Challenges and Changes to the Management of Pulmonary Embolism in the Emergency Department

Chris Moore, MD*, Katelyn McNamara, Rachel Liu, MD

KEYWORDS

• Pulmonary embolism • Venous thromboembolism • Emergency department • Thrombolysis • Thrombolytics • PE response team

KEY POINTS

- Diagnosis of PE may include the use of age adjusted D-dimer and point-of-care ultrasound.
- Classification of PE is essential for prognosis and treatment and has evolved over the last decade.
- Alternative treatments such as low dose thrombolytics may be most appropriate in some patients.
- Cutting edge therapies for life threatening PEs include nitric oxide ventilation and extracorporeal membrane oxygenation.

Video content accompanies this article at http://www.chestmed.theclinics.com.

EPIDEMIOLOGY AND DIAGNOSIS

The incidence of pulmonary embolism (PE) is slightly more than 1 per 1000 person-years, with estimates ranging as high as 900,000 PEs annually in the United States with 200,000 fatalities per year (**Box 1**).[1] Between 1 in 400 and 1 in 1500 patients presenting to US emergency departments (EDs) will be diagnosed with PE, an incidence that is highly age-related, and may increase as the population ages further.[2] With more than 140 million annual ED visits in the United States, this suggests that between 90,000 and 350,000 PEs are diagnosed annually in US EDs.[3]

In 1998 multidetector computed tomography (CT) pulmonary angiography was introduced and rapidly became the first-line test for PE.[4] CT is rapid, accurate, and essentially universally available in EDs as a diagnostic option. However, despite a near doubling of diagnostic incidence since CT replaced ventilation perfusion scanning, the age-adjusted mortality from PE has remained relatively stable, suggesting "overdiagnosis."[4]

At the same time, it is frequently posited that PE remains missed in the ED setting, and medicolegal concerns are prominent. It has been suggested that PE "should be suspected in all patients who present with worsening dyspnea, chest pain, or sustained hypotension without an alternate obvious cause."[5] However, the hallmark symptoms of PE—chest pain and shortness of breath—are among the most common presenting ED complaints. This makes ruling out a PE by objective means in all such patients neither feasible nor desirable. There are several validated clinical decision rules that can aid in deciding whether further diagnostic testing (D-dimer or CT) is needed, including the PE rule-out criteria (PERC), Wells score for PE, and the Geneva score.[2]

The PERC score defines a population in whom no testing is needed to exclude PE. Patients in

Department of Emergency Medicine, Yale University School of Medicine, 464 Congress Avenue, Suite 273, New Haven, CT 06519, USA
* Corresponding author.
E-mail address: Chris.moore@yale.edu

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Box 1
Challenges and changes in ED management of PE

- Adjusted D-dimer for diagnosis
- Classification of PE for prognosis and therapy
- Thrombolytic therapy for intermediate-risk PE
- Low-dose thrombolysis dosing
- Adjunctive therapies for large PEs
  - Nitric oxide ventilation
  - Extracorporeal membrane oxygenation
- Multidisciplinary PE response teams

whom PE is considered a possible diagnosis but who are "PERC negative" should not have D-dimer performed. An important concept with PERC is that it does not necessarily completely rule out all possibilities of a PE, but it defines a population in whom the likely harm of performing a D-dimer (false-positive results leading to likely unnecessary testing) outweighs the benefit based on defining a threshold level of diagnostic likelihood (~2%). It is also important not to apply the PERC rule indiscriminately—if there is no real concern for PE then it should not be used.

The Wells score for PE is the predominant scoring system and has been well validated in the ED setting.[6] It can be divided into either a two- or three-level score, with D-dimer testing used to exclude PE in low- or intermediate-risk patients. The Geneva score (including simplified and revised Geneva) is an alternate approach that is more common in Europe and has been shown in some studies to be more consistently reliable.[1] The decision about whether and which clinical prediction rule to use may be guided by the local prevalence of PE.[7] Although objective clinical prediction rules are recommended by some analyses, others have suggested that gestalt clinician pretest probability may be used and even preferred in some cases.[8,9]

Challenges and Changes: Adjusted D-dimer

D-dimer is a cornerstone of PE diagnosis. Quantitative enzyme-linked immunoassay D-dimer tests are sensitive enough to essentially rule out a PE in all but high-risk patients. Although sensitive for ruling out PE, the problem is that D-dimer is not specific and can be elevated in the absence of PE. This is the basis of the PERC score—an attempt to ensure D-dimers are not ordered indiscriminately, leading to increased CT scanning without improving diagnostic yield. D-dimer may be elevated without PE in pregnancy, malignancy, trauma, or simply as people age. Recently several publications have supported the use of an age-adjusted D-dimer, allowing the threshold for CT angiography testing to increase with age. The most commonly used adjustment is to use age times 10 ng/mL, so while a normal threshold for abnormal is typically 500 ng/mL, an 80 year-old patient's cutoff would be 800 ng/mL. This approach is supported by the literature and expert opinion.[10] In pregnancy, D-dimer level also increases with each trimester, and a pregnancy-adjusted D-dimer along with a modified PERC rule may be considered (heart rate cutoff of 105; D-dimer threshold 50%, 100%, and 125% higher than normal cutoff by trimester).[11]

Challenges and Changes: Echocardiography and Focused Cardiac Ultrasound

Transthoracic echocardiography (TTE) can be used in both the diagnosis and prognosis of PE and can thus also influence therapy.[12] Although echo is insufficiently sensitive to completely rule out PE, the presence of findings (usually indirect evidence of right ventricular [RV] strain, occasionally actual visualized thrombus) increases the likelihood of the diagnosis and defines a subset that may benefit from more aggressive therapy.[13] When available, TTE can be performed by a certified sonographer and interpreted by a cardiologist; however, availability of cardiology echo is often limited or delayed in the ED setting.[14] The specificity of echo may be particularly helpful for "rule-in" of patients with hemodynamic instability in the ED setting.[12]

One of the more recent challenges and changes to the ED diagnosis and management of PE has been the potential incorporation of point-of-care ultrasound, or specifically focused cardiac ultrasound (FoCUS), which is an ultrasound performed by the emergency physician at the bedside.[15,16] Although echo performed by emergency physicians (EPs) has been described for at least 3 decades, evidence for FoCUS evaluation in suspected or confirmed PE has been more recent.[17] The evaluation of the right heart has consistently been included in consensus statements about FoCUS since 2010.[15,18,19] Available ultrasound technology has become higher in quality and more affordable, but the issue has always been what level of training is required to adequately perform FoCUS.[19]

The most prevalent and reliable sign of a significant PE on echo is RV strain, based on RV enlargement or hypokinesis (**Figs. 1** and **2**). RV enlargement relative to the left ventricle (LV) is

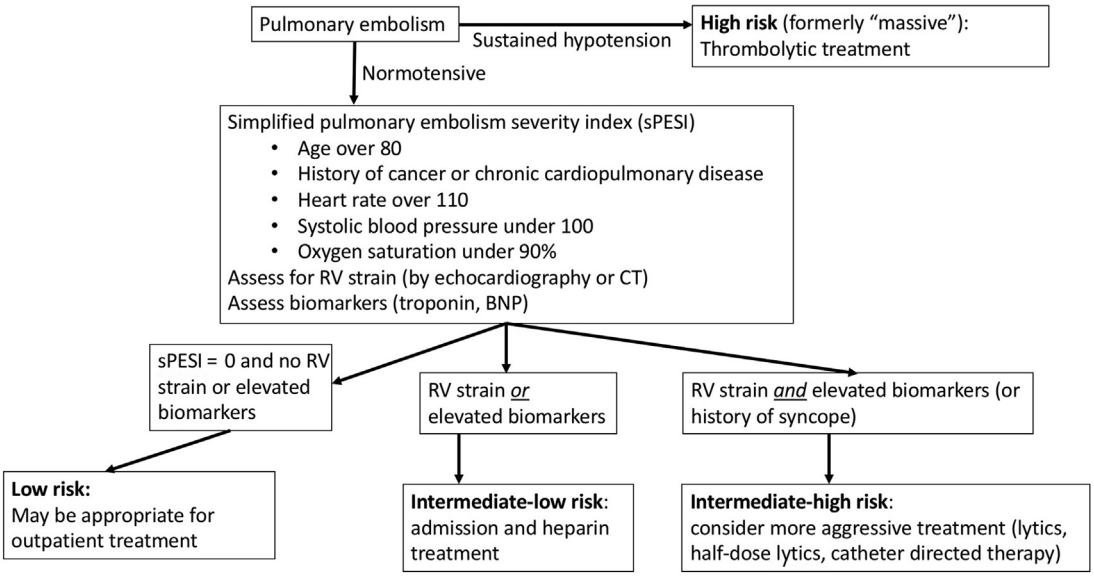

Fig. 1. This chart shows a classification scheme based on most current literature, with potential impact on therapy.

the most frequently described FoCUS measure. A normal ratio of the RV to LV is approximately 0.6:1 (measured across tips of valves in an apical view); however, a typical cutoff used for RV enlargement is an RV:LV ratio of 1:1 or greater,

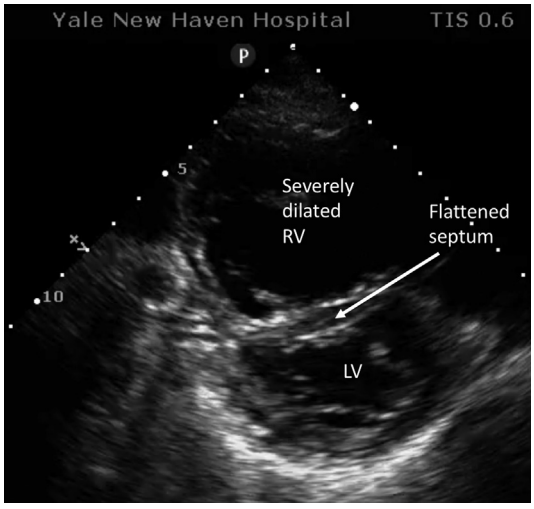

Fig. 2. This is a point-of-care FoCUS of a 37-year-old patient in cardiac arrest who came in to the ED. This is a parasternal short-axis view showing a markedly enlarged right ventricle (RV) compressing the septum into the left ventricle (LV) in a characteristic "D-shaped" pattern. Initial blood pH was 6.85 with lactate of 18 mmol/L. This patient received a total of 150 mg bolus dose tissue plasminogen activator, nitric oxide via the ventilator, and extracorporeal membrane oxygenation in the intensive care unit. Videos 1 and 2 show pre- and postthrombolysis. The patient recovered fully.

which favors specificity over sensitivity. Detection of RV enlargement by RV:LV ratio has been shown to have good interobserver agreement.[20] In a study of 146 ED patients, 30 of whom had PE, the presence of RV dilatation (1:1 or greater ratio) had a specificity of 98% for the diagnosis of PE, although sensitivity was only 50%.[21] Another study of 411 of patients by 69 different emergency providers in whom 6.2% had RV strain showed moderate agreement when comparing EPs to consultative echo.[22] In addition to aiding in diagnosis, the presence of RV strain identified by EPs in diagnosed PE has been shown on multivariate analysis to predict adverse outcomes.[23]

A potentially more objective and reliable measure of RV dysfunction secondary to PE is tricuspid annular plane systolic excursion (TAPSE). First described in the cardiology literature for more chronic diseases such as congestive heart failure and pulmonary hypertension, it has been shown to be a more reliable measure of RV dysfunction and to correlate well with other markers of acute PE severity.[20,24] A normally functioning RV contracts from base to apex and can be measured quantitatively using m-mode (motion mode), with normal movement typically being more than 16 to 20 mm, but may also be categorized qualitatively as normal or abnormal.[25] Although TAPSE also lacks sensitivity in diagnosing undifferentiated PE, a recent study showed that when PE is suspected in patients with abnormal vital signs it was sensitive for the diagnosis.

SPECTRUM OF PULMONARY EMBOLISM FOR PROGNOSIS, THERAPY, AND DISPOSITION

PE presents with a wide spectrum of severity, which is important to define for both prognosis and therapy. There is some confusion and heterogeneity regarding use of these terms and they have continued to evolve. Hemodynamic instability or hypotension at presentation is the strongest predictor of mortality and identifies patients for aggressive therapy such as thrombolysis. Fig. 1 shows a classification scheme based on the most commonly used current stratification schema.[26–28]

Presence of hemodynamic instability has more recently been termed "high-risk" PE, previously termed "massive," and is typically defined as presence of hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes not from another cause), cardiac arrest, or persistent bradycardia (<40bpm with signs and symptoms of shock).[27] Within normotensive patients there are intermediate-high and intermediate-low (formerly grouped as "submassive") and low-risk.[27,28] Although there is some variability in this area, a simplified pulmonary severity index (sPESI) score of zero has been used to define low-risk patients who may be appropriate for outpatient PE treatment. The sPESI includes age greater than 80 years, history of cancer or chronic cardiopulmonary disease, heart rate greater than 110, systolic blood pressure less than 100, or oxygen saturation less than 90%.[26] If the sPESI is greater than zero and the patients are normotensive, the presence of RV strain or elevated biomarkers (or neither) identifies intermediate-low risk (appropriate for heparin alone and admission). RV assessment may be performed using either echocardiography or CT, and elevated biomarkers typically include troponin or b-type natriuretic peptide. The presence of both RV strain and elevated biomarkers, or a history of syncope, would classify someone as having intermediate-high risk PE. Intermediate-high risk PE patients may be considered for more aggressive therapy, including full- or half-dose thrombolytics (or catheter-directed therapies). Patients presenting with hemodynamic instability from PE are estimated to have a 30-day mortality rate of ~50%, with intermediate-risk PE around 10% to 20% (perhaps lower now with improved therapy), and low-risk PE of about 1%.[27,29]

Other scoring systems include the HESTIA score and the original PE severity index (PESI).[30,31] The PESI score divides patients with diagnosed PE into 5 risk classes and was originally designed to delineate patients appropriate for outpatient treatment of PE, although it may be used to help guide patient selection for more aggressive therapy as well.[1] Both the HESTIA and PESI/sPESI scores may be used to select patients for outpatient treatment of PE, with HESTIA potentially safely identifying a larger proportion.[32] Although evidence continues to emerge, there is no consensus that there is validated data about these scoring systems for definitive treatment.[33]

THERAPY

Anticoagulation is the mainstay treatment of PE. Unfractionated heparin (UFH) can be considered a default initial treatment of PE that can be titrated and reversed if necessary, but must be administered in an inpatient setting. Low-molecular-weight heparins (LMWH) have been shown to be equivalent or better than UFH in treatment efficacy and can be administered as an outpatient.[34] Recently, novel oral anticoagulants (NOACs) that inhibit factor Xa have been approved for use in PE and may be initiated in the ED setting. Currently the NOACs approved by Food and Drug Administration (FDA) for PE treatment include apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto), and edoxaban (Savaysa). Outpatient treatment represents a potential opportunity for more efficient care that may also be more favorable to the patient. In patients who are at low risk (no RV strain, hypoxia, elevated biomarkers, or hemodynamic instability) and/or have low HESTIA/PESI/sPESI scores, it has been shown that they may be safely discharged from the ED on either LMWH or an NOAC with a low rate of complications.[35] It is also arguable that in some cases isolated subsegmental PEs may either be false-positive diagnoses or may be so insignificant that the harms from anticoagulation outweigh the benefits, although trials on this approach are lacking.[36]

Thrombolysis

UFH, LMWH, and NOACs have the effect of preventing new thrombus formation and allow natural processes to resolve clots but do not actively dissolve the thrombus. Thrombolytic agents (tissue plasminogen activator [tPA]) will actively dissolve clot but carries a higher risk of hemorrhage. Systemic thrombolysis is a recommended option for hemodynamically unstable (massive) PE given the high risk of death without aggressive intervention.[27] The risk of bleeding makes use of thrombolysis contraindicated for low-risk PEs. Submassive or intermediate-risk PEs represent a particular challenge in the management of PE. Systemic lysis may be of benefit, but the risk-benefit balance is

slimmer and other options such as reduced dose or catheter-directed lysis may be considered.

Challenges and Changes: Thrombolysis in Intermediate-Risk Pulmonary Embolism

A 2011 review summarized the outcomes of 4 registries that reviewed thrombolysis for submassive PE, finding that data "suggest a trend towards a decrease in all-cause mortality from PE."[27] In addition to citing this mortality "trend," this review also addressed potential morbidity from submassive PEs such as pulmonary hypertension and decreased exercise tolerance. It concluded that there was also evidence to suggest decreased morbidity from thrombolytic therapy. They established with class IIb, level C evidence that "fibrinolysis may be considered for patients with submassive PE judged to have clinical evidence of adverse prognosis" but did not recommend it with "minor" RV dysfunction or "minor" myocardial necrosis (not specifically defined). In 2014 a meta-analysis in JAMA determined that "among patients with PE who were hemodynamically stable with right ventricular dysfunction, thrombolytic therapy was associated with lower rates of all-cause mortality and increased risks of major bleeding."[37] This meta-analysis included data from the ULTIMA study that used ultrasound-assisted thrombolysis and lower-dose thrombolytics, which may lower the risk of bleeding.[38]

The results of the pulmonary embolism thrombolysis (PEITHO) trial were published in 2014, representing the largest prospective evaluation of intermediate-risk PE to thrombolytic treatment, randomizing 1005 patients in a double-blind placebo controlled trial. The overall rate of "death or hemodynamic compensation" was statistically lower in the thrombolysis group (2.6%) compared with the placebo group (5.6%). A hemorrhagic stroke occurred in 2.0% of thrombolytic patients. Regarding actual patient-level decision-making, an accompanying editorial stated "data from the PEITHO trial provide valuable insight but no definitive answer."[39] A recent review of this issue in the emergency medicine literature concluded that risks and benefits be considered on a case by case basis, with incorporation of shared decision-making.[40] For a younger patient who may be more concerned about long-term morbidity and less likely to suffer an intracranial hemorrhage, lysis may be more attractive although this decision will rest on preferences and the risk tolerances of both the patient and provider. Although prior guidelines have raised the possibility of thrombolysis in intermediate-high risk patients,[27] an analysis of the PEITHO trial found no long-term difference between heparin and thrombolysis.

Thrombolytic Dosing

FDA-approved agents available for thrombolytic therapy include alteplase or recombinant tPA (brand name Activase, rt-PA) and streptokinase. The abbreviation tPA is used to encompass the class of tissue plasminogen activators, and it is recommended this abbreviation not be used when dosing medication to avoid errors.[41] Streptokinase and urokinase were used in many older trials but most EDs now have rt-PA. The FDA-approved regimen for systemic rt-PA is 100 mg infused over 2 hours. Tenecteplase (brand name TNKase, TNK) and reteplase (Retavase) are tPAs that are approved for myocardial infarction but have not been FDA-approved for PE treatment. TNK was the agent used in the PEITHO trial and has the advantage of being a single weight-based dose that ranges from 30 mg (patient weight less than 60 kg) to 50 mg (90 kg or more). It does not need an infusion, as opposed to tPA.

Challenges and Changes: Low-Dose Tissue Plasminogen Activator

In 2010 Wang and colleagues[42] published a randomized trial of 118 patients receiving full-dose tPA (100 mg over 2 hours) versus half-dose (50 mg over 2 hours). This dosing trial demonstrated similar improvements in measures of efficacy (RV dysfunction on echo and clot burden) for half-dose tPA compared with full-dose, with lower rates of significant bleeding (2% vs 10%). The MOPPET trial compared heparin alone to half-dose tPA and found improvement in symptoms without adverse events using half-dose tPA.[43] A recent meta-analysis confirmed that "low-dose" rt-PA had similar efficacy with a better safety profile.[44] Half-dose treatment thus may be more appropriate when electing to use thrombolytic for intermediate-high risk PE, although evidence is not considered definitive.[40,45]

In patients with intermediate-high risk and a subset of massive PEs (eg, low blood pressure but who are mentating and oxygenating reasonably well), a 2-hour infusion of a thrombolytic agent may be well-tolerated. However, there is a subset of ED patients who are in or near cardiac arrest from suspected or confirmed PE and who may be unlikely to survive 2 hours without more aggressive intervention. In this case, bolus dose tPA may be appropriate. At the authors' institution they have successfully used bolus dosing of tPA to resuscitate patients in near or full arrest from PE, typically using an initial bolus dose of 50 mg of rt-PA followed by

infusion of the remainder, and repeated if necessary. Although this is not an FDA-approved regimen, it has been used at other institutions.[46]

Of note, the American Heart Association has recommended against thrombolysis in undifferentiated pulseless electrical activity (PEA).[27] However, they do recognize that in a patient with a high pretest probability of PE and RV dysfunction on TTE who is unstable to undergo CT scanning, aggressive therapy including thrombolysis is warranted. TTE in the ED has been described as guiding therapy in massive PE and may also help exclude other causes of hypotension.[47,48] Thus the combination of PEA with a massively dilated RV on bedside echocardiography likely merits an attempt at thrombolysis.

Another consideration in systemic thrombolysis treatment is concurrent utilization of heparin. Often these patients are started on heparin before the decision to initiate thrombolytics. The half-life of tPA is often short (~5 minutes for rt-PA) and there is a risk of rethrombosis if this medication wears off without other anticoagulants present. This needs to be balanced against the potential for increased bleeding. In the PEITHO trial, UFH was continued during the TNK infusion in both arms.[49] In another trial, the heparin dose during infusion was 10U per hour (vs regular dose of 18U/h).[43] We recommend continuing an unfractionated heparin infusion during thrombolytic infusion, possibly at reduced levels. Following thrombolytic infusion, the heparin can be adjusted to an activated partial thromboplastin level of 2.0 to 2.5 times normal.

Other Therapeutic Approaches to Large Pulmonary Embolism

In addition to systemic thrombolysis, other options for large PEs include catheter-directed thrombolysis (CDT), ultrasound-accelerated catheter-directed thrombolysis (UACDT), percutaneous mechanical thrombectomy (PMT), and surgical embolectomy. The availability of these therapeutic options vary depending on the institution and are likely only available at larger tertiary care institutions.

In PE without cardiac arrest, CDT has been shown to provide similar clinical outcomes as systemic thrombolytic therapy, while minimizing the risk of major bleeding.[50] This is achieved by the administration of thrombolytic agents locally, which allows for a much lower dose, around one-third of what would be used systemically. A 2009 meta-analysis found pooled success rates for CDT of 86.5% with major complications of 2.4%, lower than the cited risk of hemorrhagic stroke in many series of systemic thrombolysis.[51]

Another approach that is used in Europe and increasingly available in the United States is the UACDT, which delivers uniform radial ultrasound energy in addition to small continuous doses of thrombolytic. A study using the EKOS EkoSonic© UADCT system was shown to decrease the pulmonary artery pressure, lower the RV/LV ratio, and clear greater than 90% of the thrombus in more than three-quarters of patients without major bleeding complications.[52]

PMT may include clot aspiration, fragmentation, or rheolysis (high pressure saline) and may be combined with catheter-directed pharmacologic treatment. Mechanical approaches alone have a success rate of ~80% but with low rates of bleeding; inclusion of pharmacotherapy can increase success rates to 95% but increases the rate of hemorrhage.[27]

Lastly, surgical embolectomy has a history of more than 100 years and may remain an option when thrombolysis is contraindicated or fails.[53] Mortality has typically been high, although controlled trials are lacking and numbers may be skewed due to its assignation as a therapy of "last resort." Recent improvements in technique have cited improvements in outcomes, with survival approaching 90% at an experienced center using state-of-the-art techniques.[54]

Challenges and Changes: Adjunctive Therapies for Massive Pulmonary Embolism

Although mechanical obstruction by thrombus may be a primary cause of hypoxia and hemodynamic instability, pulmonary arterial vasoconstriction may play a large role. Inhaled nitric oxide (NO) ventilation can decrease pulmonary resistance and has been used as a temporary therapy to help stabilize a hemodynamically deteriorating patient pending other management options such as thrombolysis or surgical embolectomy.[55] Gas exchange and hemodynamics can improve within minutes, with as little as 1 to 2 parts per million (ppm) although optimal dosing is probably 10 to 20 ppm.[56,57] It is important that when used, NO be weaned slowly to avoid rebound pulmonary hypertension. An ongoing trial using NO in the ED setting for acute intermediate-risk PE has enrolled 78 patients to date without adverse outcomes.[58] This protocol titrated the concentration from 2 to 50 ppm and demonstrates feasibility in the ED setting.

Another option described in the literature for temporizing hypoxia and hemodynamic instability from massive PE is the use of extracorporeal membrane oxygenation (ECMO).[57,59] ECMO can be veno-venous (VV, providing no hemodynamic support) or veno-arterial (VA, providing complete cardiopulmonary bypass). Although there are no large trials, both VV and VA ECMO have been

reported with survival rates of 50% to 70% and 20% to 50%, respectively.[60] The use of ECMO has increased more than 4-fold since 2006, and some centers are training ED personnel to institute ECMO.[61] Another option is a device such as the Impella RP, which is now FDA-approved for right heart failure.[62] The Impella RP is threaded through the femoral vein into the pulmonary artery, with an intake at the IVC/right atrial junction and an outlet into the pulmonary artery; it has been described as an option for massive PE.[63]

Challenges and Changes: Pulmonary Embolism Response Teams

As detailed earlier, for patients with submassive or massive PEs there are multiple options and multiple potential specialties that may be involved in patient care, including emergency medicine, pulmonary/critical care, radiology, interventional radiology, cardiology, and cardiothoracic surgery. In many cases decisions may be time critical. For high-volume centers with the capacity to do so, the creation of a multidisciplinary "pulmonary embolism response team" (PERT) has been described.[64] Over the last year the authors have implemented a PERT team at their center. Although this approach offers the potential for timely involvement of all relevant specialties, challenges include coordinating when all specialties may be available (we have only been able to staff it during daytime hours) and ensuring that involvement of "too many cooks" does not actually delay needed intervention.

SUMMARY

PE remains a common disease that is increasing in prevalence and encompasses a wide spectrum of severity and treatment options. The optimal diagnosis, prognosis, and therapy in the acute setting provide challenges that will likely continue to evolve. These include avoiding both over- and undertesting, determining appropriate prognosis and tailoring therapy to the individual situation. A multidisciplinary approach to more serious PEs is likely to provide optimal outcomes.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.ccm.2018.04.009.

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