Submassive Pulmonary Embolism

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Abstract

Pulmonary embolism (PE) presents a spectrum of hemodynamic consequences, ranging from being asymptomatic to a life-threatening medical emergency. Management of submassive and massive PE often involves clinicians from multiple specialties, which can potentially delay the development of a unified treatment plan. In addition, patients with submassive PE can deteriorate after their presentation and require escalation of care. Underlying comorbidities such as chronic obstructive pulmonary disease, cancer, congestive heart failure, and interstitial lung disease can impact the patient's hemodynamic ability to tolerate submassive PE. In this review, we address the definitions, risk stratification (clinical, laboratory, and imaging), management approaches, and long-term outcomes of submassive PE. We also discuss the role of the PE response team in management of patients with PE.

Keywords: submassive pulmonary embolism; intermediate pulmonary embolism; pulmonary embolism response team; pulmonary embolism risk stratification; catheter-directed thrombolysis

Pulmonary embolism (PE) is the third most common cause of death among hospitalized patients (1). Older age, comorbid cardiopulmonary diseases, and thrombolytic treatment are associated with increased healthcare costs and worse outcomes (2). Patients with PE can have mild to moderate functional impairment even after 18 months from the initial event (3). In one study, impaired quality of life as measured by the SF-36 questionnaire (36-item Short Form Health Survey) was comparable between patients with PE and patients with acute myocardial infarction (4). A single episode of venous thromboembolism (VTE) itself increases the risk of recurrent VTE (5, 6). The incidence of recurrent VTE is 11.2% within 2 weeks of the initial presentation despite adequate anticoagulation (7). Prolonged immobilization, postoperative state, obesity, recent hospitalization, and active cancer are risk factors for VTE (8, 9).

Epidemiology

The National Hospital Discharge Survey demonstrates an increase in VTE occurrence (10). A total of 246,000 cases of PE were reported in 2006 (11). Similarly, in Europe, more than 1 million VTE events or deaths occur each year in six large countries (12). Untreated PE has a mortality rate of 30% (13). Submassive PE–related mortality has been reported to be 3–14.2%, with a trend toward lower mortality in recently published registries (8, 14–17). The 2007 Healthcare Cost and Utilization Project Nationwide Inpatient Sample showed an overall PE-related mortality of around 3.5% (18). Recent positive outcomes are attributable to more frequent use of low-molecular-weight heparin compared with unfractionated heparin, aggressive use of thrombolytic therapy, and performance of surgical embolectomy (16). Isolated deep vein thrombosis (DVT) has better 1-year survival than PE or PE with DVT (5). The incidence rate of VTE has remained constant despite an increase in the rate of prophylaxis. The majority of VTE events occur postdischarge, suggesting that in-hospital prophylaxis is not sufficient to prevent VTE (19).

Definition and Classification

PE is generally described as an obstruction in the pulmonary artery due to a clot, tumor, air, or fat (20). A saddle pulmonary embolism is described as a clot located in the main pulmonary artery that traverses the right and left pulmonary arteries (Figure 1). Lobar, segmental, and subsegmental PEs are clots located in the branches of the pulmonary artery corresponding to the anatomical lung segment. Saddle PE is often associated with a higher clot burden and right ventricular (RV) dysfunction but not necessarily with increased mortality (15, 21). Most patients with saddle PE are hemodynamically stable and receive heparin (87%) (21).

(Received in original form November 22, 2017; accepted in final form April 19, 2018)

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CME will be available for this article at www.atsjournals.org.

Am J Respir Crit Care Med Vol 198, Iss 5, pp 588–598, Sep 1, 2018

Originally Published in Press as DOI: 10.1164/rccm.201711-2302CI on April 19, 2018
Internet address: www.atsjournals.org

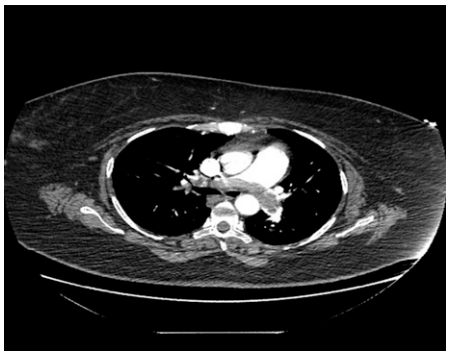

Figure 1. Computed tomographic angiogram showing saddle pulmonary embolism.

Terms such as "acute," "subacute," and "chronic pulmonary embolism" refer to a time frame from the initial event to a confirmation of the diagnosis. Signs of chronic PE on a computed tomographic angiogram (CTA) are suggested by eccentric thrombus location, calcification within the thrombus, the presence of pulmonary arterial webs or bends, and post-stenotic dilation of the pulmonary artery (22). Table 1 summarizes definitions of PE derived from American Heart Association (AHA), American College of Chest Physicians (ACCP), and European Society of Cardiology (ESC) guidelines (14, 23, 24). One of the major advantages of the ESC classification of PE, unlike the ACCP or AHA classification, is the focus on short-term PE-related mortality (in-hospital or 30-day mortality) (23, 24). To integrate patients' clinical status and comorbidities, ESC guidelines recommend the best validated Pulmonary Embolism Severity Index (PESI) or simplified Pulmonary Embolism Severity Index score (sPESI; discussed in detail below). Any patient with a positive sPESI score falls into the intermediate-risk PE category (equivalent to submassive PE in the AHA/ACCP classifications). ESC guidelines further risk stratify intermediate PE (submassive PE) into intermediate low risk and intermediate high risk (Table 1).

Pathophysiology of RV failure

The right ventricle is a thin-walled (1–3 mm) structure compared with the left ventricle (10 mm). The right ventricle is divided into three different regions: RV inflow, the apical region, and RV outflow. Movement of the interventricular septum that is anterior to the RV free wall contributes to 50% of RV function (25). The pulmonary circulation is a low-pressure system. Pulmonary vascular resistance is regulated by oxygen-sensing mechanisms. RV failure can be caused by an increase in preload, an increase in afterload, or a decrease in myocardial contractility resulting from ischemia (20). Mechanical obstruction resulting from clots and inflammatory cytokines increases pulmonary vascular resistance (26). Inflammation-induced neutrophil release contributes to RV dysfunction in murine models (27). Thrombotic occlusion creates a dead space, leading to hypoxic vasoconstriction and hypercapnia (15). Mechanical obstruction, hypoxemia, hypercapnia, and cytokine-induced hypoxic vasoconstriction increase RV afterload, leading to RV dilation. These events ultimately lead to bowing of the interventricular septum into the left ventricle and profound hypotension resulting from obstructive shock (24).

Risk Stratification for PE

Various clinical scores, imaging modalities, and biomarkers used to risk stratify acute PE have direct implications for short-term mortality and therapeutic decisions.

Clinical Risk Prediction Scores

PESI and sPESI scores have been validated for predicting 30-day mortality in patients with acute PE (28) (Table 2). The PESI score has a sensitivity of 91% and a negative predictive value of 99% for predicting mortality (29). The PESI score identifies patients with PE in low-risk groups I (<65 points) and II (65–85 points) and in high-risk groups III (86–105 points), IV (106–125 points), and V (>125 points). Short-term mortality increases from 1% in

Table 1. Definition of Pulmonary Embolism Based on Severity according to American College of Chest Physicians, American Heart Association, and European Society of Cardiology Guidelines

	sPESI Score	Shock	RV Dysfunction or Biomarker Elevation*
ACCP			
Low risk	N/A	No	No
Intermediate risk	N/A	No	Either one present
High risk	N/A	SBP <90 mm Hg for 15 min	N/A
AHA			
Submassive without RV strain	N/A	No	No
Submassive with RV strain	N/A	No	Either one present
Massive	N/A	SBP <90 mm Hg for 15 min or needing inotropic support, pulselessness, or profound bradycardia (HR <40 beats/min with shock)	N/A
ESC			
Low risk	0	No	No
Intermediate to low risk	1 or more	No	Either one positive
Intermediate to high risk	1 or more	No	Both positive
High risk	1 or more	Yes	N/A

Definition of abbreviations: ACCP = American College of Chest Physicians; AHA = American Heart Association; BNP = brain natriuretic peptide; ESC = European Society of Cardiology; HR = heart rate; N/A = not applicable; RV = right ventricular; SBP = systolic blood pressure; sPESI = simplified Pulmonary Embolism Severity Index.
*RV dysfunction based on imaging study (computed tomographic angiogram or echocardiogram); biomarker elevation refers to BNP/troponin.

Table 2. Original and Simplified Pulmonary Embolism Severity Indexes

Parameter	Original PESI Points	sPESI Points
Age	Age in yr	1 point (if aged >80 yr)
Male sex	+10 points	N/A
History of cancer	+30 points	1 point
History of chronic lung disease*	+10 points	1 point
History of heart failure*	+10 points	
HR ⩾110 beats/min	+20 points	1 point
SBP <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths/min	+20 points	N/A
Temperature <36°C	+20 points	N/A
Altered mental status	+60 points	N/A
Oxygen saturation <90%	+20 points	1 point

Definition of abbreviations: HR = heart rate; N/A = not applicable; PESI = Pulmonary Embolism Severity Index; SBP = systolic blood pressure; sPESI = simplified Pulmonary Embolism Severity Index.
*In sPESI scoring, 1 point is given for history of chronic cardiopulmonary disease (history of chronic lung disease, or history of heart failure, or history of both).

group I to 24% in group V. The low-risk PESI group has low short-term mortality even with positive troponin and can safely be managed on an outpatient basis (30). Decreases in PESI score from admission to 48 hours are associated with reduced short-term mortality. The sPESI score uses 6 risk factors as compared with 11 risk factors in the original PESI score (28, 31). A low-risk sPESI score (score of 0) has a short-term mortality risk of 2.5% and a negative predictive value of 97.5% compared with the original PESI score. A meta-analysis of 21 studies that included an aggregate of 50,000 patients demonstrated that both scores (PESI and sPESI) are equally effective in identifying patients with low-risk PE (32). The PESI and Hestia scores have been validated for predicting early home discharge from hospitalization for PE (33–35).

Biomarkers

Brain natriuretic peptide and N-terminal pro-brain natriuretic peptide are markers of RV pressure overload. Troponin I and troponin T are markers of myocardial ischemia. Elevation of biomarkers carries an independent risk of short-term mortality and RV dysfunction (24, 36). Use of elevated troponin to predict short-term mortality in PE is controversial (37, 38). We recommend against making decisions based solely on elevated biomarkers and instead paying attention to alternative causes of biomarker elevation.

Imaging

RV dysfunction on a CTA or an echocardiogram can risk stratify PE (24). Even though CTAs are usually immediately available, concomitant RV strain on CTAs and echocardiograms is a better predictor of an adverse outcome (39). The location of the thrombus or clot burden seen on a CTA is not part of the risk stratification (40). The role of quantitative clot burden indices (Mastora or Qanadli) in immediate risk stratification is limited (40). However, a right ventricle/left ventricle ratio greater than 0.9 on the basis of a CTA or echocardiogram indicates RV dysfunction and is associated with adverse clinical outcomes (41–44) (Figure 2). Interventricular septal flattening and reflux of contrast into the inferior vena cava (IVC) and hepatic veins also implicate RV dysfunction (40). In experienced hands, bedside echocardiography can identify RV dysfunction (45) (Figure 3). McConnell's sign (decreased RV free wall function with apical sparing) is specific for PE. Tricuspid annular plane systolic excursion less than 18 mm, lack of IVC collapsibility, and elevated RV systolic pressure have been associated with increased mortality (44). RV fractional area change, RV myocardial performance (Tei index), and RV longitudinal strain might be useful, but they are often time consuming when rapid risk stratification is needed. Comparison with previous echocardiograms and RV free wall thickness may help to delineate acute versus chronic RV failure.

Combined Modalities of Biomarkers, Laboratory Tests, and Imaging

No single clinical score, imaging modality, or laboratory test in isolation can predict the prognosis of acute PE. An integrative approach may help to drive therapeutic

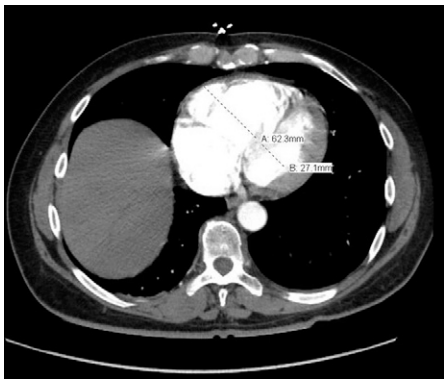

Figure 2. Evidence of right ventricular dysfunction on a computed tomographic angiogram with a right ventricle (A)/left ventricle (B) ratio greater than 1 (62.33 mm/27.1 mm = 2.29).

decisions for patients with submassive PE. The PROTECT (Prognostic Significance of Multidetector CT in Normotensive Patients with Pulmonary Embolism) multimarker index, FAST score (based on a positive heart-type fatty acid-binding protein test, syncope, and tachycardia), and Bova score predict a complicated course (e.g., all-cause mortality, need for vasopressors, mechanical ventilation, recurrent PE) in 22–29.2% of patients with PE (46–48) (Table 3). PE with DVT has higher mortality than PE alone (49). We do not recommend using any specific risk stratification model over another, but we do emphasize the value of incorporating clinical, radiological, laboratory, and other comorbid illnesses into the therapeutic decision-making process.

Treatment of Submassive (Intermediate-Risk) PE

Patients with confirmed PE or high pretest probability should be started on anticoagulation

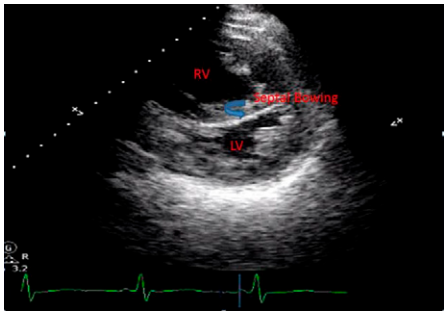

Figure 3. Short-axis view of two-dimensional echocardiogram showing evidence of right ventricular dysfunction with septal bowing toward the left. LV = left ventricle; RV = right ventricle.

Table 3. Multimarker Short-Term Mortality Prediction Scoring System for Pulmonary Embolism

PROTECT Multimarker Index	FAST Score	Bova Score
Troponin I	H-FABP >6 ng/ml (1.5 points)	SBP 90–100 mg Hg (2 points)
BNP	HR >100 beats/min (2 points)	HR >110 beats/min (1 points)
sPESI	Syncope (1.5 points)	RV dysfunction (2 points)
DVT		Troponin I (2 points)

Definition of abbreviations: BNP = brain natriuretic peptide; CT = computed tomography; DVT = deep vein thrombosis; FAST score = based on a positive heart-type fatty acid-binding protein test, syncope, and tachycardia; H-FABP = heart-type fatty acid binding protein; HR = heart rate; PROTECT = Prognostic Significance of Multidetector CT in Normotensive Patients with Pulmonary Embolism; RV = right ventricular; SBP = systolic blood pressure; sPESI = simplified Pulmonary Embolism Severity Index. PROTECT multi-marker model (all four variables present), FAST score (>3), and Bova score (>4) predict a complicated course (e.g., all-cause mortality, need for vasopressors, mechanical ventilation or cardiopulmonary resuscitation, recurrent pulmonary embolism) in 22–29.2% of patients with pulmonary embolism (46–48).

as soon as possible unless contraindicated. Decisions for advanced therapies should be individualized. In this section, we focus on bleeding risk scores and available treatment options for submassive PE.

Bleeding Risk Scores

Bleeding risk should be considered in selecting advanced treatment options. Definitions of major bleeding vary in the literature. The International Society on Thrombosis and Haemostasis defines major bleeding as a decrease in Hb greater than 2.0 gm/dl; a transfusion of more than 2 U of packed red blood cells; or a critical bleeding site such as intracranial, intraarticular, retroperitoneal, intraspinal, pericardial, or intramuscular with compartment syndrome (50). Various bleeding risk scores have been described in the literature, mainly for potential bleeding with vitamin K antagonist (VKA) therapy. One of the best-described bleeding risk scores is the RIETE (Registro Informatizado de Enfermedad Thrombo Embólica) score (51). The RIETE score includes age above 75 years (1 point), recent bleeding (2 points), cancer (1 point), creatinine concentration greater than 1.2 mg/dl (1.5 points), anemia (1.5 points), and pulmonary embolism at baseline (1 point) (51) (Table 4). A recently published trial showed that at least four VKA-related bleeding prediction scores held their relevance when tested for rivaroxaban therapy. The RIETE score performed the best at predicting bleeding with rivaroxaban therapy (52). There is growing evidence in support of direct oral anticoagulants (DOACs) having a better safety profile for bleeding than VKAs (53). We recommend DOACs over VKAs as a first-line therapy for VTE, except in special situations such as cancer, advanced renal failure, and antiphospholipid antibody syndrome.

Table 4. Major Bleeding Risk–Predicting Scores in Pulmonary Embolism Treatment

Score	Percent Predicted
RIETE score for major bleeding (51) (VKA-related bleeding score)	
Low risk (0 points)	0.3%
Intermediate risk (1–4 points)	2.6%
High risk (>4%)	7.3%
PE-CH score for ICH (55) (systemic thrombolysis–related bleeding risk score)	
0	1.2%
1	2.9%
2	3.4%
>5	17.8%

Definition of abbreviations: ICH = intracranial hemorrhage; PE-CH = peripheral arterial disease: 1 point, elderly age >65 years: 1 point, prior cerebrovascular accident with residual effect: 1 point, history of heart attack: 5 points; RIETE = Registro Informatizado de Enfermedad Thrombo Embólica; VKA = vitamin K antagonist.

Age above 65 years and kidney disease increase the intracranial hemorrhage (ICH) risk with thrombolysis (54). The PE-CH score (peripheral arterial disease, 1 point; elderly age >65 yr, 1 point; prior cerebrovascular accident with residual effect, 1 point; history of heart attack, 5 points) is one of the novel bleeding risk scores for predicting the risk of ICH with thrombolytic therapy (55) (Table 4).

The predictive value of bleeding risk scores is only modest, for several reasons. Bleeding risk scores were derived from patients who were already deemed appropriate for anticoagulation therapy by the treating physicians. This bias could have excluded patients at high bleeding risk in the first place. The safety data for DOACs appear to derive from clinical trial settings in which the majority of patients at high bleeding risk were excluded.

Systemic Thrombolysis

The role of systemic thrombolysis in submassive PE is controversial. Patients with submassive PE with clinical deterioration are potential candidates for thrombolysis (23). Alteplase is given as a 100-mg infusion over 2 hours; tenecteplase is given as a push dose injection. A double-blind randomized trial demonstrated a mortality benefit with alteplase when compared with heparin only in submassive PE without additional bleeding risk (56). The researchers in the PEITHO (Pulmonary Embolism Thrombolysis) trial compared tenecteplase plus heparin versus placebo plus heparin in 1,006 patients with submassive PE (57). The tenecteplase group had reduced hemodynamic decompensation and all-cause mortality but increased ICH (2%) and major bleeding (6.3%). Three-year follow-up data from the PEITHO study showed no long-term mortality benefit or difference in the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) in either group (58). Chatterjee and colleagues, in a meta-analysis of 1,775 patients, showed a mortality benefit with thrombolysis with increased risk of major bleeding (9.24%) and ICH (1.46%) (59). In another

meta-analysis, which included 1,833 patients, Riera-Mestre and colleagues showed no mortality benefit but an increased risk of major bleeding (5.9%) and ICH (1.74%) (60). It is interesting to note that the risk of ICH and major bleeding was higher with tenecteplase than with alteplase (60). There have been several systematic reviews since publication of the PEITHO trial, with varying results regarding mortality benefit and bleeding risk. Riva and colleagues performed an extensive review of 12 meta-analyses and found that systematic reviews were largely concordant in findings of reduced all-cause mortality but increased bleeding risk (61). ACCP 2016 guidelines suggest considering systemic thrombolysis in patients with submassive PE with clinical decline and low bleeding risk. Low-dose tissue plasminogen activator (50 mg/2 h or 0.6 mg/kg) has a potential role in submassive PE. It has dual advantages of rapid clot resolution similar to a full-dose thrombolytic and a bleeding risk profile comparable to that of heparin (62). The researchers in the upcoming PEITHO-3 trial plan to address the role of half-dose thrombolytics in submassive PE in a larger clinical trial.

Catheter-based Treatment

Catheter-based treatment (CBT) has an emerging role in the management of PE. CBT includes catheter-directed thrombolysis (CDT), mechanical fragmentation, or a combination of both. CDT includes positioning catheters directly in the thrombosed pulmonary artery and infusing thrombolytic drugs into the artery. CDT catheters can be positioned unilaterally or bilaterally in the pulmonary artery. The main pulmonary artery or lobar branches with heavy clot burden are the ideal locations. CDT can be performed with standard 5-French multihole catheters or an EkoSonic catheter (EKOS/BTG). The EkoSonic catheter (Figure 4) adds high-frequency low-power ultrasound waves that induce reversible disaggregation of un–cross-linked fibrin fibers, which creates additional binding sites for thrombolytic agents. Ultrasound waves may increase thrombus penetration of thrombolytic drugs by acoustic streaming. Catheter-directed mechanical fragmentation techniques include either clot fragmentation or clot extraction without thrombolytics.

A multicenter trial involving 59 patients with submassive PE demonstrated that ultrasound-facilitated catheter-directed thrombolysis (USCDT), when compared with heparin, reduced the right ventricle/left ventricle ratio at 24 hours (63). There was no incidence of ICH or major hemorrhage in the USCDT group. The SEATTLE II trial (A Prospective, Single-arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) included 31 patients with massive PE and 119 with submassive PE ($n = 119$) (64). The USCDT group had a statistically significant reduction in right ventricle/left ventricle ratio, mean pulmonary artery systolic pressure (mPAP), and modified Miller index obstructive score without any ICH. A retrospective study involving 14 patients with massive PE and 38 with submassive PE showed significant improvement in cardiac index, right ventricle/left ventricle ratio, and pulmonary artery pressure after USCDT. Two deaths occurred in a 3-month follow-up period, and two episodes of nonfatal major bleeding were noted in the study (65). A recently published multicenter registry involving 101 patients supported the effectiveness and safety profile of CBT in patients with massive PE ($n = 28$) and patients with submassive PE ($n = 73$) (66). The investigators in the OPTALYSE-PE (Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Pulmonary Embolism) trial compared the efficacy of reduced dosing and duration of USCDT in 101 patients divided into four cohorts (67). All four cohorts had similar reductions in right ventricle/left ventricle ratio at 48 hours, with one case of ICH (cohort D; 2 mg/h for 6 h) and three major bleeding cases were noted. Even though the role of CBT is evolving, the effectiveness of USCDT versus standard CDT has been questioned in a recent meta-analysis involving 700 patients (68). Table 5 summarizes all major CBT trials.

Catheter-directed embolus fragmentation can be achieved via simple rotational pigtail catheters or balloon angioplasty catheters. A potential disadvantage of such a technique is distal embolization (69). High-pressure saline jet injection via the AngioJet device (Boston Scientific) has received a black box warning owing to serious adverse events such as bradycardia, massive hemoptysis, and renal failure. The Amplatz thrombectomy device (ATD; Microvena), which uses a hydrodynamic vortex and

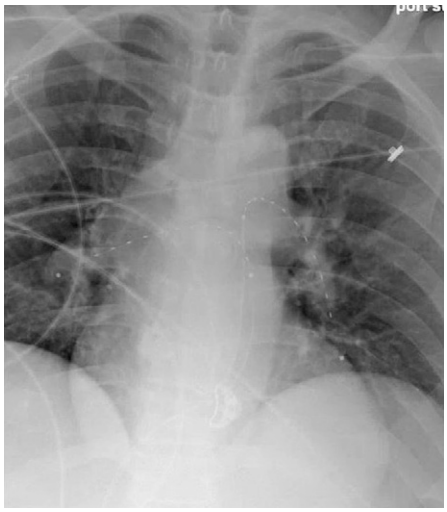

Figure 4. Chest radiograph showing bilateral ultrasound-assisted thrombolysis catheters placed in the lower lobe pulmonary arteries.

Aspirex spiral rotating catheters (Straub Medical) to dissolve emboli, was studied in a small series of patients with PE. The FlowTriever device (Inari Medical) is another mechanical clot retrieval device being studied in in a large prospective trial with patients with submassive PE (70). The AngioVac Cannula (Angiodynamics) is a U.S. Food and Drug Administration–approved device that requires a venous drainage cannula (26 French), a reperfusion cannula (18 French), a centrifugal pump, and perfusionist support to remove emboli from the IVC or clot in transit (71). The Penumbra device (Penumbra Inc.) is approved for peripheral arterial or venous thrombus removal and requires only small-size venous access (6–8 French) (72).

The risk of ICH appears to be as low as 0.5% with CDT (73, 74). Given the lack of randomized trials, different clinical endpoints, and lack of long-term follow-up data on the safety and efficacy of CBT, we do not recommend routine use of CBT in all patients with submassive PE. Patients with intermediate- to high-risk PE with high bleeding risk should be considered for CBT over systemic thrombolysis.

IVC Filter

Use of the IVC filter is reserved for patients who cannot be anticoagulated or are progressively thrombosing despite anticoagulation (23, 75). The American College of Radiology–Society of Interventional

Table 5. Characteristics of Major Clinical Trials of Catheter-based Interventions in Pulmonary Embolism

Trial	Primary Endpoint	Adverse Events	Thrombolytic Dose
Kucher *et al.* (63) (ULTIMA) (*N* = 59), multicenter randomized trial	Reduction of RV/LV ratio at 24 h from baseline Safety outcome: major bleeding, minor bleeding, ICH, and recurrent VTE at 90 d	Major bleeding: none ICH: none Minor bleeding: three in USCDT, one in heparin group Death: one in heparin arm	1 mg/h for 5 h followed by 0.5 mg/h for next 10 h; total dose of rtPA 10 mg for unilateral catheters and 20 mg for bilateral catheters
Piazza *et al.* (64) (SEATTLE II) (*N* = 150, 31 massive PE, 119 submassive PE), multicenter, single-arm prospective study	Reduction CTA measured RV/LV ratio, reduction in mean pulmonary artery systolic pressure, and Miller obstruction index at 48 h	Severe bleeding: *n* = 1 ICH: none Moderate bleeding: *n* = 16	1 mg/h for 24 h for unilateral catheters and 1/mg for 12 h for bilateral catheters; total fixed dose of 24 mg regardless of one or two catheters
Engelberger *et al.* (65) (*N* = 52, 14 high-risk PE, 38 intermediate-risk PE), retrospective series	Reduction in pulmonary artery pressure and improvement in cardiac index	Major bleeding: *n* = 2 Death in 3-mo follow-up: *n* = 2 ICH: none	1 mg/h for 5 h followed by 0.5 mg/h for next 10 h; total dose of tPA 10 mg for unilateral catheters and 20 mg for bilateral catheters
Kuo *et al.* (66) (PERFECT registry) (*N* = 101, 28 massive and 73 submassive), prospective multicenter registry	Stabilization of hemodynamics; improvement in pulmonary hypertension, right-sided heart strain, or both; and survival to hospital discharge	Major bleeding: none ICH: none	tPA dose was 28 ± 11 mg of tPA (*n* = 76); urokinase dose was 2.7 ± 1 million IU of urokinase (*n* = 23)

Definition of abbreviations: CTA = computed tomographic angiogram; ICH = intracranial hemorrhage; LV = left ventricle; PE = pulmonary embolism; PERFECT = Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis; rtPA = recombinant tissue plasminogen activator; RV = right ventricle; SEATTLE II = A Prospective, Single-arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism; tPA = tissue plasminogen activator; ULTIMA = Ultrasound Accelerated Thrombolysis of Pulmonary Embolism; USCDT = ultrasound-facilitated catheter-directed thrombolysis; VTE = venous thromboembolism.

Radiology guidelines extend the recommendation for IVC filters in patients with free-floating iliocaval thrombus, those with massive PE with DVT, and those with severe cardiopulmonary disease (76). The PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) and PREPIC2 trials showed no role of IVC filters in patients with acute PE or DVT to prevent recurrent VTE events. The IVC filter itself can serve as a trigger for DVT (77, 78). The Angel Catheter (Bio2 Medical) is a triple-lumen central venous catheter with an IVC filter at the tip that has recently been approved by the U.S. Food and Drug Administration. It can be placed at bedside via the femoral vein in critically ill patients. The device must be removed before discharge (79).

Surgical Embolectomy

Surgical embolectomy should be reserved for patients with absolute contraindications to or failed thrombolysis, clot in transit, and clot traversing a patent foramen ovale. Surgical embolectomy for submassive PE has a very good survival rate (86.7%), except in the older age group (>80 yr) (80). It has a low incidence of major bleeding compared with systemic thrombolysis (81). Surgical embolectomy requires median sternotomy and potentially cardiopulmonary bypass. Surgical candidates must be able to tolerate anticoagulation. Patients may need venoarterial extracorporeal membrane oxygenation as a bridge to surgery or postoperatively. We recommend that surgical embolectomy be reserved for special situations in patients with submassive PE at expert centers. Table 6 summarizes all available treatment options for pulmonary embolism.

Long-Term Outcomes of Acute PE

CTEPH is a well-known entity, but "chronic thromboembolic disease" (CTED) and "post-PE syndrome" are relatively new terms (82, 83). The incidence rates of CTEPH are around 0.56% in all patients with PE and 3% in PE survivors at 2 years (84). Recurrent VTE and unprovoked PE are the strongest predictors for CTEPH. CTEPH is defined as mPAP greater than 25 mm Hg; pulmonary capillary wedge pressure less than 15 mm Hg; and at least one (segmental) perfusion defect detected on a $\dot{V}/\dot{Q}$ scan, CTA, or pulmonary angiogram after 3 months of effective anticoagulation. CTED is defined as pulmonary vascular obstruction with mPAP less than 25 mm Hg at rest. In a recent study, patients with CTED and patients with CTEPH showed reductions in oxygen uptake and work rate compared with control subjects in cardiopulmonary exercise testing (83). There is no standardized treatment for CTED, even though these patients are functionally impaired. There has been growing interest in the role of pulmonary endarterectomy in the management of CTED. Another overlapping term described in the literature is "post-PE syndrome," which can be described as follows: "It is the time line following an acute episode of PE where patient initially experiences functional impairment (reduce QOL) that may progress and lead to CTEPH" (82). Persistent mPAP, RV dysfunction, and thrombotic burden appear to play a role in the development of post-PE syndrome. It is hard to say at this point whether CTED leads to post-PE syndrome or

Table 6. Treatment Options Based on Pulmonary Embolism Risk Category

Types of PE	Definitions	Treatment Options
Low-risk PE	Hemodynamically stable and no imaging or biomarker signs of right ventricular strain	Systemic anticoagulation Low-molecular-weight heparin Oral anticoagulant IVC filter*
Intermediate-risk (submassive) PE†	Hemodynamically stable but with imaging and/or biomarker evidence of right ventricular strain	Systemic anticoagulation Low-molecular-weight heparin Oral anticoagulant Catheter-directed thrombolysis Half-dose (50 mg tPA) thrombolysis IVC filter*
High-risk (massive) PE†	Hemodynamically unstable patient regardless of clot location	Systemic anticoagulation Full-dose thrombolysis (100 mg tPA) Catheter-directed thrombolysis Catheter-based thrombus fragmentation Percutaneous mechanical thrombectomy Mechanical circulatory support devices (e.g., VA ECMO) Surgical embolectomy Inotropic and vasopressor support Inhaled nitric oxide/prostacyclins IVC filter* Oral anticoagulation

Definition of abbreviations: IVC = inferior vena cava; PE = pulmonary embolism; tPA = tissue plasminogen activator; VA ECMO = venoarterial extracorporeal membrane oxygenation.
*IVC filter should be considered only in cases in which anticoagulation is absolutely contraindicated.
†All listed treatment options for intermediate- and high-risk PE are best taken in the multidisciplinary setting and should be individualized after taking bleeding risk into consideration.

falls within the spectrum of post-PE syndrome. Nonetheless, it is important to know that after an acute episode, patients can have functional limitation and impaired quality of life before occurrence of CTEPH. The true prevalence and mechanism of post-PE syndrome or CTED largely remain unknown. Recently published results of the ELOPE (Prospective Evaluation of Long-Term Outcomes after Pulmonary Embolism study) prospective cohort study demonstrated that almost half of patients with acute PE (mostly low risk) have exercise limitation at 1 year that adversely influences health-related quality of life, dyspnea, and walking distance (85). Female sex, higher body mass index, and exercise limitation in 1-month cardiopulmonary testing were the independent predictors of functional impairment. High pulmonary artery pressure on a Day 10 echocardiogram and increased pulmonary artery diameter were associated with adverse quality of life as measured by SF-36 and pulmonary embolism quality-of-life measures in the same cohort (85).

Role of Pulmonary Embolism Response Team

The concept of the pulmonary embolism response team (PERT) is based on the rapid response team that leverages input from clinical specialists from varied disciplines to provide a time-sensitive comprehensive management plan for acute PE (86) (Figure 5). The PERT represents a formal pathway for evaluating all possible treatment modalities in real time (Table 6). It can also incorporate a process to identify the low-risk patient for early home discharge. Being a multidisciplinary model, the PERT can make team-based decisions rather than individualized decisions that take longer and may at times be feared to be driven by proceduralists. PERT members can follow patients closely in the outpatient setting after an acute episode. Outpatient follow-up also provides the opportunity to investigate the etiology of PE, decide on the type and duration of anticoagulation, and consider the removal of an IVC filter if present. Patients with persistent symptoms after an initial event can be screened for post-PE syndrome, CTED, or CTEPH.

Conclusions

The following important points summarize this review:

1. There is a high incidence of VTE after hospital discharge, even after adequate VTE prophylaxis.
2. ESC guidelines focus on short-term PE-related mortality by integration of PESI or sPESI score into the classification of intermediate-risk PE (submassive PE). It further reclassifies intermediate-risk PE into low- and high-risk PE.
3. Clot burden seen on a CTA should not have any direct implication for treatment decision making.
4. Clinical, radiological, laboratory, and bleeding risks should be used in conjunction to drive the therapeutic decision-making process.
5. Bleeding risk scores have modest predictive value at best, and numerous scores are described in the literature.
6. DOACs are preferred over VKAs. The safety profile of DOACs is based on clinical trials only; real-world data on

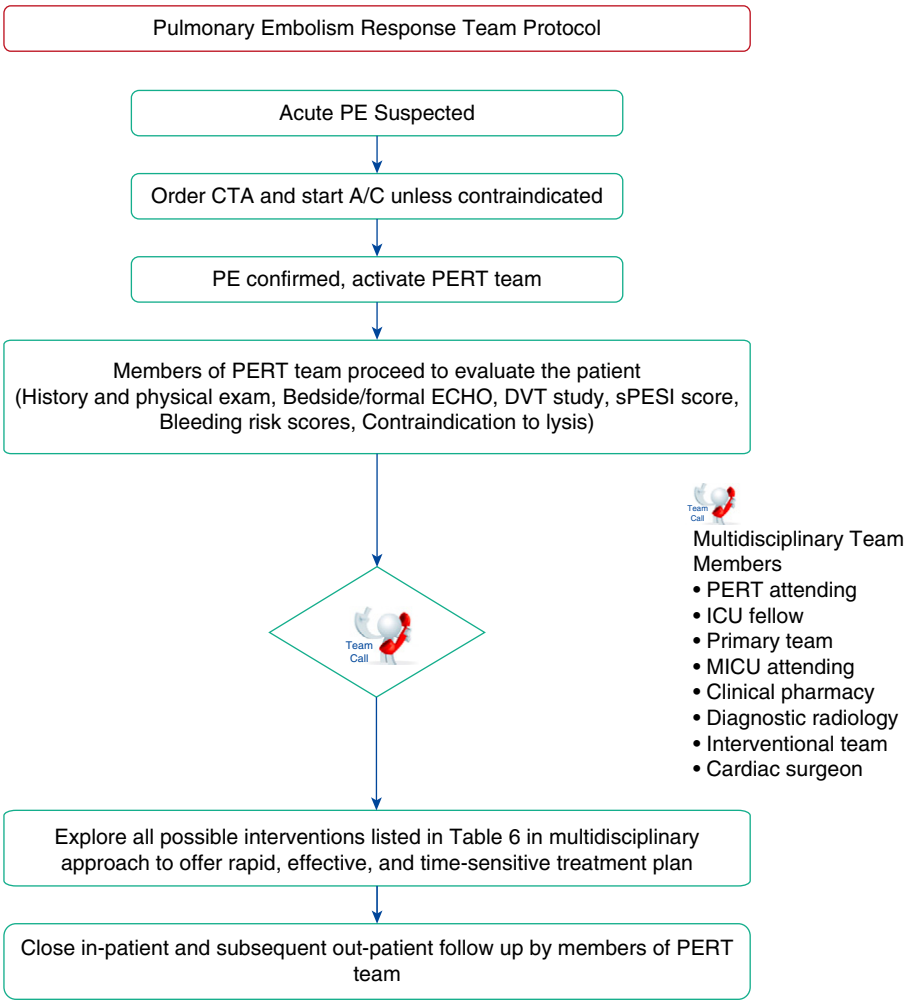

Figure 5. Pulmonary embolism response team (PERT) flowchart. A/C = anticoagulation; CTA = computed tomographic angiogram; DVT = deep vein thrombosis; ECHO = echocardiogram; MICU = medical ICU; PE = pulmonary embolism; sPESI = simplified Pulmonary Embolism Severity Index.

DOAC-related bleeding is limited at best.

7. Full-dose systemic thrombolysis should be reserved only for patients with signs of clinical deterioration with a low risk of bleeding and younger age in submassive PE. Half-dose tissue plasminogen activators appear to be a relatively safer option.
8. CDT appears safe in terms of risk of ICH (0.5%) and major bleeding compared with full-dose systemic thrombolysis. Ideal patient selection should be done in a multidisciplinary setting. There is no evidence to suggest that USCDT is superior to standard CDT.
9. IVC filters should be used only when anticoagulation is absolutely contraindicated. They should be removed as soon as possible when no longer indicated.
10. Recurrent VTE and unprovoked PE remain the most common risk factors for development of CTEPH.
11. Recent evidence suggests that the incidence of CTEPH is close to 3% in PE survivors. Patients with post-PE syndrome or CTED have functional limitations without CTEPH.
12. Multidisciplinary PERTs should become the standard of care to provide comprehensive care for patients with PE.

This is an exciting time in the field of PE with the availability of new diagnostic and therapeutic techniques together with involvement of multiple disciplines working to improve short-term and long-term outcomes for patients with submassive PE. These developments also bring the responsibility to identify the most immediate research targets to support and justify the use of new technologies that ultimately should be targeted toward nothing but patient care. We propose the following targets for future research or quality improvement initiatives:

1. There is a high risk of VTE after hospital discharge. Establish the role of posthospital VTE prophylaxis.
2. It is very important to have uniform definitions of PE that are endorsed by all societies (ESC, ACCP, AHA) to reduce practice variations.
3. Definitions of major bleeding should be more precise and clinically relevant when comparing major adverse outcomes associated with different modalities of treatment; for example, the International Society on Thrombosis and Haemostasis defines a drop in Hb greater than 2 gm/dl as a major bleeding event. Patients often have a drop in Hb without obvious clinically relevant bleeding (i.e., intravenous fluid administration, repeated blood draws).
4. Develop and validate standardized patient selection criteria for CBT in submassive PE.
5. Determine an ideal time for CDT after diagnosis of submassive PE. Does the time to intervention predict short-term outcomes (i.e., hemodynamic decompensation) and long-term outcomes (i.e., post-PE syndrome or CTED)?
6. Establish the role of ideal dosing and duration for CDT.
7. Establish the best way to determine the effectiveness of CBT: clinical improvement versus right heart catheterization pre- and post-CBT treatment versus CTA before and after CBT treatment versus cardiac biomarkers before and after CBT treatment. This may have a direct impact on length of stay in the ICU, hospitalization cost, and resource allocation and use.
8. Study the effect of catheter-based treatment in prevention of CTED/post-PE syndrome or CTEPH.
9. Study the effect of weight reduction programs and structured post-PE exercise or rehabilitation programs on

improving functional limitation after acute PE.

10. Compare the effectiveness of half-dose thrombolytics with catheter-based treatments in prevention of hemodynamic decompensation in submassive PE, risk of major and minor bleeding, and reduction in long-term functional outcomes.
11. Examine the role of upfront surgical embolectomy to improve long-term functional outcomes in recurrent VTE. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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