Pulmonary Embolism: The Astute Interventional Radiology Clinician

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Abstract

Keywords

- ▶ submassive pulmonary embolism
- ▶ catheter-directed thrombolysis
- ▶ massive pulmonary embolism
- ▶ inferior vena cava filters

There has been a resurgence of interest in defining the optimal treatment for severe pulmonary embolism (PE), fueled by pivotal and provocative trials, new catheter-based medical devices, and growing evidence of deleterious short- and long-term outcomes. In this environment, and especially given the multidisciplinary nature of PE care, the interventional radiologist (IR) needs to become an astute, disease-specific expert. This review article describes the following “steps” an IR can take to reach this level: (1) understand PE stratification and epidemiology; (2) recognize the treatment goals for massive PE; (3) recognize the wide range of attitudes toward therapeutic escalation for submassive PE; (4) recognize what we do not know about the treatment of submassive PE and the limitations of current studies; (5) know the literature surrounding inferior vena cava filter insertion for severe PE; (6) integrate into the longitudinal care of the patient; and (7) be at the leading edge of new trials and technologies.

Objectives: Upon completion of this article, the reader will be able to discuss pulmonary embolism (PE) stratification and epidemiology, the evidence characterizing the risks and benefits of systemic thrombolysis, surgical embolectomy, and catheter-directed therapy for severe PE, and the role of inferior vena cava filters in severe PE.

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There has been renewed interest in interventional therapy for pulmonary embolism (PE) in the past several years,

partially spurred by a pivotal systemic thrombolysis trial (PEITHO),¹ a small, randomized trial of catheter-directed thrombolytic (CDT) therapy (ULTIMA),² and the largest single-arm cohort study of CDT to date (SEATTLE II).³ In addition, industry interest in the PE space has grown, with ultrasound-assisted thrombolysis catheters, novel aspiration devices, and ventricular support devices being trialed in the setting of PE.

In this environment, it behooves the interventionalist to become familiar with the epidemiology, pathophysiology, stratification, literature, and all possible treatments for severe PE and their limitations. There are significant data gaps that ought to be understood and acknowledged. Armed with this information, the interventional radiologist (IR) can successfully integrate into a multidisciplinary PE team and offer the group informed advice, eschewing the traditional proceduralist's role for that of an astute IR clinician.

This review is structured around the current and future landscape of PE care. It takes the form of specific “steps” an IR can take to become an effective partner in the multidisciplinary PE landscape.

Step 1: Understand PE Stratification and Epidemiology

Several guidance documents have stratified PE according to the risk of short-term mortality, typically into three categories defined by systemic and right ventricular hemodynamics, which correlate with short-term deleterious outcomes.^{4,5} The 2011 American Heart Association guidelines use the terms “massive,” “submassive,” and “low-risk” PE, with massive PE referring to PE associated with hypotension (systolic blood pressure <90 mm Hg for >15 minutes or a 40 mm Hg drop from baseline) or requiring vasopressor support or bradycardia (heart rate <40 beats per minute with signs of shock). Submassive PE is defined by a normal blood pressure but a compromised right ventricle, identified by any combination of imaging (echocardiography, computed tomography), biomarkers (serum troponin, brain natriuretic peptide), and electrocardiography (S1Q3T3 pattern, new right bundle-branch block, among other findings). Low-risk PE has none of these features. This segregation is derived from mortality rates—massive PE carries a mortality rate of 25 to 65% and low-risk PE carries a mortality rate of lower than 1%. Submassive PE is more controversial—registry data from the late 1990s showed that right ventricular dysfunction was associated with a 19% 90-day mortality,⁶ whereas contemporary randomized trials demonstrate a much lower mortality rate of 2 to 3% with prompt initiation of anticoagulation.^{1,7} Patients in the submassive PE group have a 5% risk of clinical deterioration with anticoagulation alone.¹

2014 European Society of Cardiology Guidelines on Pulmonary Embolism acknowledge that submassive PE encompasses a broad range of presentations, and the authors sought to provide further granularity to this subcategory.⁸ They use the term “intermediate PE” instead of submassive, and define a “high-risk” intermediate PE patient as having a simplified Pulmonary Embolism Severity Index (sPESI) score of 1 or more,⁹ right ventricular dysfunction or dilation on echocardiography or computed tomography, and biomarker elevation (brain natriuretic peptide or troponin). They define a “low-risk” intermediate PE as having an sPESI score of 1 or greater with either right ventricular dysfunction/dilation or biomarker elevation or neither of these. They suggest that low-risk intermediate PEs should be managed without therapeutic escalation, whereas the high-risk intermediates should be monitored more closely because of a higher risk of clinical deterioration and may benefit from advanced therapies if the risk of bleeding is low.

All this stratification should be placed in the context of each subcategory's incidence, as low-risk PE is the most common presentation and requires anticoagulation alone. Twenty five percent to 40% of PE cases will be in the submassive category, and 5% will present in the massive category. These data should be remembered when allocating resources and personnel to treat PE, and in the development of treatment algorithms.

Step 2: Recognize the Treatment Goals for Massive Pulmonary Embolism

Given the high mortality associated with massive PE, the physicians taking care of such a patient are obliged to take

aggressive action to save that patient's life. Societal guidelines provide the most clarity about massive PE, at least suggesting all three advanced therapies (systemic thrombolysis, catheter-based thrombus removal, and surgical embolectomy) over no such treatment.⁵

Because massive PE is rare compared with the other PE categories, and because randomization is extremely challenging in this subgroup, it is highly unlikely that a structured trial will clarify which therapy is most appropriate. Overall, emergency and critical care physicians should have a low threshold to administer intravenous thrombolytics, given the rapidity of administration. Cardiothoracic surgeons should be ready to perform a thrombectomy and provide cardiopulmonary support through extracorporeal membrane oxygenation, especially if the patient is a poor candidate for thrombolytic drugs. There has been a resurgence in surgical embolectomy for PE; improvement in techniques and patient selection have made this operation a valuable and viable option for massive PE in some centers.¹⁰ In a 115-patient, single-center retrospective cohort, massive PE patients undergoing embolectomy had a 10.2% mortality, which compares favorably to historic mortality rates.¹¹ Another 20-patient, single-center series with a mix of submassive and massive PE cases demonstrated a 95% survival rate.¹² Clearly patient selection is essential for superior outcomes, and routinely operating on patients after they have arrested will skew mortality data. The series mentioned here argue that, at experienced embolectomy centers, there should be a lower threshold for considering embolectomy. Special circumstances, including clot in transit or a patent foramen ovale, may be particularly suited toward surgical intervention.

If the interventionalist is called upon to save a patient who is a poor candidate for either of the aforementioned therapies, she or he should be prepared with a multitude of tools, including aspiration and maceration devices. Kuo et al conducted a comprehensive review of published data for catheter-directed therapy in the setting of massive PE and found a high rate of survival to hospital discharge, although numerous included studies were retrospective in nature or were case series, connoting a potential for publication bias.¹³ The review cited numerous devices that were used and effective in this setting, with the exception of the AngioJet (Boston Scientific, Marlborough, MA) rheolytic catheter which was associated with a disproportionate number of deaths. The overall message is that the interventionalist has considerable leeway to use mechanical methods to improve pulmonary blood flow and increase left ventricular filling pressures, because the alternative is cardiovascular collapse.

Step 3: Recognize the Wide Range of Attitudes toward Therapeutic Escalation for Submassive PE

The standard therapy for PE is anticoagulation, which unquestionably reduces mortality in the vast majority of patients. It is also widely recognized that anticoagulation is not enough in the setting of massive PE. However, submassive PE is clearly a “gray” zone, filled with considerable

equipoise, and with good reason. The registry data from the late 1990s raised significant concern when right ventricular dysfunction without hypotension was associated with a 90-day mortality rate as high as 19%.⁶ However, subsequent randomized trials demonstrated a 2 to 3% mortality rate for submassive PE patients with anticoagulation alone. Thrombolysis did not affect mortality in these individual trials, although a recent meta-analysis attributed a slight mortality reduction to thrombolytic use in the setting of submassive PE.¹⁴ Regardless, it is clear that systemic thrombolytics markedly increases the risk of intracranial and major bleeding. To summarize, given the low event rate in the control arm, many have concluded that the vast majority of submassive PE patients should not receive aggressive therapies that increase the risk for iatrogenic bleeding.

Given this backdrop, a high bar has been set for catheter-directed therapy. The adage to “do no harm” is clearly in play for submassive PE. Procedural risks are added to the risk of bleeding from a thrombolytic drug, albeit the risk of the latter may theoretically be lower because of local administration and lower total dose (although this concept has not been rigorously proven) compared with systemic thrombolysis. Mechanical catheter-based techniques need to prove that they do not worsen pulmonary hemodynamics and create instability where there was none before. While some intensivists view catheter-directed therapy for submassive PE as an elegant and safe method to prevent serious sequelae, many others are wary of what they consider an unnecessary and unproven intervention for patients who are, after all, hemodynamically stable.

There is a similar attitude toward surgical embolectomy in the setting of submassive PE. Few would routinely advocate for embolectomy to treat a condition with low mortality. There may be certain circumstances, including large clot in transit and concern for impending right ventricular failure, especially in the setting of absolute contraindications to thrombolysis, that make surgical intervention a viable choice, and the positive outcomes in the retrospective case series mentioned earlier are partially due to enrichment with submassive PE cases.

Step 4: Recognize What We Do Not Know About the Treatment of Submassive PE and the Limitations of Current Studies

There are numerous unanswered questions regarding submassive PE, ranging from patient selection for therapeutic escalation to the ideal drug and dose for both systemic and catheter-directed thrombolysis, physiologic consequences of residual thrombus, and long-term well-being. The largest systemic thrombolysis trials have used full-dose thrombolytic drugs (r-tPA and tenecteplase) and have only examined short-term outcomes such as early mortality and clinical deterioration.^{1,7} Many have asked whether the provocative but far from conclusive results of the MOPETT reduced-dose thrombolytic trial warrants further investigation into lower thrombolytic dosing strategies for submassive PE.¹⁵ The

interventionalist will likely be challenged by advocates of lower dose thrombolysis to prove that CDT is superior.

Unfortunately, patient selection for therapeutic escalation in submassive PE is far from well defined. Guidelines suggest that those who are trending toward clinical deterioration or are at high risk for it may benefit from systemic thrombolysis or CDT if they are at a low risk for bleeding.^{4,8} However, what exactly constitutes impending massive physiology is unclear. Concerning signs include persistent hypoxia, elevated lactate, liver dysfunction secondary to right heart failure, a history of syncope, rapid breathing, marked tachycardia, and an inability to ambulate short distances. Echocardiography may provide insight into the kinetics and size of the right ventricle, but the decision to escalate therapy is seldom made by echocardiographic results in isolation.

CDT has yet to be rigorously tested. ULTIMA is the only randomized CDT trial to date, and it included 59 patients. SEATTLE II had a larger sample size of 150 patients, most of who had submassive PE, but had no control arm. The primary endpoint in each of these studies was the ratio of right ventricular to left ventricular (RV/LV), a *nonclinical* assessment. PERFECT was a registry of CDT that showed a high clinical success rate but also lacked a control arm.¹⁶ While no intracranial bleeding was seen in any of these studies, there was an 11% major bleeding rate (GUSTO II, requiring transfusions) in the SEATTLE II cohort. These trials demonstrated efficacy, but lack the methodological rigor to allow providers to conclude that CDT is clinically effective (i.e., improves outcomes that are meaningful to patients) and should be routinely offered.

One of the largest knowledge gaps is whether aggressive acute management of submassive PE will lead to better longer-term outcomes. PE survivors are at higher risk of having reduced exercise capacity and quality of life.^{17–21} There appears to be a correlation between reduced exercise capacity and residual pulmonary artery thrombus.^{19,22} Early thrombolytic therapy may improve long-term outcomes. However, a randomized trial of CDT and/or systemic thrombolysis with clinically relevant short- and long-term endpoints is badly needed to definitively answer the question of which patients benefit from early therapeutic escalation and whether the risks of therapy are outweighed by improved outcomes.

Step 5: Know the Literature Surrounding Inferior Vena Cava Filter Insertion for Severe PE

There are few topics that have received more attention from a broad audience beyond interventional radiology than IVC filters. The risks of filters are well documented. However, in the setting of severe PE, there are several key points that ought to be considered. First, massive PE patients should receive IVC filters. Based on both ICOPER data and a discharge review, there appears to be a mortality benefit.^{6,23} Submassive PE, unsurprisingly, is more controversial. Some argue that if therapeutic escalation is being considered, IVC filter insertion should be as well. The results of PREPIC 2, however, argue against routine placement of IVC filters in submassive

PE patients if they can be anticoagulated.²⁴ In this randomized study that evaluated patients with symptomatic PE and clinical features felt to connote a higher risk of recurrence, there was no difference in mortality or in the rate of symptomatic PE between subjects who received anticoagulation alone and those who received a filter plus anticoagulation. Of note, greater than 60% of these patients had submassive PE.

Step 6: Integrate into the Longitudinal Care of the Patient

Many PE programs are appreciating the importance of longitudinal follow-up for PE patients with massive and submassive PE. Outpatient follow-up ensures adequate anticoagulation, provides reassurance, and ensures that patients who have unresolved dyspnea and exercise intolerance receive the proper diagnostic evaluation and are referred to the appropriate specialist. The interventionalist at the least should maintain a clinic that follows up patients who were treated with CDT, as patients value such interactions and appreciate the continuity of care. These visits also act as a safety net for patients who may not be receiving optimal medical management. Another opportunity may reside in multidisciplinary clinics in which there is a rotating schedule of physicians who may include pulmonologists, cardiologists, and interventionalists. Participating in longitudinal follow-up tends to improve the interventionalist's "gestalt" and allows him or her to better inform patients in the acute setting.

Step 7: Be at the Leading Edge of New Trials and Technologies

Stroke and myocardial infarction have outstripped PE in terms of quality data on percutaneous interventions, and many are now turning their attention to this third leading cause of cardiovascular death. In the coming months and years, several provocative and exciting trials are likely to be sponsored by industry and nonindustry organizations that will potentially address some of the key data gaps discussed earlier. Interventionalists should make every effort to be the site principal investigator or coinvestigator for these trials as they emerge, as such participation lends legitimacy to a PE program and contributes to the IR becoming the local expert on the topic.

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