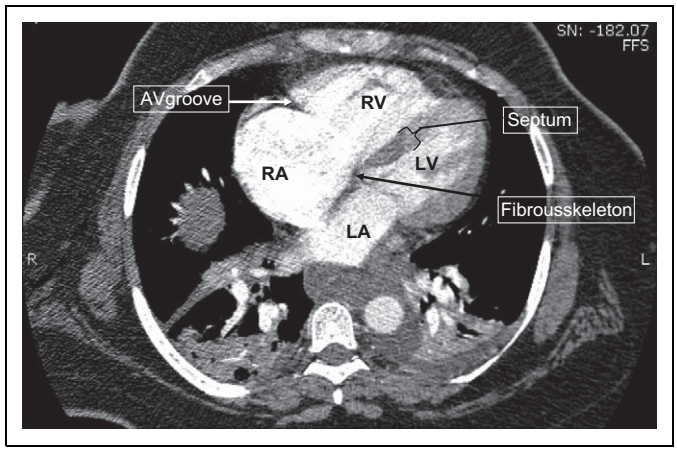

Figure 2. Computed tomographic pulmonary angiography (CTPA) with 4 chambers visualized demonstrates RV enlargement, RA enlargement, and flattening of interventricular septum in a patient with PE. RV indicates right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium.

echocardiographic findings showing the same.[85] Another retrospective analysis of consecutive patients with hemodynamically stable PE[86] examined the ability of the RV diameter/LV diameter ratio and obstruction index[87] to predict 3-month mortality. For an RV/LV diameter ratio >1.0 (Figure 2), the positive predictive value for 3-month mortality was 10.1% (95% CI 2.9%-17.4 %); the negative predictive value for the RV/LV diameter ratio <1.0 was 100% (95% CI 94.3-100).[86] Among patients with an obstruction index greater than 40%, the risk of dying was increased 11.2-fold.[86]

In normotensive patients, the CTPA may allow risk stratification prior to the availability of an echocardiogram. Unfortunately, no data are available yet to determine whether CTPA evaluations of the RV can be used to effectively guide

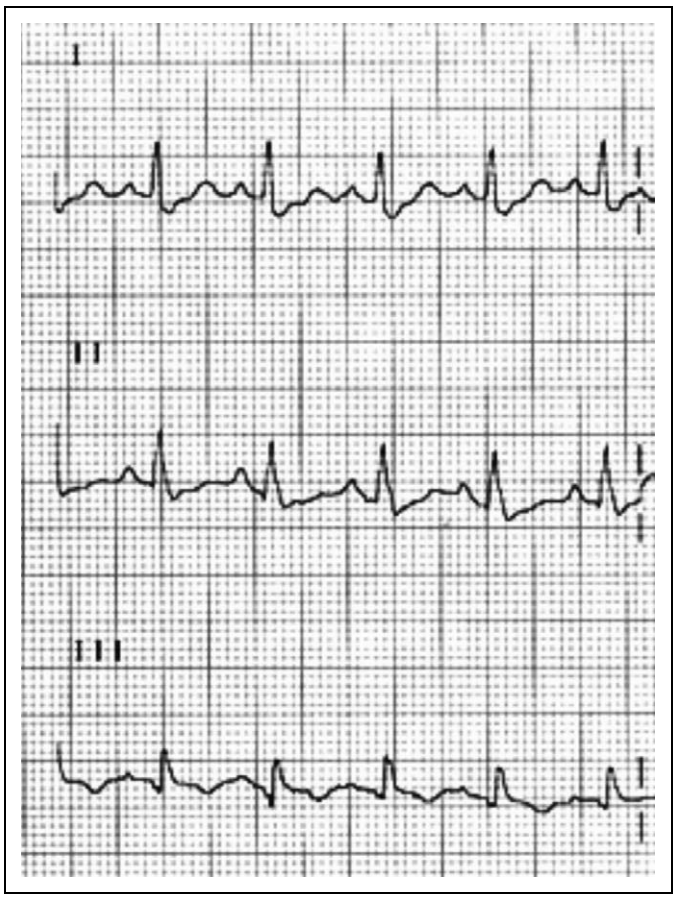

Figure 3. Electrocardiogram (EKG) showing acute RV strain with large S-wave in lead I, large Q-wave in lead III, and inverted T-waves in lead III. RV indicates right ventricle.

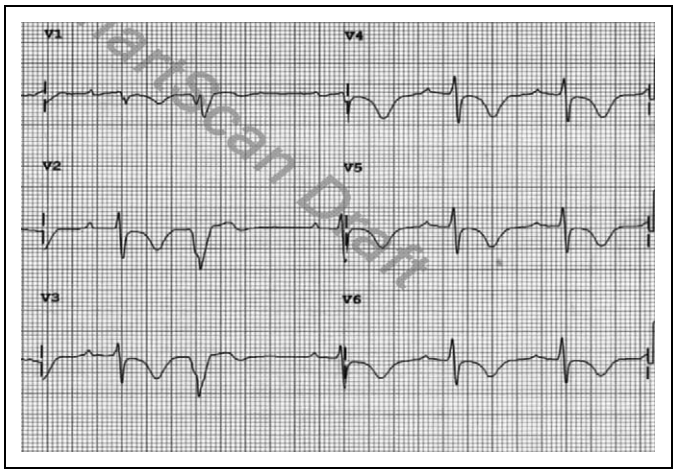

Figure 4. Electrocardiogram (EKG) showing acute RV strain with inverted T-waves across precordial leads. RV indicates right ventricle.

treatment decisions. Pending such data, we recommend using the CTPA to prompt further risk assessment, and not to use it alone to decide whether to pursue aggressive therapies such as thrombolysis or thrombectomy.

Electrocardiogram. The EKG can be used to identify patients at increased risk of complications.[88] The classical pattern of large S-wave in lead I, large Q-wave in lead III, and inverted T-wave in lead III is often used to detect RV strain on EKG (Figure 3). In one series, T-wave inversions (Figure 4) were the most common and most predictive of RV strain among patients with a high degree of PA obstruction or elevated mean PA pressure with preserved cardiac index.[49] Eighty-one percent of patients with T-wave inversions in the precordial leads had mean PA pressures greater than 30 mmHg. These changes resolved with thrombolytics and resolution predicted good outcome.[49]

One study showed that QrV1 and an inverted T-wave in V2 had a positive predictive value for RV strain of 97% ($P > .01$) and 90% ($P < .001$), respectively.[89] The EKG can be used to identify normotensive patients with anatomically significant PE and RV strain but cannot reliably exclude RV strain.

Cardiac Biomarkers

Troponin. Cardiac troponins are released from the RV in response to pressure overload and RV ischemia/infarction.[88,90] Elevated troponin I and T levels are associated with RV dysfunction.[88,91] In one study,[92] for a troponin T > 0.01 ng/mL, the odds ratio for poor outcomes (death, thrombolysis, cardiopulmonary resuscitation, and intravenous vasopressor use) was 24 (95% CI 2.9-200).

A meta-analysis of 20 studies (7 studies with normotensive patients) reported that in hemodynamically stable patients, elevated troponin is associated with mortality (OR 5.90; 95% CI 2.68-12.96).[93] In another meta-analysis, the sensitivity of troponin for in-hospital mortality among normotensive patients was 84% (95% CI 77%-90%).[83] The positive predictive value for in-hospital death is only 14% for troponin I and, depending upon the cutoff value used, 12% to 44% for troponin T.[88]

A negative troponin predicts an uncomplicated hospital course (no death, lysis, vasopressor support for blood pressure, intubation, or cardiopulmonary resuscitation).[91,94] A cutoff level for troponin I of < 0.07 ng/mL has a negative predictive value of 98% for in-hospital mortality, and a cutoff level for troponin T of < 0.04 ng/mL has a negative predictive value of 97%.[88] Despite the high negative predictive value cited in many reports, in a multivariate analysis of hemodynamically stable patients with troponin I < 0.1 ng/mL, it failed to independently predict all-cause mortality.[76] Troponin I was able to predict PE-specific mortality, however.

In summary, Troponin I or T can be used to identify normotensive patients with PE at increased risk of early PE-specific deaths and complications. The cutoff used for troponin can affect its performance. Normotensive patients with negative troponin have a low risk of in-hospital death,[93] and negative troponin assays can help exclude sub-massive PE. To more accurately identify low-risk patients, a combination of the normal troponin with other tools (PESI, for example) is required.[76] At the time of diagnosis, approximately 10% of patients with sub-massive PE will have normal troponin levels;

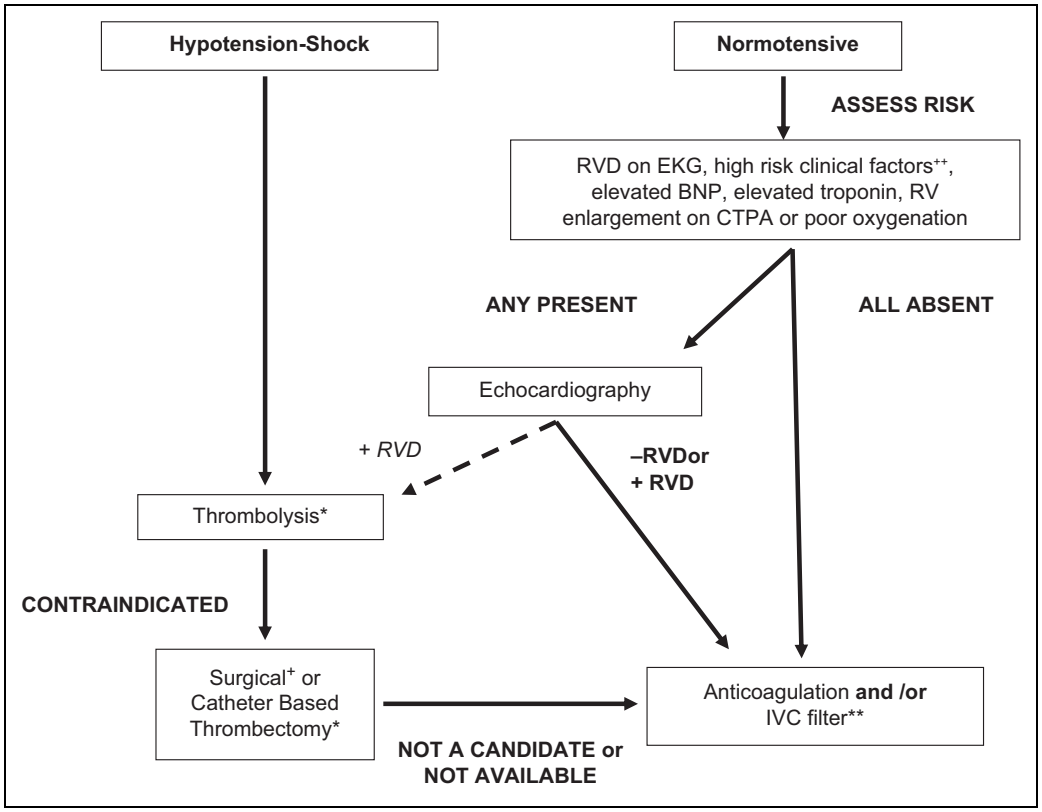

Figure 5. Proposed algorithm for risk stratification and treatment of confirmed PE. The presence of any one poor prognostic indicator should prompt echocardiography. The dashed arrow indicates this option may be considered, but current evidence does not support a firm recommendation. *Thrombolysis and thrombectomy should be followed by anticoagulation if no contraindications. +Many place filters at the time of surgical thrombectomy. ++PE severity index (PESI) may aid in risk assessment. **If anticoagulation is contraindicated, one should usually place an IVC filter as a therapeutic alternative. In patients with sub-massive or massive PE and in those with deep vein thromboses, an IVC filter may considered in addition to anticoagulation because the patient may not tolerate another embolus. RVD indicates right ventricular dysfunction; CTPA, computed tomography pulmonary angiogram; EKG, electrocardiogram; IVC filter, inferior vena cava filter.

therefore, serial testing is advisable.[88,92] The finding of an elevated troponin warrants a TTE (or use of the CTPA) to determine whether RV dysfunction exists because of the low positive predictive value.[95] No prospective clinical trials exist which have used elevated troponin as a basis for aggressive therapy (such as thrombolytics).[93]

Brain natriuretic peptide. Brain natriuretic peptide is a neurohormone synthesized and released from cardiac ventricles in response to ventricular strain.[96] Two forms of BNP have been studied for the purpose of risk stratification of patients with acute PE: BNP and the inactive N-terminal proBNP (NT-proBNP).[90] Elevated levels of BNP are associated with RV dysfunction in acute PE.[97,98]

In a meta-analysis of 12 prospective studies using BNP and NT-proBNP, 6 included only patients who were normotensive at presentation.[96] For normotensive patients, the sensitivity of the biomarkers was 93% for predicting death (95% CI 85%-98%) and 89% (95% CI 83%-93%) for serious adverse events. The negative predictive value was 99% (95% CI 97%-100%) and 94% (95% CI 90%-96%) for death and serious adverse events, respectively. Brain natriuretic peptide levels less than 50 to 85 pg/mL identify low-risk patients.[81,99] For NT-proBNP, levels less than 500 to 1000 pg/mL identify low-risk patients.[7,100] The specificity of BNP and NT-proBNP for death and serious adverse events was 48% (95% CI 44%-51%) and 48% (95% CI 44%-52%), respectively, suggesting that an elevated BNP does not reliably predict a complicated course.[96]

There is an obligatory delay in serum BNP increase after PE because messenger RNA (mRNA) must be upregulated.[96] Several hours may pass before elevated levels of BNP are detected in those with RV dysfunction. Obtaining a BNP upon presentation and several hours later may be more informative if the onset of symptoms is within minutes to hours of evaluation.[101]

In normotensive patients with PE, BNP biomarkers can be used to identify patients who do not have RV dysfunction or are at low risk because of its high sensitivity. It does not appear to be superior to troponins for predicting in-hospital morality. The significance of normal troponin values in the presence of elevated BNP (and vice versa) is unknown. The poor specificity (and poor positive predictive value) of NT-proBNP (or BNP) means that the assay cannot definitively diagnose RV dysfunction and elevated levels should prompt evaluation by echocardiography.[95,96] Because of the high negative predictive value

for poor outcomes or death and the fact that abnormal echocardiograms are rarely encountered in the presence of normal NT-proBNP (or BNP), patients with normal or low NT-proBNP (or BNP) can forego echocardiography, assuming that no other indicators of poor outcome are present.

Other cardiac biomarkers. Heart-type fatty acid-binding protein (H-FABP) and myoglobin are being studied for the purpose of risk assessment. Preliminary reports suggest that H-FABP may be a better predictor of mortality than troponins, BNP, or TTE.[102,103]

Routine Laboratory Studies

Arterial Blood Gas (ABG) and oxygen saturation. Poor oxygenation in patients with PE suggests an anatomically large PE and hemodynamic compromise. A significant negative correlation ($r = -.442$, $P = .03$) exists between Pao_2 and the CTPA occlusion score.[87,104] In one study of normotensive patients, an oxygen saturation greater than 95% was associated with reduced in-hospital complications and 30-day mortality.[105]

D-dimer. The D-dimer is more sensitive at detecting PE in segmental or larger pulmonary arteries (93%, $P < .01$) than sub-segmental emboli (50%, $P < .01$).[106] This would imply that a strongly positive D-dimer is associated with more extensive proximal, therefore, larger emboli. The D-dimer level cannot exclude or diagnose RV dysfunction, but levels less than 1500 mcg/mL can identify patients at low risk of poor outcomes (99% negative predictive value for 3-month all-cause mortality).[107]

Algorithms for Stratifying Risk

Several authors have proposed algorithms for risk stratifying patients presenting with PE using a combination of hemodynamic data, cardiac biomarkers, and echocardiography.[3,13,14,34,89,90] Use of biomarkers (BNP or troponin) to screen for RV dysfunction is reasonable, given their high sensitivity for poor outcomes. The poor specificity of biomarkers means that positive results suggest the need for further testing, for example by echocardiogram. The high negative predictive value of troponin and BNP suggests that in patients having negative biomarkers, lacking multiple clinical risk factors (low PESI, for example), lacking EKG findings suggestive of RV dysfunction, and lacking CTPA evidence of RV dysfunction may forego an echocardiogram to further risk stratify.[13,34,90,108] Omitting the TTE solely on the basis of negative biomarkers cannot be recommended at this time.

Figure 5 depicts a suggested algorithm that combines clinical factors, cardiac biomarkers, EKG, CTPA and echocardiography to assign risk, and possibly guide management. The algorithm requires validation but it provides a reasonable method, based on available literature, of integrating available prognostic variables and using them in a systematic way to assign risk.

Management

Management of PE should be based on the patient's risk of mortality (or complicated clinical course) and contraindications to potential therapies. In patients with high or moderate pretest probability for adverse outcomes, or hemodynamic instability, empiric anticoagulation should be initiated immediately.[7] Hemodynamic stabilization should be addressed at the same time as anticoagulation.

Triage. Although no specific guidelines exist for triage, patients with sub-massive PE are at risk of rapid clinical deterioration[10] and are generally best served by initial admission to a monitored or ICU bed. Those with advanced age, malignancy, poor oxygenation (oxygen saturation < 90% with or without supplemental oxygen), tachycardia (HR > 110 per minute) and major cardiopulmonary illness have significant 30-day mortality[36] and should be admitted to a monitored or ICU bed. Should the need for vasopressors, mechanical ventilation, or thrombolytics arise, a deteriorating patient can be promptly recognized and managed appropriately. Patients with massive PE require admission to an ICU.

General Supportive Care

Respiratory support. Hypoxemia can be treated with supplemental oxygen via nasal cannula or face mask.[13] Supplemental oxygen may reduce the contribution of hypoxemia to elevated PVR and alleviate RV ischemia. Goal oxygen saturation above 92% seems reasonable although no guidelines for acceptable levels of oxygenation exist.

Mechanical ventilation may be necessary for progressive respiratory failure refractory to supplemental oxygen.[8] Intubation may precipitate cardiovascular collapse for several reasons: (1) sedative hypnotics used for intubation can blunt endogenous catecholamines, (2) increased intrathoracic pressures may reduce venous return, and (3) mechanical ventilation can increase PVR and worsen RV dysfunction.[3] Should it be necessary to intubate a patient with massive PE, positive end expiratory pressure should be minimized, and low tidal volumes (approximately 6 mL/kg) should be used in an effort to keep the plateau pressures less than 30 cm H_2O, recognizing that limited data are available to specifically guide mechanical ventilation strategies in this population.[13]

Intravenous fluids. Fluids may be given cautiously to reverse possible hypovolemia.[7] Increasing RV end-diastolic volume may be useful if preload is inadequate; however, too much fluid can cause adverse effects on hemodynamics in the presence of RV dysfunction. Excessive end-diastolic volume increases RV wall stress, which has two detrimental effects: (1) it worsens RV ischemia and (2) causes further interventricular shift, thus impeding LV filling.[3,7,109] A small volume of fluid (250-500 cc - milliliter) may be given initially. Decisions regarding additional fluids may require hemodynamic assessment or TTE.[110]

Vasopressors. In hemodynamically unstable patients, vasopressors should be started immediately if a small volume fluid challenge fails to stabilize the patient, recognizing that large volumes of fluid may worsen hemodynamic instability. Potential agents include norepinephrine, dopamine, and phenylephrine. In dog models, both norepinephrine and dopamine improve RV function and increase flow through the pulmonary arteries.[111] Both agents can increase systemic vascular resistance (dopamine at higher doses).[7,111] The ability of norepinephrine to increase systemic vascular resistance means that the mean arterial pressure and RV coronary perfusion pressure are maintained in patients with RV dysfunction or RV ischemia.[112] The same may be true of dopamine.

Phenylephrine results in less improvement in cardiac output and less improvement in RV coronary perfusion pressure than norepinephrine.[111] Phenylephrine may increase systemic arterial pressure when added to other vasopressors or inotropes[7] and may have a role as a second agent.

Inotropes. Inotropes such as dobutamine increase cardiac output and tissue oxygenation.[111] They also have potent vasodilator effects and may contribute to systemic hypotension.[109] In patients with massive PE, it may be reasonable to initiate support with a vasopressor to raise systemic arterial pressure and then add an inotrope if signs of ongoing shock or low cardiac output persist.[109]

PA vasodilators. Some reports suggest that inhaled nitric oxide can lower PA pressures and increase cardiac index.[113] Experimental models of PE have noted reduced PA pressures using sildenafil infusions.[114,115] Others have studied inhaled prostacyclin and levosimendan for acute PE.[13] Use of these agents in vasopressor refractory shock may be helpful if there is a delay in definitive therapy (thrombolysis, catheter-directed therapies, or surgical thrombectomy) or a contraindication to these interventions.

Anticoagulation

Patients should receive empiric anticoagulation unless there is a contraindication.[7,116] In the ICU, unfractionated heparin (UFH) is typically the first choice for anticoagulation but other options include low-molecular-weight heparin (LMWH), fondaparinux, lepirudin, and argatroban.[34] In critically ill patients, the ability to monitor the partial thromboplastin time (PTT) and intravenous delivery provides assurance that adequate dosing is achieved.

Unfractionated heparin. Recommended dosing for intravenous UFH is an 80-unit/kg bolus, followed by an 18-unit/kg per h continuous intravenous infusion.[116] The goal PTT is 80 seconds (in the high therapeutic range) because subtherapeutic dosing can be fatal.[7] Standard doses of UFH often do not achieve therapeutic anticoagulation in patients with massive PE[7] so frequent monitoring of the PTT (every 4 hours for example) with appropriate adjustment of the infusion rate is warranted.

Low-Molecular-Weight Heparins. LMWHs (enoxaparin, dalteparin, tinzaparin) are delivered subcutaneously. Uncertainty exists regarding the efficacy of subcutaneous anticoagulation in critically ill patients with PE.[110] Unfractionated heparin is preferred over LMWH in unstable patients because dosing can be easily adjusted and, if held in preparation for the use of thrombolytics,[116] its effects wear off quicker than those of LMWH. Low-molecular-weight heparins have not been tested in combination with thrombolysis.[34] The potential for a decline in clinical status is significant for those with sub-massive PE and the use of LMWH may complicate matters in the event that thrombolysis is required later.[34] Patients with low-risk PE may be candidates for anticoagulation with LMWH. Low-molecular-weight heparin should be used cautiously or not at all in those with renal insufficiency because it is cleared by the kidneys and excessive anticoagulation may result.[34,116]

Fondaparinux. Fondaparinux is a synthetic pentasaccharide anticoagulant. An open-label trial demonstrated that fondaparinux was noninferior compared to UFH in hemodynamically stable patients.[117] As with LMWH, concerns about subcutaneous delivery in the critically ill and lack of data regarding use with thrombolytics limits its use in life-threatening PE. Intravenous UFH is preferred over fondaparinux in patients with renal insufficiency[116] and fondaparinux should not be used in those with severe renal insufficiency.

Complications. The main complications of anticoagulant therapy include bleeding and heparin-induced thrombocytopenia. Patients at risk of anticoagulant bleeding include those with renal insufficiency, hepatic insufficiency, stress ulcers, disseminated intravascular clotting, and postoperative patients.[110] Surveillance in critically ill patients should include serial physical examinations for evidence of bleeding (abdominal distension, flank hematoma) and serial hemoglobin values.[110] Agents useful for reversing anticoagulation[110] in the event of serious bleeding (depending on the anticoagulant in use) include protamine, Desmopressin (DDAVP), factor VIII inhibitor bypass activity, fresh frozen plasma, vitamin K, and recombinant factor VIIa.

Heparin-induced thrombocytopenia may be associated with venous and arterial thromboembolism[118] and should be suspected when there is a greater than 50% decrease from baseline in platelet count or a new thromboembolic event while on heparin.[14] Patients at risk of heparin-induced thrombocytopenia include those receiving heparin for 4 or more days and those with prior exposure to heparin.[14] Low-molecular-weight heparin is associated with less heparin-induced thrombocytopenia than UFH but the risk is not zero (1% vs 3%-5%).[34] The incidence of heparin-induced thrombocytopenia is negligible with fondaparinux and there is no need to monitor platelet counts.[34] When there is a moderate-to-high index of suspicion for heparin-induced thrombocytopenia, all heparins should be stopped and

an intravenous thrombin inhibitor like lepirudin or argatroban should be used.[34] Fondaparinux is also an option.[14]

Vitamin K antagonists. For massive PE, warfarin is best initiated once patients are hemodynamically stable, after thrombolysis, or after planned invasive procedures (such as central line placement, catheter-based treatments for PE, or surgical thrombectomy). The difficulty reversing warfarin in the event of clinical decline, bleeding, or invasive procedure makes its use complicated in the critical patient. In hemodynamically stable patients with PE, warfarin may be initiated at the same time as UFH, LMWH, or fondaparinux.[14]

Massive PE

Therapies used in massive PE to rapidly reverse PA obstruction include thrombolysis, catheter-directed therapies, and surgical embolectomy. These definitive therapies offer rapid reversal of PA occlusion, should reduce PVR and reduce RV pressure overload; thus restoring normal hemodynamics.[3,13]

Thrombolytic Therapy

Assuming there are no contraindications, thrombolytics should be strongly considered in patients with massive PE.[13,116] Compared to heparin alone, thrombolytics appear to improve clinical outcomes and reduce the risk of recurrent PE.[119] As a result, thrombolytic therapy is felt to be a key component in the treatment of massive PE. Several trials have documented rapid angiographic and hemodynamic improvement when thrombolytics are used.[120,121] In one study, use of tissue plasminogen activator (rTPA or alteplase) as a 2-hour infusion results in a 30% reduction in PA pressures and a 15% increase in cardiac index.[120] Trends toward a reduction in recurrent PE and all-cause mortality have consistently been demonstrated, but studies often lack statistical significance.[116,122] In a meta-analysis analyzing patients with massive and sub-massive PE, a statistically significant reduction in the combined outcome of recurrent PE and death was found (OR 0.45, 95% CI 0.22-0.92).[123] A recent meta-analysis failed to show any difference in all-cause mortality, PE-specific mortality, or recurrence of PE[124]; however, the analysis included studies with hemodynamically unstable and hemodynamically stable patients.

The choice of thrombolytic regimen should take into account the fact that prolonged infusions are associated with higher rates of bleeding, and shorter infusions ($\leq$2 hours) achieve more rapid clot lysis. Shorter infusion times reverse hemodynamic compromise more rapidly.[125] Two-hour infusions of streptokinase or rTPA provide equivalent and effective improvement in hemodynamic parameters.[126] Streptokinase, urokinase, and rTPA are all approved for use in PE; no agent has proven superiority over another.[127,128] Detailed comparisons of thrombolytic agents are provided by Kearon et al and Konstantinides.[116,127,129]

One commonly used regimen is rTPA 100 mg infused over 2 hours.[13,116] For patients in imminent danger of cardiovascular collapse or death, an accelerated regimen of 0.6 mg/kg rTPA infused over 15 minutes (maximum dose 50 mg) can be delivered.[130] Unfractionated heparin should be stopped as soon as the decision to deliver thrombolytics is made.[131] Once the thrombolytic infusion is completed, UFH can resume without a bolus. The greatest benefit of thrombolytics is obtained when delivered within 48 hours of symptom onset.[13] Some benefit may still be observed up to 14 days after symptom onset.[132]

Table 4. Contraindications to Thrombolytic Therapy[13,15]

Absolute Contraindications	Relative Contraindications
Major trauma, surgery, head trauma within 3 weeks	Cancer
Prior hemorrhagic stroke	Age > 75-80
Ischemic stroke within prior 6 months	Transient ischemic attack within 6 months
Central nervous system neoplasm	Oral anticoagulant therapy
Gastrointestinal bleeding within one month	Noncompressible punctures
Active bleeding	Traumatic resuscitation
	Refractory hypertension
	Advanced liver disease
	Infective endocarditis
	Active peptic ulcer
	Pregnancy or within one week postpartum

Thrombolytics may be associated with increased risk of bleeding and intracranial hemorrhage, making it essential that candidates for therapy are chosen carefully. Cumulative evidence from several studies revealed an overall rate of major bleeding of 13%.[13] In the International Cooperative PE Registry, 21.7% had major bleeding complications[9] and the rate of intracranial or fatal hemorrhage was 1.8% to 3.0% in carefully selected patients.[9,13,116] More recent pooled data failed to show an increase in bleeding risk with thrombolytic therapy.[124] Thrombolytics should be reserved for those without contraindications (Table 4) and the benefits of therapy should be carefully weighed against the risks of bleeding. Despite the risks of thrombolytic therapy, it is considered first-line definitive therapy in massive PE because it is widely available, probably improves survival, and less invasive than alternatives (catheter-directed therapies or surgical embolectomy).

Catheter-Directed Therapies

Catheter-directed therapies provide an alternative to thrombolysis in those with massive PE. It may be an option in those with contraindications to thrombolytic therapy. Several investigators have used catheter-directed therapies to treat patients with massive PE.[133-135] In some instances, those with an inadequate response to primary thrombolysis were selected to receive catheter-directed therapy.[129] When initial thrombolytic therapy fails, repeat thrombolysis has been associated with a 38% mortality and a 15% rate of significant bleeding.[132] Catheter-directed therapies (without thrombolytics) may be appropriate salvage therapy for those failing thrombolytics.

Table 5. Catheter-Directed Therapies[a]

Technique	Description	Comments
Thrombolysis[129,137]	Catheter in main PA, bolus of thrombolytic followed by infusion Often combined with mechanical fragmentation to increase surface area of thrombus exposed to thrombolytic	No reduced risk of bleeding documented [110] No evidence of benefit of catheter-directed lysis over systemic unless combined with fragmentation[156,157]
Fragmentation[137,140]	Breaking up large, central clot with catheter device; device rotated by operator Fragments migrate distally Often combined with local thrombolysis	Improved recanalization with thrombolytics Example: Cook Europe rotatable pigtail catheter
Embolectomy[137]	Catheter directed to thrombus and manual suction used to remove thrombus	Examples: Greenfield embolectomy device
Balloon angioplasty[137]	Compression of embolus Often combined with local thrombolysis	Results in partial fragmentation of embolus Difficult to tell if thrombolytic explains hemodynamic benefits when combined Examples: Wallstent, Gianturco Z stents
Percutaneous thrombectomy[7,131,137,140]	Clot pulverized and removed via catheter by rotation of device or hydrodynamic vortex	Examples: Amplatz thrombectomy device, the Hydrolizer, Aspirex

Abbreviations: PA, pulmonary artery; RV, right ventricular
[a] Potential complications include[129,137,138]: PA perforation, RV perforation, ventricular arrhythmias, contrast nephropathy, mechanical hemolysis (resulting in hypotension & pancreatitis), hematoma, pseudoaneurysm, arteriovenous fistulas

Several authors have described techniques for catheter-directed thrombolysis, thrombus fragmentation, percutaneous embolectomy, balloon angioplasty, and percutaneous thrombectomy (Table 5).[131,133,134,136] A detailed review of techniques and devices has been published.[137]

In order to achieve the promising results reported in case series, operators must be comfortable with the technique and the management of these critically ill patients.[138] Procedures should be terminated once hemodynamic (not radiographic) improvement has been obtained to minimize the risk of complications, which include pulmonary hemorrhage, PA perforation, PA dissection, arrhythmias, hypotension, and death.[137]

A recent meta-analysis of catheter-directed intervention in massive PE, reported clinical success rates of 86.5%, defined as improved hemodynamics, resolution of hypoxia, and survival to discharge.[139] In-hospital survival rates as high 83% have been reported with few procedure-related complications.[134] These rates compare favorably with the 70% to 83% survival reported in the literature for those with massive PE.[3,7,15,128]

Selection criteria for patients receiving catheter-directed therapies should include hemodynamic instability, evidence of RV dysfunction (or RV infarct), contraindications to thrombolysis (if not going combine with local thrombolytic therapy),[137] and the presence of large central clot.[129,140] Although there are a limited number of centers with expertise, available evidence suggests that catheter-directed therapy is an acceptable alternative to systemic thrombolysis in those unable to receive thrombolytics (or anticoagulation) or those who have failed primary thrombolysis.[116,137]

Surgical Embolectomy

Surgical embolectomy, like catheter-directed therapy, can provide an alternative for patients with contraindications to thrombolysis (or those who have failed thrombolysis). It also provides a reliable way to remove PA clot under direct visualization.[13] Initially, the technique was reserved for those requiring cardiopulmonary resuscitation, those with patent foramen ovale, those with intracardiac thrombus, and those with contraindications to thrombolysis.[13] Over time, surgical embolectomy has been used in a broader patient population with massive PE[13] and, combined with better surgical technique, results have improved. The perioperative mortality has fallen from as high as 26% in the 1990s to 6% in the 2000s.[141]

In one study, surgical embolectomy was performed on 47 consecutive patients with central, large PE.[141] Indications for surgical embolectomy included contraindication to thrombolysis, failed medical treatment, large right atrial (or RV thrombus), large patent foramen ovale, and RV dysfunction. Only 24 patients had hemodynamically massive PE (hypotension, syncope, cardiac arrest). A 3-year survival of 86% (95% CI 70%-90%) was reported for all categories of PE. It is difficult to determine how much patients with massive PE benefited from the procedure because all categories of PE were included in the analysis. Other studies report that the risks of bleeding are less than those associated with thrombolytic therapy.[142]

Surgical embolectomy is invasive and requires cardiopulmonary bypass. Time is required to mobilize the surgical team. The availability of surgical embolectomy during night hours is limited in most centers. The delay required to arrange surgical

Table 6. Thirty-Day Mortality for RV/LV Ratio and Troponin I[a,b,c]

TTE*	Troponin - I > 0.1 mcg/L	Troponin - I < 0.1 mcg/L
RV/LV > 0.9	38%	9%
RV/LV < 0.9	23%	< 5%

Abbreviations: RV/LV, right ventricular/left ventricular end-diastolic diameter ratio.
[a] *Am J Cardiol.* 2005;96(2):303-305.[143]
[b] N = 141 and 16 had systolic blood pressure < 100 mmHg.
[c] The ratio is used as an echocardiographic measure of right ventricular enlargement and sign of RV dysfunction.

embolectomy in a patient with life-threatening PE may render it impractical in many instances.

Currently, patients with patent foramen ovale or intracardiac thrombus should be considered for surgical embolectomy. Surgical embolectomy should also be considered for patients with massive PE if contraindications to thrombolytics exist, contraindications to anticoagulation exist, or if there has been a failure of primary thrombolysis

Sub-Massive PE

Categories of Sub-massive PE

Several findings may be used to help refine prognosis for individual patients (eg, PESI, BNP, troponin, and EKG). One study retrospectively examined the impact on 30-day mortality of the presence of both an elevated biomarker and an enlarged RV (Table 6).[143] Among normotensive patients, the presence of both RV enlargement and elevated troponin I resulted in a hazard ratio for mortality of 5.6 (95% CI 1.2-25.9) compared with 2.2 (95% CI 0.37-13.2) for the presence of only an elevated RV/LV ratio. This study supports the notion that subgroups exist within the sub-massive category with a spectrum of severity. Patients at high risk of death may benefit from more aggressive treatment approaches. To date, treatment studies usually analyze sub-massive patients as a single group, making it difficult to identify which individuals stand to benefit from specific treatments.

Thrombolytics

Controversy exists regarding the use of thrombolytic therapy in those with sub-massive PE. Some feel that the poorer prognosis of those with sub-massive PE (as compared to low-risk PE) warrants more aggressive therapy than anticoagulation. However, although thrombolytics may improve PA pressures and pulmonary perfusion more quickly than anticoagulation alone,[121] no studies have documented a definite survival benefit of thrombolysis in this group.

A randomized controlled trial of hemodynamically stable patients and RV dysfunction (as assessed by echocardiography) showed that rTPA resulted in greater improvement of RV function at 24 hours, greater improvement in pulmonary perfusion (as assessed by VQ scan), and a reduced incidence of recurrent PE compared to UFH alone.[121] A retrospective cohort of normotensive patients with evidence of RV dysfunction (RV/LV dilatation > 0.6 on TTE) and large anatomic PE (as assessed by PA gram or VQ scan) failed to show a benefit of thrombolysis over UFH.[144] Patients in the thrombolysis group received 1 of 3 thrombolytic regimens (rTPA, urokinase, or saruplase) in addition to UFH or LMWH or LH. Patients in the control group received UFH and LMWH. The study failed to show any difference in recurrent PE or in-hospital mortality. There was a significant increase in severe bleeding episodes (intracranial hemorrhage, reduction in hemoglobin levels >4 g/dL, bleeding requiring surgery, or transfusion of greater than 2 units of red blood cells) in the thrombolysis group, however. Severe bleeding occurred in 3 patients, 2 of whom were over 80 years of age.

A randomized clinical trial with normotensive patients and RV dysfunction suggested benefit from thrombolysis compared to UFH.[145] The primary end point was a combination of death and escalation of treatment (defined by the use of vasopressors, secondary lysis, rescue embolectomy, endotracheal intubation, or cardiopulmonary resuscitation). The study showed a reduction in the primary end point, reduction in escalation of treatment, and less secondary thrombolysis in the rTPA group compared with the control group. No mortality difference at 30 days was detected. There was no significant difference in major bleeding.

In carefully selected patients, thrombolytics may be given safely and can result in less recurrent PE, less escalation of treatment, and faster hemodynamic improvement. Patients with sub-massive PE who are considered candidates for thrombolytic therapy should be those with more severe disease.[116] Candidates should have low bleeding risk (no contraindications and few relative contraindications) and be less than 75 to 80 years of age (Table 4). Currently, the routine use of thrombolytics in patients with all severities of sub-massive PE cannot be recommended because of the lack of evidence of survival benefit and potential risk of life-threatening bleed. The decision must be made on an individual basis. A large multinational trial in patients with sub-massive PE is currently underway and may determine whether thrombolytic therapy can offer survival benefit to this group of PE patients (Clinical Trials.gov number, NCT00639743).

Catheter-Directed Therapy

Available research regarding the use of catheter-directed therapies in sub-massive PE is difficult to interpret. Case series available [131,133,134,136] include patients with sub-massive PE and massive PE. Most published series report excellent outcomes with few procedure-related complications. However, it is difficult to determine whether the published benefits of catheter-directed therapies are mainly due to the benefits observed in massive PE because the 2 categories are studied together or whether publication bias may have contributed.

Catheter-directed therapies may be considered for patients with sub-massive PE if there are contraindications to anticoagulation, if there is clinical deterioration, or if there is a failure of primary systemic thrombolytic therapy. No firm recommendations exist.

Surgical Embolectomy

The efficacy of surgical embolectomy in patients with sub-massive PE is difficult to determine based on available studies. Available studies of surgical embolectomy include patients with massive and sub-massive PE.[141,146] It is difficult to discern how much of the benefit reported is due to benefit in patients with massive as opposed to sub-massive PE. A 30-day survival[146] of 89% compares favorably to the 87% to 92% reported in the literature.[108,144]

As with catheter-directed therapy, surgical embolectomy for sub-massive PE may be considered if there is a contraindication to anticoagulation (or thrombolytic therapy), if there is clinical deterioration, or if there is a failure of primary systemic thrombolytic therapy. Unfortunately, no randomized trials comparing surgical embolectomy to anticoagulation (or thrombolysis) exist.

Role of IVC Filters

Inferior vena caval filters are indicated to prevent recurrent PE in patients with VTE who have contraindications to anticoagulant therapy (or thrombolytic therapy).[116,147,148] Their placement after surgical embolectomy is also recommended,[142] given the 5% rate of recurrent PE in patients after surgical therapy.[141]

In the ICOPER registry, IVC filters appeared to reduce recurrence of PE and mortality at 90 days in massive PE.[9,31] Uncertainty exists regarding the risks and benefits of using an IVC filter as an adjunct to thrombolytic therapy in massive PE.[116] The short-term and long-term benefits (reduced risk of PE at 8 years)[147] of an IVC filter should be weighed against the potential long-term complications (recurrent DVT, filter thrombosis, and filter migration). Because of the risk of recurrent DVT with IVC filter, if a contraindication to anticoagulation is temporary, patients should be anticoagulated once the contraindication is no longer present.[149,150] Removable filters exist and can be removed up to 3 months after placement (some reports indicate 1 year),[151,152] if the risk factor for VTE is temporary (ie, trauma). They can also be removed if the contraindication to anticoagulation is temporary.

Clinicians caring for patients with massive or sub-massive PE with documented DVT (even if receiving thrombolysis and or anticoagulation) may consider placement of an IVC filter to prevent recurrent PE. There is little evidence for reduced mortality, however.[31,147] These patients are likely to have marked worsening of their already critical status, should another PE develop. No evidence to support the routine use of IVC filters in the critically ill population exists, however.

Summary and Conclusions

The diagnosis and treatment of PE poses special challenges in the context of critical illness. The presenting signs and symptoms of PE are generally nonspecific, often making it difficult to distinguish the diagnosis from other life-threatening disorders. Computed tomographic pulmonary angiography appears to be the most useful diagnostic test for PE in this population. If CTPA is unavailable or contraindicated, echocardiography, VQ scan, and Doppler ultrasound offer important alternatives.

Risk stratification is a key component of the initial evaluation of patients with PE, helping to guide decisions regarding admission to the ICU and whether treatment beyond simple anticoagulation is needed. Key findings that suggest increased risk include simple clinical findings such as vital sign abnormalities and severity of hypoxia, ECG abnormalities, elevated cardiac biomarkers such as troponin and BNP, and evidence of RV strain on the CTPA and echocardiogram. Currently, use of risk factors in combination offers the most accurate risk assessment.

Anticoagulation remains the mainstay of therapy for almost all patients with PE unless there is a contraindication. For those at increased risk of poor outcome directly related to the size and hemodynamic impact of the PE, thrombolytics, surgical embolectomy, and catheter-directed therapies offer important treatment adjuncts. Thrombolysis is central to the treatment of patients with massive PE and may also be helpful in patients with more severe presentations of sub-massive clot. If thrombolysis is contraindicated, surgical embolectomy and potentially catheter embolectomy may provide useful alternatives. For those at risk of recurrent clot, particularly when anticoagulation is not an option, placement of an IVC filter is an essential consideration.

Despite the high risk of mortality, patients with massive and sub-massive PE offer Intensivists a unique opportunity to intervene effectively on the patient's behalf. Rapid, accurate diagnosis, thoughtful risk stratification, and intelligent use of available therapies should improve survival in patients with this life-threatening but highly treatable disorder.

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