25 Venous Thromboembolism in the Intensive Care Unit

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Case Presentation

Case Scenario

A 72 year-old retired family physician with a history of hypertension and prostate cancer was admitted to the hospital with complaints of worsening dyspnea over 48 h. On presentation, he was tachycardic with a heart rate 112, tachypneic with a respiratory rate of 22, normotensive with a blood pressure of 110/70 and his pulse oximetry revealed an O_2 saturation of 88 % on room air. He had 2+ left lower extremity edema (with trace edema on the right). A chest x-ray showed no acute cardiopulmonary disease, and his EKG revealed sinus tachycardia with non-specific T wave changes. Laboratory studies were within normal limits with the exception of a troponin I which was elevated to 1.5 ng/ml (reference < 0.30 ng/ml). A CT-pulmonary angiogram revealed bilateral central pulmonary artery emboli (Fig. 25.1) and an enlarged right ventricle. The patient was admitted to the intensive care unit and started on an intravenous (IV) heparin drip.

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Question If the decision is made to administer thrombolytic therapy, how would this treatment alter the patient's overall outcome? His survival?

Answer Treatment with thrombolytic therapy would likely prevent hemodynamic collapse but would not affect his chances of survival.

In the PEITHO trial, 1005 patients with submassive pulmonary embolism, defined by right ventricular enlargement or dysfunction and myocardial injury as indicated by an elevated troponin I or troponin T, were randomized to receive IV heparin and placebo versus IV heparin and recombinant Tissue plasminogen activator (t-PA) [1]. The primary endpoint was a clinical composite of death or hemodynamic decompensation within 7 days after randomization. The investigators also assessed a safety endpoint of bleeding complications. The results of this study revealed that treatment with t-PA significantly reduced the primary endpoint of death or hemodynamic decompensation within 7 days after randomization (2.6 % versus 5.6 %, p = 0.02). The difference in the primary endpoint was driven by a reduction in hemodynamic collapse as mortality was not different between the two treatment groups. The benefit of a reduction in the primary outcome with t-PA treatment came with the expense of an

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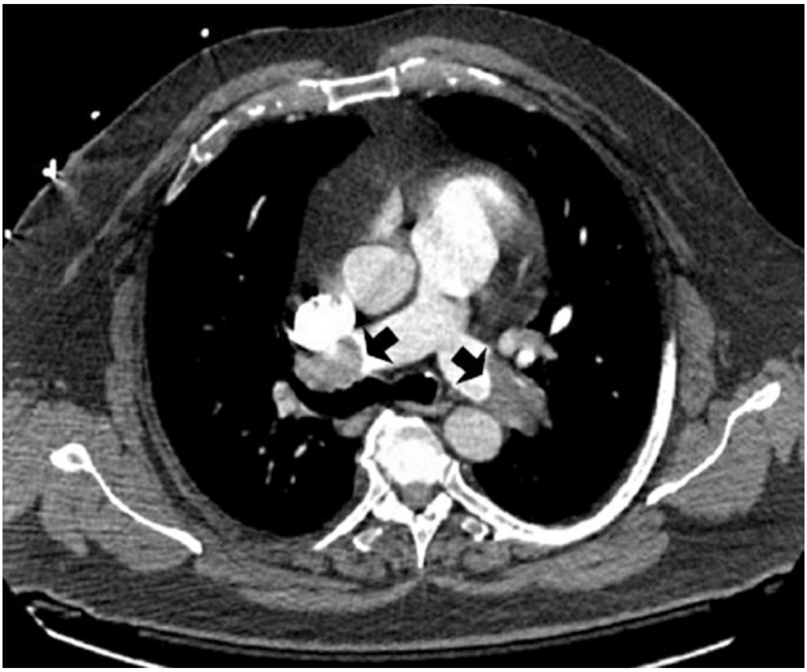

Fig. 25.1 Large central thrombi in the main bilateral pulmonary arteries (*arrows*) in a 72-year-old man who presented with submassive pulmonary embolism

increased risk of major bleeding events including extracranial bleeding ($p < 0.001$) and strokes ($p = 0.003$).

Standard Approach to Diagnosis and Management

Risk Factors

Pulmonary embolism is a consequence of thrombosis in the deeps veins of the lower extremities, pelvis, and less commonly, the upper extremities. The classic triad of risk factors for the development of deep venous thrombosis, known as Virchow's triad, includes stasis of blood flow, hypercoagulability, and endothelial injury. Patients admitted to the intensive care unit frequently experience all of these risk factors and are therefore at a heightened risk for deep venous thrombosis (DVT) and, in turn, pulmonary embolism (PE). Specifically, mechanical ventilation, sedation, and the use of paralytic agents accentuate the immobility of critical illness and thereby contribute to stasis of blood flow. In addition, central lines inserted into the upper and/or lower extremity deep veins serve as a nidus for thrombosis secondary to local endothelium disruption. Central lines placed in the femoral and internal jugular veins are associated with a particularly high risk, and the likelihood of this complication increases with the duration of catheter placement [2, 3]. Finally, the clinical diagnosis that necessitates ICU admission can modify the risk of venous thromboembolism (VTE). For example, immobility secondary to infection was associated with a shorter duration until the onset of thromboembolism as compared to patients whose immobility was due to dementia (less than 4 weeks in 94.2 vs. 25.9 % of cases; $p < 0.001$) [4]. The clinical presentations of severe sepsis and septic shock are also associated with a high rate of VTE [5]. The mechanistic connection between infection and venous thrombosis is in part explained by inflammation-induced: (1) elaboration of tissue factor, (2) impairment of anticoagulant pathways, and (3) suppression of fibrinolysis secondary to the overproduction of plasminogen activator inhibitor-1 [6].

Epidemiology of VTE in the ICU

The presence of multiple risk factors for VTE in ICU patients confers a high risk of disease. Clinical studies demonstrate that both unfractionated heparin and low molecular weight heparin decrease the risk of DVT in the critical care unit [4, 7]. As a result of this evidence, current practice guidelines recommend the administration of thromboprophylaxis in the critical care setting. Therefore, it is not surprising that, in a multivariate analysis of risk factors for PE in a Tunisian ICU, the absence of pharmacologic prevention was identified as a significant predictor for PE [8]. However, even in the presence of prophylactic heparin treatment, the risk of VTE is significant. In the PROTECT study, the efficacy of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) were compared in the prevention of DVT in critically ill patients [9]. Evidence for new DVT formation was determined by the performance of twice-weekly compression ultrasonography. Despite the administration of prophylactic anticoagulation, the rates of DVT were 5.1 % in patients treated with LMWH and 5.8 % in patients treated with UFH. The risk of DVT appears to be even greater in patients with acute decompensated COPD who undergo mechanical ventilation [10]. In this population, treatment with weight-adjusted LMWH was associated with a DVT incidence of 15.5 % while patients receiving placebo experienced a 28.2 % incidence of clot.

Although evidence indicates that the incidence of DVT in the ICU is high, it is less clear how often this complication results in pulmonary embolism. In the PROTECT trial, PE was evaluated when clinically indicated, and in patients treated with LMWH, there was a 1.2 % incidence of definite or probable PE as compared to a 2.1 % incidence in the group treated with UFH. While these incidences are low and reassuring, results from a 2012 study suggests that the diagnosis of PE may be frequently missed in the ICU [11]. In this investigation, 176 consecutive mechanically ventilated patients who required a CT scan for any indication underwent the standard imaging protocol for pulmonary embolism detection. The investigators discovered that the incidence of PE was 18.7 %, and in 61 % of these patients, there was no clinical suspicion of disease. Importantly, the study protocol called for the performance of lower extremity compression ultrasonography in all patients within 48 h of their CT scan, and only 33 % of individuals with a PE were found to have a concurrent DVT. Collectively, these studies demonstrate that both DVT and PE are relatively common in the ICU despite thromboprophylaxis. Perhaps even more concerning is the observation that the majority of patients diagnosed with a PE lacked clinical features of the disease.

Clinical Presentation

The clinical presentation in the accompanying case scenario is highly suggestive of pulmonary embolism. However, in the ambulatory population, the clinical features of venous thromboembolic disease are largely non-specific. The lack of specificity in both symptoms and signs of pulmonary embolism was highlighted in PIOPED II, a study in which patients with suspected PE were enrolled to evaluate the predictive value of Computed-tomography pulmonary angiography (CT-PA) [12]. As part of this study, the frequency of symptoms and signs in patients with confirmed PE were compared to enrolled patients who ultimately ruled out for thromboembolism. Surprisingly, this investigation revealed that the presentation of hemoptysis or pleuritic chest pain was more common in PE-negative patients than in the PE-positive group (56 vs 44 %, $p < 0.01$). Furthermore, there was no difference between the two groups in the frequency of presenting with circulatory collapse. The presence of uncomplicated dyspnea (i.e. dyspnea without accompanying symptoms of chest pain, hemoptysis or circulatory collapse) was more common in patients diagnosed with PE than the PE-negative group but the overall percentages were similar (36 % versus 26 %, P<0.01). With respect to specific symptoms or signs, the complaint or clinical detection of calf or thigh swelling or pain was most discerning for those who did versus those who did not have a PE.

In the critical care patient, co-morbid conditions that are associated with hypotension and hypoxemia make it even more challenging to identify patients with VTE. In a single center study of 4408 ICU patients, 87 (1.9 %) were diagnosed with pulmonary embolism [8]. Abnormalities in this group that led to the evaluation and diagnosis of PE included hypotension (57.5 %), positive SIRS criteria (72.4 %), respiratory distress requiring mechanical ventilation (81.6 %), and clinical manifestations of DVT (17.2 %). These derangements, perhaps with the exception of clinical manifestation of DVT, are not specific for PE and can be observed in other conditions that commonly lead to ICU admission including septic or hemorrhagic shock, congestive heart failure, and pneumonia.

The low sensitivity and specificity of symptoms and signs for VTE motivated the development of clinical prediction tools including the Wells Criteria (Table 25.1) and the Geneva Scoring System (Table 25.2) to aid clinicians in the evaluation of VTE. The Wells criteria either dichotomizes or trichotomizes patients into VTE risk categories [13]. This prediction tool has been well validated in the outpatient setting, but in hospitalized patients, it was found to perform less well for the diagnosis of DVT [14]. The Wells Criteria and the Geneva Score have not been explicitly evaluated in the critical care setting. However, based on the challenge of evaluating symptoms in the ICU patient who may be intubated, sedated, and/or delirious and in the presence of concurrent critical illnesses that commonly result in tachycardia and lower extremity edema, it is likely that the predictive value of this tool, like the inpatient setting, is weak in the critical care population. The limitation of these tools in the ICU setting is supported by the findings of Bahloul and colleagues who calculated both the Wells and Geneva scores in 87 patients who were diagnosed with PE in the critical care setting [8]. In this study, only 5 (5.7 %) patients had a high

Table 25.1 Wells criteria for pulmonary embolism risk

Variable	Points
Clinical signs and symptoms of DVT	3
Alternative diagnosis less likely than PE	3
Heart rate >100/min	1.5
Immobilization (>3d) or surgery in the prior 4 wk	1.5
Prior PE or DVT	1.5
Hemoptysis	1
Malignancy (receiving treatment, treated in last 6 mo, palliative)	1

Score	Clinical probability	PE incidence
Trichotomized score		
0–1	Low	0.2–7.0 %
2–6	Moderate	12.4–26.6 %
≥6	High	27.2–72.8 %
Dichotomized score		
≤4	Unlikely	2.3–9.4 %
≥4	Likely	27.6–51.6 %

From Wells et al. [13]

Table 25.2 Revised Geneva Score for pulmonary embolism risk

Variable	Points
Risk factors	
Age > 65 y	1
Prior PE or DVT	3
Surgery (under general anesthesia) or fracture of the lower limbs within 1 mo	2
Active malignant condition (solid or hematologic, currently active or considered cured < 1 y)	2
Symptoms	
Unilateral lower-limb pain	3
Hemoptysis	2
Clinical signs	
Heart rate	
75–94 beats/min	3
≥95 beats/min	5
Pain on lower-limb deep venous palpation and unilateral edema	4

Score	Clinical probability	PE incidence
0–3	Low	5.0–12.0 %
4–10	Intermediate	24.6–32.8 %
≥11	High	61.0–83.4 %

From Le Gal et al. [39]

probability score using Wells Criteria and only 6 (6.9 %) patients were classified as high probability according to Geneva Score. Based on these findings, it is crucial to maintain a high index of suspicion for VTE as a potential etiology of subtle (and not so subtle) physiologic changes in an ICU population.

Pulmonary Embolism Severity

Patients with pulmonary embolism can be categorized into low, intermediate, and high risk groups. Stratifying individuals into risk categories can be useful in decisions about disposition and treatment. The presence of hemodynamic collapse, which results from an acute increase in pulmonary artery pressure and associated right heart failure, readily classifies patients into a high-risk group with an estimated mortality of 30–50 % and mandates a treatment strategy that includes vascular reperfusion (see section "Treatment"). Hemodynamic stability in the presence of right ventricular (RV) dysfunction defines an intermediate risk category. Evidence of RV dysfunction can be detected on imaging studies including echocardiography (Fig. 25.2) and CT-PA and with elevated biochemical markers such as brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin-I, and troponin-T levels.

Several systematic reviews reveal an increased risk of death in patients with pulmonary embolism who also have evidence of abnormal RV function by imaging or elevated biomarkers. For example, in a recent meta-analysis, CT-PA evidence of right heart dysfunction carried an odds ratio of death from PE of 7.4 (95 % confidence interval 1.4–39.5) [15]. A separate study found that either CT-PA or echocardiographic evidence of RV dysfunction was associated with an unadjusted risk ratio for death of 2.4 (95 % confidence interval 1.3–4.4) [16]. In this same systematic review, elevations in brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and troponin also predicted an increased risk of death, but the threshold values for these biomarkers varied considerably between studies. Because of the higher rate of death, patients in this intermediate risk group may hypothetically benefit from aggressive treatment to reestablish vascular reperfusion (see section "Treatment").

Beyond categorizing patients based on the presence/absence of hemodynamic instability or RV dysfunction, several prognostic scoring systems have been developed to estimate the 30-day mortality in patients with PE. These tools primarily aid clinicians in their decisions about patient disposition. Individuals with low scores may be safely managed as outpatients while patients with high scores require hospitalization in an acute

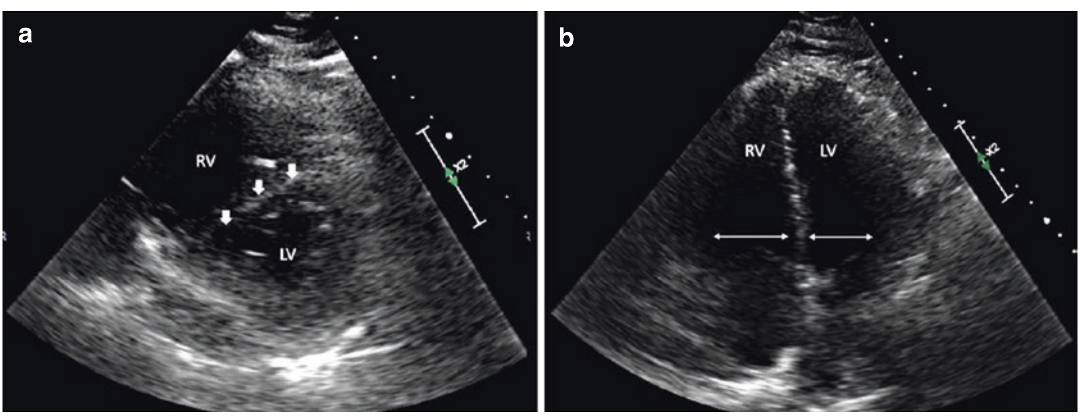

Fig. 25.2 (**a**) Right ventricular (*RV*) strain seen on parasternal short axis view with the intraventricular septum (*arrows*) bowing into the left ventricle (*LV*). The result is known as a "D-sign". (**b**) Increased RV/LV ratio seen on apical four chamber view

Table 25.3 Pulmonary embolism severity index

Predictors	Points
Demographics	
Age, per year	Age in year
Male sex	+10
Comorbid illnesses	
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Clinical findings	
Pulse ≥ 100/min	+20
Systolic blood pressure < 100 mmHg	+30
Respiratory rate ≥ 30/min	+20
Temperature < 36 °C	+20
Altered mental status	+60
Arterial oxygen saturation < 90 %	+20

Score	Risk class	30-day mortality
≤65	I, very low	0–1.6 %
66–85	II, low	1.7–3.5 %
86–105	III, intermediate	3.2–7.1 %
106–125	IV, high	4.0–11.4 %
>125	V, very high	10.0–24.5 %

From Aujesky et al. [17]

care bed or in the intensive care unit. The Pulmonary Embolism Severity Index (PESI) and the simplified PESI are examples of these risk predictor tools (Table 25.3). The PESI is comprised of 11 simple patient variables that are each independently associated with PE mortality [17]. The composite score assigns individuals to one of five risk categories. In class I and II, the lowest risk categories, 30-day mortality rates were between 0 and 3.5 % in the derivation and validation groups. In contrast, patients in the highest risk category (Class V) exhibited 30-day mortality rates ranging between 10.0 and 24.5 %. More recent data suggests that combining the PESI with echocardiographic and biomarker data can further refine risk stratification [18]. Whether these tools of risk prediction play any role in an ICU patient with VTE is unclear. However, for those individuals diagnosed with PE outside of the intensive care unit, it may be prudent to consider admission to a higher level of care such as a critical care unit if a patient is determined to be in the highest risk category for mortality.

Diagnosis

With a few exceptions, the diagnostic approach to VTE in the ICU should not be fundamentally different than in the emergency department or on the general care wards. The initial step in evaluating an ambulatory patient (i.e. presenting to the emergency department or clinic) with suspected pulmonary embolism is to assess the clinical probability of disease. The implementation of a clinical probability tool such as Wells Criteria greatly facilitates this assessment. Those individuals determined to have a low likelihood of PE (Table 25.1) should be initially evaluated with a d-dimer. Patients with a high clinical likelihood of disease (or low clinical likelihood and a positive d-dimer) should undergo a diagnostic study for PE such as a ventilation-perfusion scan or a CT-PA. The latter imaging approach is often the preferred modality because it also allows for the detection of other abnormalities that might explain a patient's clinical syndrome, and it can provide information about the status of the right ventricle. Based on the results of PIOPED I and PIOPED II, additional diagnostic studies such as pulmonary angiography should be entertained when the results of the CT-PA or ventilation/perfusion scan are discordant with the clinical probability of disease.

When evaluating a patient in the ICU with suspected PE, the clinical likelihood tools, as detailed previously, are not well validated. In addition, d-dimer levels are elevated by a variety of ICU conditions and, as a result, lack predictive value. Therefore, patients with suspected PE should preferably undergo a PE-CT (or possibly a ventilation-perfusion scan) to evaluate for disease. However, this imaging study necessitates patient transfer from the ICU to the radiology department, which may be challenging in the setting of clinical instability. In such a case, an alternative approach to the diagnosis is required. Compression ultrasonography to evaluate for the presence of DVT is one consideration, as a positive test would warrant treatment for VTE. However, as previously noted, DVT is only identified in approximately one-third of patients in the ICU with PE, so a negative test does not exclude the diagnosis and additional work-up is then required.

Echocardiography, either transthoracic or transesophageal, offers alternative bed-side modalities for PE evaluation. In a prospective study, the sensitivity and specificity of an abnormal transthoracic echocardiography (TTE) (defined by two of the following criteria: RV hypokinesis, RV dilation, or tricuspid regurgitation) was compared to pulmonary angiography for the diagnosis of PE. This study determined that the sensitivity of TTE was only 56 % (with a specificity of 90 %), indicating that this study is useful only if abnormal [19]. In comparison, transesophageal echocardiography (TEE) offers the advantage of central pulmonary artery visualization and can thereby detect proximal PE. In a study of 49 consecutive patients with clinical suspicion of PE and unexplained right ventricular overload on transthoracic echocardiography, TEE detected pulmonary arterial emboli in 32/40 patients (80 %) who had centrally located disease (i.e. main or lobar arteries) [20]. Unfortunately, this test is not useful for peripheral emboli. A final diagnostic consideration for the patient who is too unstable for transfer is a bedside perfusion scan. A normal scan would provide reassurance that a PE is not responsible for a patient's clinical instability. An abnormal scan, in the absence of a concurrent ventilation scan, will not define a probability of PE and should be interpreted with caution.

Treatment

Once the diagnosis of PE is made, the principles of treatment do not differ significantly between the ICU, emergency department, and general ward. In patients with an acceptable bleeding risk, anticoagulation should be administered promptly with the goal of achieving therapeutic dosing within 24 h. A failure to achieve therapeutic anticoagulation within this time period resulted in a much higher recurrence rate of VTE (23.3% vs 4 %) for those whose activated partial thromboplastin time exceeded the therapeutic threshold by 24 h (P = .02) [21]. Delays in instituting anticoagulation are also associated with an increased in-hospital (1.5 % vs 5.6 %; P = .093) and 30 day (5.6 % vs 14.8 %; P = .037) mortality [22]. Heparin is the preferred agent for initial anticoagulation. Based on more predictable dosing (usually without the need for monitoring), lower risk of drug-induced thrombocytopenia, and equivalent (if not superior) efficacy, low molecular weight preparations are often preferred over the intravenous administration of unfractionated heparin [23]. However, in the ICU, unfractionated heparin with utilization of weight-based dosing protocols (Tables 25.4a and 25.4b), is considered a better choice particularly in an unstable patient due in large part to its

Table 25.4a Unfractionated heparin nomogram for VTE using aPTT

Initial dose	80 units/kg, followed by 18 units/kg/h
aPTT, <35 s	80 units/kg bolus, then increase rate 4 units/kg/h
aPTT, 35–45 s	40 units/kg bolus, then increase rate 2 units/kg/h
aPTT, 36–70 s[a]	No change
aPTT, 71–90 s	Decrease rate by 2 units/kg/h
aPTT, > 90 s	Hold 1 h, then decrease rate by 3 units/kg/h

Adapted from Garcia et al. [40]

Testing is repeated every 6 h until therapeutic range is reached for two consecutive tests, and then daily

[a]Therapeutic aPTT range is considered 46–70s and corresponds with an anti-Xa activity of 0.3–0.7 units/mL. Target range at institutions may vary depending on reagents/equipment used to perform assay

Table 25.4b Unfractionated heparin nomogram for VTE using anti-Xa

Initial dose	80 units/kg, followed by 18 units/kg/h
Xa, < 0.2	80 units/kg bolus, then increase rate 1.5 units/kg/h
Xa, 0.2–0.29	40 units/kg bolus, then increase rate 1 units/kg/h
Xa, 0.3–0.7	No change
Xa, 0.71–0.8	Decrease rate by 1 units/kg/h
Xa, 0.81–0.99	Decrease rate by 1.5 units/kg/h
Xa Greater than or equal to 1	Decrease rate by 3 units/kg/h

Adapted from University of Michigan Health Systems Heparin Dosing Nomogram

Testing is repeated every 6 h until therapeutic range is reached for two consecutive tests, and then daily shorter half-life (45 min versus 4–5 h for LMWH). This shorter half-life is advantageous in the critical care patient population that may require invasive procedures and/or is at increased risk of bleeding. Also, close monitoring of the aPTT/anti-Xa is less of an issue in the ICU setting. In non-ICU patients, heparin is typically used as a bridge to long-term anticoagulation, and warfarin is started within the first 24 h of therapy after the patient is therapeutic on heparin. In the ICU, because of the bleeding risk and procedural requirements, it is prudent to delay the initiation of warfarin until the patient is ready to transition to a lower level of care.

Patients with hemodynamically unstable disease (defined by a systolic blood pressure < 90 mmHg for greater than 15 min) require reperfusion therapy in addition to anticoagulation. Options include systemic thrombolysis, catheter-directed thrombolysis and embolectomy (surgical versus mechanical). Systemic administration of a thrombolytic does not require mobilization of the interventional radiology team and therefore avoids delays in treatment. Catheter directed thrombolysis, on the other hand, allows for the administration of a lower thrombolytic dose, which carries the potential to reduce bleeding complications. Otherwise, the decision should be dictated by local availability/expertise as there have been few head to head comparisons of the different modalities, and what data exists suggest equivalency. For example, in patients with acute massive pulmonary embolus (n = 25), a retrospective analysis of catheter-directed thrombolysis versus mechanical embolectomy with ultrasound-accelerated thrombolysis found no difference in mortality between the two approaches (9.1 % in the mechanical embolectomy group and 14.2 % in the catheter-directed thrombolysis group, p = NS). Notably, mechanical embolectomy did result in improved embolus removal (p < .02), more rapid thrombolysis (17.4 ± 5.23 versus 25.3 ± 7.35 h, p = .03), and fewer treatment-related hemorrhagic complication (0 % versus 21.4 %, p = .02) [24]. Therefore, if mechanical embolectomy is available, one could make the argument to use this modality preferentially, especially in patients at increased bleeding risk.

In patients with active bleeding (or deemed to be at a high risk of bleeding complications as a result of an intracranial neoplasm, recent (i.e., <2 months) intracranial or spinal surgery or trauma, hemorrhagic stroke, or a bleeding diathesis) anticoagulation is contraindicated. As a result, an inferior vena cava is required in these individuals to prevent further episodes of embolism.

Evidence Contour

Reperfusion Therapy in Patients with Hemodynamically Stable Pulmonary Embolism

Hemodynamically stable PE patients with evidence of right heart dysfunction (based on abnormal imaging or elevated biomarkers) are at increased risk of death (see section "Pulmonary Embolism Severity"). The worse prognosis in this subgroup has motivated several investigations to assess the efficacy of reperfusion strategies. As detailed in the section "Case Presentation", in the PEITHO trial, patients with sub-massive pulmonary embolism as defined by RV enlargement or elevated cardiac biomarkers were randomized to receive IV heparin and placebo versus IV heparin and recombinant t-PA (as a reperfusion strategy). The results of this study revealed that t-PA significantly reduced the primary composite outcome of death or hemodynamic decompensation within the first week after randomization. However, there was no difference in survival between groups. The findings of this study are similar to two previous randomized controlled trials in which systemic thrombolysis was found to improve hemodynamic endpoints (as assessed by echocardiography or need for secondary thrombolysis) [25, 26]. Mortality was a component of the composite endpoint in only one of the two study protocols and, as was the case in the PEITHO trial, was not different between the two treatment arms. The failure of the hemodynamic benefits of thrombolysis treatment to translate into a survival benefit in these studies is at least in part due to the low event rates. Furthermore, in PEITHO, hemorrhagic complications led to four deaths in the t-PA group, and this complication offset any potential mortality benefit of reperfusion therapy. Subgroup analysis in the PEITHO trial suggests that patients less than 75 years of age have fewer bleeding complications, suggesting a more favorable benefit to risk ratio in these individuals.

Ultrasound-assisted catheter-directed thrombolysis in conjunction with low dose t-PA has also been evaluated as a reperfusion strategy in intermediate risk PE patients (n = 59) [27]. The primary outcome in this study was echocardiographic assessment of the right ventricle/left ventricle ratio from baseline to 24 h. Safety outcomes including death, and major and minor bleeding were also assessed. Catheter-mediated thrombolysis successfully reduced the mean right ventricle/left ventricle ratio by 0.30 ± 0.20 versus a minimal improvement (0.03 ± 0.16) in the heparin alone control group ($P < 0.001$). With respect to safety, there were no major bleeding events in this trial and only four episodes of minor bleeding (three in the catheter-mediated thrombolysis group; $P = 0.61$). Also, there was only a single death (in the placebo group). Several additional safety and efficacy trials have since been published demonstrating minimal major bleeding rates with significant improvement in pulmonary artery systolic pressure [28, 29]. Catheter-directed therapy may therefore be an option at capable centers for the patient with increased risk of bleeding, although long-term and comparative data are lacking.

A recent meta-analysis of thrombolytic therapy in submassive PE concluded that treatment did not significantly reduce the risk of mortality or recurrent PE, but does prevent clinical deterioration requiring escalation of care [30]. The failure to achieve a survival benefit may be a byproduct of inadequate power for this endpoint alone. As such, guidelines around this issue are nebulous but generally recommend therapy for the decompensating patient [31–33] (Table 25.5).

Table 25.5 Guideline recommendations for systemic thrombolysis in hemodynamically stable acute PE

	ACCP 2016[a]	ESC 2014[b]	AHA 2011[c]
Low bleeding risk	Routine use of systemic thrombolysis not recommended (Grade 1B). Close monitoring in patients with severe symptoms and marked cardiopulmonary involvement (Grade 2C). Systemic thrombolysis suggested if cardiopulmonary deterioration[d] occurs (Grade s2C)	Routine use of systemic thrombolysis not recommended (Class III, level B). Close monitoring in intermediate-high-risk[e] PE. (Class I, level B). Systemic thrombolysis should be considered in intermediate-high-risk PE if clinical signs of hemodynamic decompensation (Class IIa, level B)	Routine use of systemic thrombolysis not recommended for low risk or stable submassive PE. (Class III, level B) Consider for patients who have clinical evidence of adverse prognosis[f] (Class IIb, level C).
High bleeding risk	Mechanical catheter directed therapy with or without catheter directed thrombolysis recommended if hypotension (Grade 2C)	Surgical embolectomy (Class IIb, level C) or catheter-directed treatment (Class IIb, level B) may be considered in intermediate-high-risk patients	Surgical embolectomy or catheter embolectomy may be considered in those who have clinical evidence of adverse prognosis (Class II, level C)

[a]Kearon et al. [32]
[b]Kostantinides et al. [2]
[c]Jaff et al. [33]
[d]Cardiopulmonary deterioration includes shock, impending shock, progressive increase in heart rate, worsening gas exchange, progressive right heart dysfunction on echocardiography, increase in cardiac biomarkers
[e]Intermediate-high-risk PE defined as absence of shock or hypotension, PESI class III-V, signs of RV dysfunction on imaging test (Echocardiography: RV-LV diameter >0.9 or 1.0, hypokinesis of the RV free wall, increased velocity of the tricuspid regurgitant jet; Computed tomographic angiography: increased end diastolic RV/LV ratio > 0.9 or 1.0), positive cardiac biomarkers (troponin, natriuretic peptide)
[f]Adverse clinical prognosis includes new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis

Table 25.6 Considerations for bleeding following systemic thrombolytic therapy

Absolute contraindications[a]
Prior intracranial hemorrhage
Known intracranial neoplasm, arteriovenous malformation, or aneurysm
Ischemic stroke < 3 mo
Recent surgery in proximity to brain or spinal canal
Recent closed-head or facial trauma with radiographic evidence of fracture or brain injury
Active bleeding or bleeding diathesis
Suspected aortic dissection
Relative contraindications[a]
Age >75
Ischemic stroke > 3 mo
Current use of anticoagulation
History of poorly controlled hypertension
Uncontrolled hypertension (systolic blood pressure > 180 or diastolic blood pressure > 110)
Dementia
Pregnancy
Major surgery within 3 weeks
Non-compressible vascular punctures
Cardiopulmonary resuscitation for > 10 min
Internal bleeding within 2–4 weeks
Other risk factors
INR > 1.7[b]
Female gender[c]
Age > 65[d]
Renal disease[d]

[a]Jaff et al. [33]
[b]Curtis et al. [34]
[c]Meyer et al. [1]
[d]Stein et al. [35]

Certainly, significant bleeding complications have countered the benefit of thrombolysis. In addition, we lack the ability to predict major bleeding with thrombolysis in patients with acute PE. Historically, contraindications to thrombolysis for patients with PE have been drawn from data collected in patients with myocardial infarction [33]. Several recent studies have identified bleeding risk factors specific to patients with PE, including age > 65–75, renal failure, INR > 1.7 and female gender which may contribute directly to bleeding risk [1, 34, 35] (Table 25.6). However, it is unclear how these risk factors should modify clinical practice. Therefore, until further data is available, it remains at the clinician's discretion to determine whether the potential benefits of reperfusion treatment outweigh the risks of hemorrhagic complications in the individual patient.

IVC Filter Placement

Beyond using IVC filters for patients who cannot be anti-coagulated due to a heightened bleeding risk, it has been hypothesized that the employment of these devices in conjunction with heparin might improve outcomes in high risk PE patients. This hypothesis was best addressed in a recent trial in which patients with acute pulmonary embolism, lower-extremity venous thrombosis, and at least 1 additional risk factor were randomized to treatment with a retrievable inferior vena cava filter plus anticoagulation (n = 200) or anticoagulation alone (n = 199) [36]. Retrievable filters were used in light of previous evidence demonstrating an increased risk of DVT in patients with permanent devices, and the study protocol called for removal at 3 months post-deployment (which occurred successfully in 153 of 164 attempts). The primary endpoint of this study was symptomatic recurrent PE at 3 months, and this event occurred rarely. Furthermore, there was no difference in this outcome between the two groups. Specifically, six patients who had received a filter experienced a recurrent PE (3.0 %, all fatal) while three patients (1.5 %, two fatal) in the control group received this diagnosis (p = .50). The results of this study are consistent with an investigation in cancer patients in which filter placement had no effect on the incidence of PE, but again the event rates were low (3 %) [37]. Whether temporary filter placement in hemodynamically unstable PE patients, particularly those individuals already undergoing catheter-directed thrombolysis in Interventional Radiology, is beneficial has not been adequately studied, and this approach is at the preference of the treating physician.

Direct Factor Xa and Thrombin Inhibitors

Recent studies indicate that direct factor Xa and thrombin inhibitors have equivalent efficacy to standard anticoagulation in stable patients with

VTE (reviewed in [38]). These agents are attractive because they are administered at a fixed dose and do not require monitoring. However, to our knowledge, they have not been evaluated in hemodynamically unstable individuals and should therefore not be used in this population. In addition, the inability to reverse these agents renders them less attractive in the ICU, even in the individual who is diagnosed with a hemodynamically stable PE. With the advent of a monoclonal antibody to reverse dabigatran (one of the direct thrombin inhibitors), the comfort level with using these particular agents in the critical care unit may increase in the future. However, until more data is available in the ICU population, we recommend using these agents with extreme caution.

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