Overview of Management of Intermediate- and High-Risk Pulmonary Embolism

Victor F. Tapson, MD[a,*], Aaron S. Weinberg, MD, MPhil[b]

KEYWORDS

• Intermediate-risk • Submassive pulmonary embolism • High-risk
• Massive pulmonary embolism • Anticoagulation • Thrombolysis
• Catheter-directed therapy • Simplified pulmonary embolism severity index

KEY POINTS

- Anticoagulation should be initiated as soon as possible when pulmonary embolism (PE) is strongly suspected, if the risk of bleeding is deemed acceptable.
- Risk stratification should be considered when PE is suspected and a plan finalized once the diagnosis is confirmed.
- Therapy more aggressive than anticoagulation should be strongly considered in high-risk (massive) PE.
- Intermediate-risk PE is subdivided into intermediate-low and intermediate-high-risk groups; anticoagulation is generally appropriate for the former.
- Intermediate-high-risk PE is a heterogeneous category; a careful assessment of patient appearance, vital signs, oxygenation, echocardiographic parameters, right ventricular biomarkers, clot burden, and comorbidities should be undertaken to aid in therapeutic decisions.

INTRODUCTION

The goal of this article is to first define high-risk (massive) pulmonary embolism (PE) and intermediate-risk (submassive) PE and then to review the overall management strategies of these entities. Because risk stratification is intimately tied to PE management, the authors offer a brief overview of this concept. Other sections in this issue offer more detailed descriptions of risk-stratification approaches and specific management strategies, including systemic thrombolysis, catheter-directed strategies,

Funding: Research grants (paid to institution) - Bayer, BMS, Daiichi, Inari, Janssen, Penumbra. Advisory boards / consulting - Bayer, BMS, Inari, Janssen, Penumbra, Thrombolex.
[a] Pulmonary and Critical Care Medicine, Cedars-Sinai Medical Center, Thalians Building Room w155, 8730 Alden Drive, Los Angeles, CA 90048, USA; [b] Cedars-Sinai Medical Center, Thalians Building, 8730 Alden Drive, Los Angeles, CA 90048, USA
* Corresponding author.
E-mail address: victor.tapson@cshs.org

Crit Care Clin 36 (2020) 449–463
https://doi.org/10.1016/j.ccc.2020.02.003
criticalcare.theclinics.com

and surgical embolectomy, as well as extracorporeal membrane oxygenation (ECMO); the authors offer an overview but leave details of the precise strategies to the other respective article authors.

DEFINITIONS

The terms "high risk" and "intermediate risk" have been gradually replacing "massive PE" and "submassive PE," respectively, in the modern PE literature and guidelines, and although they remain interchangeable, the division of intermediate risk into intermediate-low- and intermediate-high-risk PE has made this particular term more useful.[1] Furthermore, some clinicians, including radiologists, have continued to erroneously use the terms "submassive" and "massive" to refer to the actual clot burden on imaging; these terms should be used as defined above. The authors use the newer nomenclature. Importantly, high-risk, intermediate-risk, and low-risk PE all represent heterogeneous categories.

High-Risk (Massive) Pulmonary Embolism

Historically, the definition of massive PE has evolved. The definition used for a large thrombolytic therapy trial in acute PE several decades ago required a baseline Miller angiographic score of at least 17/34 and mean pulmonary artery pressure of $\geq$20 mm Hg.[2] In recent years, the definition of high-risk/massive acute PE has not included any specific anatomic clot burden requirement but simply refers to those emboli causing hemodynamic instability. Although high-risk PE can itself be stratified (**Box 1**), there are no clear evidence-based treatment recommendations that distinguish these scenarios. The term "high-risk PE" implies that therapy more aggressive than anticoagulation should be strongly considered.

High-risk, intermediate-risk, and low-risk PE all represent heterogeneous categories. For example, a patient with high-risk PE may have suffered a pulseless with electrical activity (PEA) arrest and be requiring very high-dose vasopressor support

Box 1
Categories of high-risk (massive) pulmonary embolism

Supermassive/catastrophic PE
- Cardiac arrest/need for cardiopulmonary resuscitation[a]
- Obstructive shock: Hypotension requiring pressor therapy with evidence of end-organ hypoperfusion (AMS, cold/clammy, oliguria, elevated lactate) but not resulting in cardiac arrest[a]

Systemic hypotension: Systolic blood pressure (BP) <90 mm Hg or systolic BP drop $\geq$40 mm Hg, lasting longer than 15 minutes, caused by pulmonary artery obstruction, but requiring only low-dose, or no vasopressor therapy[b]

Severe hypoxemia/acute respiratory failure[c]

[a] Cardiac arrest is most commonly pulseless with electrical activity. Patients with PE and underlying comorbid disease (eg, sepsis, left ventricular dysfunction, severe pneumonia, or other cardiopulmonary disease) may meet criteria for high-risk PE based on these hemodynamic criteria with a less extensive clot burden.

[b] Patients may deteriorate from low- or intermediate-risk PE, or from a less severely ill high-risk PE scenario, transitioning to a more critically ill status because of recurrent PE and/or worsening right ventricular dysfunction. Trends are important to closely observe.

[c] When very high O_2 requirements or requirement for mechanical ventilation results from acute PE, generally other features, such as severe right ventricular failure and hypotension, are also present.

or ECMO, or could be awake, alert, and simply have a systolic blood pressure (BP) <90 mm Hg for more than 15 minutes, or a systolic BP drop from 140 mm Hg to 95 mm Hg (ie, >40 mm Hg drop). The clinical approach may differ.

Intermediate-Risk Pulmonary Embolism

Intermediate-risk PE has been more variably defined than high-risk PE and has historically implied right ventricular (RV) dysfunction in the absence of hypotension. These patients were described as the "middle group" several decades ago and were the patients who generated the most controversy over whether thrombolysis should be administered.[3] More specifically, this middle group was defined by some investigators as patients with acute PE with evidence of RV abnormalities defined in several different ways, including elevated pulmonary artery pressure, RV dilation (RV appearing larger than the left ventricle on apical or subcostal view), paradoxic septal wall motion, loss of inspiratory collapse of the inferior vena cava, or tricuspid regurgitation.[4] Sanchez and colleagues[5] performed a (selective) metaanalysis and calculated an odds ratio for short-term mortality for RV dysfunction on echocardiography (defined variably) of 2.53 (95% confidence interval 1.17–5.50). RV dysfunction can vary from very mild to very severe; acute PE associated with very mild RV dysfunction in the absence of recurrent PE, for example, would appear very unlikely to result in an adverse outcome. These earlier definitions did not include cardiac biomarkers or clinical criteria, and although perhaps practical at the time, the definition has evolved.

Computed tomographic (CT) scan measurements of RV dilation also appear to be accurate and reproducible even when radiology residents are performing the measurement.[6] These measurements have been shown to predict adverse short-term events, including in-hospital death, 30-day mortality, and mortality at 3 months; RV diameter divided by left ventricular (LV) diameter greater than 0.9 (4-chamber view) has been a commonly used definition in clinical trials.[7] Other metaanalytic data using a CTA RV/LV ratio of 0.9 or 1.0 also support this poor outcome.[8] RV/LV ratio by computed tomographic angiography (CTA) as a measure of RV dysfunction has been shown to correlate well with echocardiographic parameters.[9–11] Because many studies have used a very mild increase in RV/LV (eg, 0.9 as lower limit) for inclusion,[7,8] many *mildly* abnormal cases have been included. Thus, it is difficult to use this specific cutoff value as a decision point for more aggressive therapy in clinical practice.

Biomarkers, including troponin and brain natriuretic peptide (BNP)/NT-pro BNP, have proven to be effective predictors of outcome in acute PE with metaanalyses supporting this finding for both troponin[12] and BNP/NT-pro BNP.[13] These biomarkers have been included more recently in the definition of intermediate-risk PE, although the most recent European Society of Cardiology (ESC) guidelines have focused on troponin, noting that these other biomarkers may also be useful (1 ESC 2019). It should be emphasized that elevations of either or both of these biomarkers, *independent of other parameters of severity*, should not be used to make clinical decisions. Notably, D-dimer testing has been shown to not only be useful in ruling out the clinical diagnosis of acute PE but also in predicting severity.[14] Finally, other prognostic biomarker measurements have been studied and may be useful, including heart-type fatty acid–binding protein, although this is not currently widely available.[15]

The pulmonary embolism severity index

Over time, the definition of submassive/intermediate-risk PE evolved to include specific clinical criteria.[16] Of the clinical criteria, the Pulmonary Embolism Severity Index (PESI) and simplified Pulmonary Embolism Severity Index (sPESI) have both been validated for predicting 30-day mortality in patients with acute PE.[17–20]

The sPESI uses 6 risk factors (as compared with 11 risk factors in the original PESI score).[18,19] An sPESI score of 0 predicts a short-term mortality risk of 2.5% and a negative predictive value of 97.5% compared with the original PESI. A metaanalysis of 21 studies that included an aggregate of 50,000 patients demonstrated that both PESI and sPESI are equally effective in identifying patients with *low-risk* PE.[21] Because the sPESI serves the same purpose as PESI but is much simpler, the authors prefer it and do not calculate the PESI routinely; sPESI is quite simple for any clinician to memorize and use.

In 2014, ESC guidelines incorporated the PESI/sPESI into the definition of intermediate-risk PE in order to integrate clinical status and comorbidities.[16] Intermediate-risk PE was defined as a patient with PESI III–IV (or sPESI $\geq$1), *or* RV dysfunction based on either echocardiography *or* an elevated troponin. Furthermore, the intermediate-risk category has been subdivided into intermediate low risk and intermediate high risk. Intermediate-low-risk acute PE is defined a PESI III–IV or sPESI score greater than 0, or RV dysfunction by *either* echocardiography *or* an abnormal troponin, whereas intermediate-high-risk acute PE is defined as RV dysfunction by *both* echocardiography *and* an abnormal troponin, with or without an abnormal PESI or sPESI. It should be emphasized that a patient is still designated intermediate risk if RV dysfunction is present even if the sPESI is zero (**Box 2**, **Table 1**).

It should be noted that other scoring systems have been studied for risk stratification of acute PE; these are discussed in another article in this issue. The authors have focused on sPESI based on its incorporation into the definition of intermediate-risk PE.

Several clinical criteria appear to be helpful in the risk-stratification process and can serve as predictors of mortality in acute PE; thus, they are commonly included when assessing the PE patient. These criteria include clinical appearance, respiratory rate, pulmonary embolic burden,[22,23] D-dimer level[14] (ie, *severity* of the elevation in D-dimer), and residual deep vein thrombosis (DVT).[24] Residual DVT in the setting of acute PE has been shown to be associated with a 2-fold increase in mortality.[24] However, clear changes in the PE treatment plan cannot generally be recommended based on residual DVT in the absence of severe acute DVT symptoms or phlegmasia.

Box 2
Intermediate-risk pulmonary embolism

Hemodynamically stable[a]

Each of the following 3 conditions (alone) defines intermediate-risk PE:
- sPESI >0 (or PESI III–IV) alone = intermediate-risk PE
- RV dysfunction alone = intermediate-risk PE[b]
- Troponin elevation alone = intermediate-risk PE[b]

Intermediate-low risk = RV dysfunction[c] *or* elevated troponin

Intermediate-high risk = RV dysfunction[c] *and* elevated troponin

[a] This implies no cardiac arrest or hypotension (systolic blood pressure not dropping below 90 mm Hg for $\geq$15 minutes because of PE, no need for vasopressors, and systolic blood pressure has not dropped by >40 mm Hg compared with baseline).

[b] Signs of RV dysfunction by echocardiography (or CTA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of I–II or an sPESI of 0; these patients are still classified as intermediate risk.

[c] RV dysfunction is generally defined by depressed RV function by echocardiography but a significantly dilated right ventricle by chest CTA also suggests RV dysfunction. There is not a specific echocardiographic parameter, which identifies an intermediate-risk patient; several clinical trials have used RV/LV >0.9 or 1.0 to designate an abnormal right ventricle (see text).

Table 1
The simplified pulmonary embolism severity index[a]

Criterion	Points
Age >80 y	1
History of cancer	1
History of chronic lung disease	1
History of heart failure	1
Heart rate >110 beats/min	1
Systolic blood pressure <100 mm Hg	1
Oxygen saturation <90%	1

[a] A low-risk sPESI (score of 0) predicts a short-term mortality risk of 2.5% and a negative predictive value of 97.5% comparable to the original PESI score.

Although the aforementioned parameters are very useful clinically, many have not been incorporated into formal risk-stratification recommendations (**Box 3**).

Whether clot burden measured by CTA predicts adverse prognosis has been controversial in studies published to date, probably because of differences in the populations studied in terms of severity of PE; several studies suggest that it does.[23] Logic dictates that the larger the PE, the more likely an adverse outcome. For example, PE that is so extensive that it causes near complete pulmonary arterial obstruction is likely to be associated with a higher risk of RV failure and death. Nonetheless, patients with very extensive PE may be quite clinically stable so that clot burden *alone* should not be used to make therapeutic decisions. Clot burden has not found its way into the intermediate- or high-risk definitions.

Box 3
Clinical parameters to consider in acute intermediate-risk pulmonary embolism

Appearance

Respiratory rate

Heart rate

Blood pressure

Clot burden by CTA or VQ scan

RV function by echocardiogram

Troponin

BNP/NT-pro BNP

Oxygen requirement

Lactate

Residual DVT

Although there are cutoff values for some of these parameters, defining, for example, an abnormal sPESI, such values do not necessarily guide clinical decisions. For example, the heart rate criterion for sPESI is >110/min, but a heart rate of 110/min does not necessarily mandate more aggressive therapy than anticoagulation. A heart rate of 130/min would appear more likely to be associated with a higher mortality and influence clinicians to be more aggressive, but there are no data proving that such an approach would reduce mortality. Clinicians should consider all of these parameters, use clinical gestalt as well as any apparent trends, and plan the therapeutic approach.

POTENTIAL BENEFITS OF ACUTE PULMONARY EMBOLISM THERAPY

Anticoagulation has proven to improve mortality in acute PE.[25] It has been generally accepted that acute high-risk PE is a high-mortality entity and that more aggressive therapy than anticoagulation is indicated. However, although intermediate-high risk PE appears to have a higher mortality than intermediate-low risk PE,[20,21] there has been no proven mortality benefit by increasing the level of aggressiveness of therapy in the intermediate-high risk group. Furthermore, it remains unclear whether early reperfusion treatment, for example, thrombolysis, has an impact on clinical symptoms, functional limitation, or the development of pulmonary hypertension.

ACUTE PULMONARY EMBOLISM: SUPPORTIVE THERAPY AND GENERAL CONCEPTS

Treatment of acute PE is not black and white and depends on the severity of the clinical parameters, the perceived bleeding risk, and the therapeutic options available to the team of physicians treating the patient.

The Pulmonary Embolism Response Team

The authors believe the pulmonary embolism response team (PERT) concept facilitates the care of high- and intermediate-risk patients as well as other complex venous thromboembolism scenarios.[26] This concept has evolved based on the lack of a strong evidence base directing clinicians in these settings. Rapidly implementing a team of clinicians well versed in PE to assist the emergency department or primary team caring for an intermediate- or high-risk PE patient can expedite sound clinical decisions.[26] Furthermore, an expert multidisciplinary team can offer recommendations in many other clinical scenarios, such as heparin-induced thrombocytopenia, high bleeding risk, symptomatic extensive DVT, complex surgical or comorbid settings, and many other situations. These multidisciplinary teams often include specialists in pulmonary/critical care, cardiology, hospital medicine, interventional radiology, hematology, clinical pharmacy, vascular medicine, vascular surgery, and cardiothoracic surgery.[27] Naturally, when relevant, other specialists, such as neurosurgery or obstetrics/gynecology, become involved. The PERT concept is evolving, and the PERT Consortium, a 501(c)3 nonprofit organization, sponsors an annual multidisciplinary PE symposium. Clinical guidelines for PE management have been published by the PERT Consortium.[28] The management of intermediate- and high-risk PE needs continued research, and the PERT Consortium encourages this and offers multidisciplinary expert input in the meantime.[28] Importantly, retrospective studies examining PERT programs and outcomes have found that most patients evaluated by PERTs are treated with anticoagulation and not more invasive techniques.[26]

Anticoagulation

Importantly, anticoagulation should be initiated immediately upon diagnosing acute PE or when there is a high or intermediate probability of PE as the workup is in progress, unless the bleeding risk appears high; this is a grade 1C recommendation in 2019 ESC/European Respiratory Society guidelines.[1]

There are no clear guidelines on which anticoagulant is appropriate to initiate in intermediate- and high-risk patients. The markedly hypotensive high-risk patient who is perfusing very poorly may be best served by a direct intravenous (IV) approach, that is, unfractionated heparin rather than subcutaneous low-molecular-weight heparin (LMWH). Most other patients are probably good candidates for initial LMWH based on its superior bioavailability and lack of need for monitoring in most cases. After the initial dose, the clinician can focus on other aspects of care rather than being

preoccupied with whether a therapeutic level has been achieved. The clinicians involved in caring for these patients should have a good understanding of their potential interventionalist's preferences. For example, although most interventionalists are comfortable proceeding with a catheter-directed thrombolysis procedure, extraction technique, or inferior vena cava (IVC) filter after LMWH administration, some might prefer the shorter-acting IV standard heparin in such cases. The authors' belief is that most patients should be administered LMWH regardless of whether a procedure is planned based on the above rationale. When the patient (with or without an interventional technique) is deemed clinically stable and has been observed long enough without deterioration (generally at 24–48 hours), transition to oral anticoagulation is appropriate. Most commonly, this would be a direct oral anticoagulant unless contraindicated. Notably, in the large randomized PEITHO trial, the mean time between randomization and death or hemodynamic deterioration was 1.79 $\pm$ 1.6 days in the heparin-only arm.[29]

Any PE patient who cannot be anticoagulated should undergo IVC filter placement. If no residual DVT is present, a delay in placement may be acceptable; there is no standard of care for how soon a filter must be placed. However, a patient who has just suffered acute PE is likely to be at continued risk and could form new DVT and reembolize.

Oxygen and mechanical ventilation

Oxygen therapy should be initiated unless a patient has a normal O_2 saturation and is comfortable at rest and with at least minimal ambulation. Oxygen saturation may be deceptive; a saturation measure, for example, of 98% does not guarantee normal gas exchange. The alveolar-arterial difference may be quite abnormal in such a patient who is breathing hard and driving down the P_{CO_2} to compensate. When necessary, noninvasive ventilation or oxygenation through a high-flow nasal cannula is favored over intubation, but the latter is sometimes unavoidable.

Naturally, when a patient with impending respiratory failure requires intubation, it should be done cautiously, realizing that positive pressure may adversely affect a failing right ventricle.[30] Intubation should be performed by an experienced anesthesiologist; a cardiac anesthesiologist is ideal when available. Mild to moderate hemodynamic instability, including pressor-dependent hypotension, does not automatically imply the need for intubation: an awake patient may improve significantly when pressors are added.

When mechanical ventilation is required, tidal volumes in the range of 6 mL/kg lean body weight should be used, and minimal positive end-expiratory pressure should be applied to keep the end-inspiratory plateau pressure less than 30 cm H_2O. If intubation is needed, anesthetic drugs less prone to cause hypotension should be used; an induction agent such as etomidate (0.2–0.4 mg/kg) is hemodynamically neutral and may help to limit hypotension; midazolam, for example, is more likely to cause hypotension.[31] Ketamine is also an alternative agent that offers hemodynamic benefit; a randomized trial is currently comparing the hemodynamic effects of etomidate and ketamine during rapid sequence intubation.[32]

Fluid administration and vasoactive therapy

No clear guidelines exist for fluid administration in the hemodynamically unstable PE patient. If the central venous pressure appears to be low, a cautious fluid challenge (eg, $\leq$500 mL) can be undertaken; this may increase the cardiac index in patients with acute PE.[33] However, overaggressive fluid administration may overload the right ventricle, leading to a reduction in cardiac output.[33,34] Assessment of central venous

pressure by echocardiographic imaging of the IVC can be useful (a small/collapsible IVC in the setting of acute high-risk PE strongly suggests hypovolemia). If the central venous pressure appears elevated, volume loading can be halted.
Use of vasopressors is based on hypotension together with evidence of underperfusion, for example, including a cold, clammy appearance and elevated lactate.

Norepinephrine, epinephrine, and high-dose dopamine have demonstrated favorable hemodynamic effects in acute PE with circulatory failure.[35,36] The authors rarely use dopamine based on its potential arrhythmogenic effects. Norepinephrine is a potent α1-adrenergic receptor agonist with modest β1-agonist activity, which renders it a powerful vasoconstrictor with less potent direct inotropic properties. It is probably the most commonly used vasopressor for acute PE.[35,36] Norepinephrine may be the preferred initial agent because α-mediated vasoconstriction leads to increased mean arterial pressure; also, its β1-mediated inotropic effect may improve RV function. Vasopressin can be added if norepinephrine doses are escalating in hopes of minimizing the increase in pulmonary vascular resistance.

Based on the results of a small series, the use of dobutamine has been considered in PE in the setting of a low cardiac index and normal BP. Although the use of this "inodilator" would appear logical for the failing right ventricle, in fact, raising the cardiac index may worsen ventilation/perfusion mismatch by redistributing flow to less obstructed vessels.[37] Furthermore, the thin-walled failing right ventricle may simply not respond to inotropic encouragement; thus, it is difficult to conceive how novel vasoactive agents could offer substantial benefit over available agents. Relieving obstruction or bypassing is crucial in patients with high-risk PE. In general, if dobutamine is used, the authors would use it concomitantly with another vasopressor. Circulatory support in high-risk acute PE is detailed in separate articles.

Intensive Care Unit Admission?

There are no clear guidelines regarding the need for intensive care unit (ICU) admission in acute PE. Patients with high-risk PE should be admitted to the ICU. Patients with intermediate-risk PE should be individualized. Patients with borderline hypotension, excessive tachypnea, and/or tachycardia (eg, heart rate >110/min), and those requiring more than low-flow O_2, should be considered for ICU admission. Patients who will receive or have already received thrombolysis should be admitted to the ICU when possible for closer monitoring, including careful observation for neurologic changes and bleeding. Hospitals vary, and the availability of monitoring, telemetry, and nighttime staff should be considered, and very importantly, clinical trends should be carefully scrutinized.

Anticoagulated patients, and in particular, those undergoing thrombolysis should be monitored for bleeding, as well as for heparin-induced thrombocytopenia. General symptom and neurologic assessment as well as vital signs and physical examinations should be carefully followed and may help identify bleeding and its potential source. Daily complete blood counts (for hemoglobin and platelets) are performed in hospitalized patients.

TREATMENT OF HIGH-RISK PULMONARY EMBOLISM

As described, this group is heterogeneous, and the treatment approaches depend on the available evidence and on the specific clinical circumstances. All patients require anticoagulation unless contraindicated. Even this is not always clear; a brain bleed 1 day before is different than spinal surgery 1 week before, and in turn, different than gastrointestinal bleeding episode 3 weeks before. Appropriate consultants

should team up with regard to the risk of anticoagulation when the risk of bleeding is concerning. The general approach to high-risk PE is suggested in Fig. 1.

Catastrophic or Supermassive Pulmonary Embolism

The extreme scenario of proven acute PE causing cardiac arrest requiring advanced cardiac life support measures with cardiopulmonary resuscitation (CPR) and other aggressive supportive measures is often deemed "supermassive" or "catastrophic" PE. Systemic thrombolysis, surgical embolectomy, and ECMO are considered in such patients; occasionally, centers with rapidly responding clinicians (or PERTs) can successfully use catheter-directed approaches as well. Thrombolysis in the setting of CPR is not contraindicated, but resulting rib fractures with bleeding, pneumothorax, and cardiac tamponade may be worsened by thrombolysis. Unfortunately,

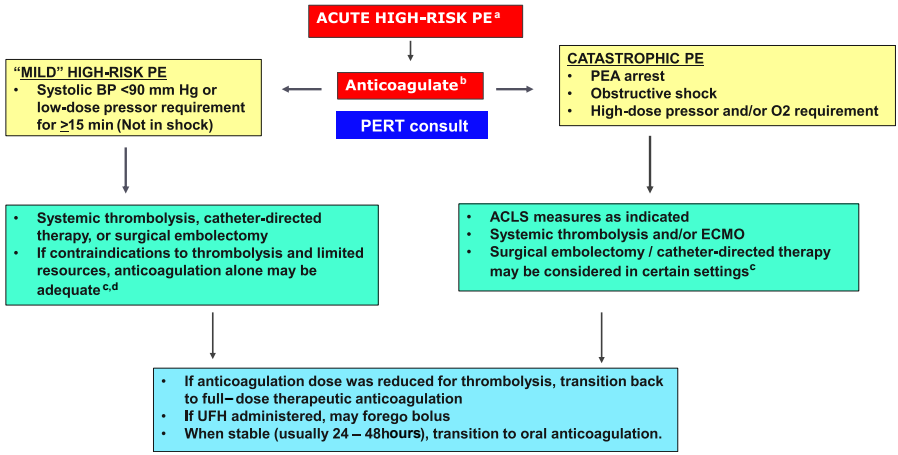

Fig. 1. High-risk acute PE: initial management. Anticoagulation should be initiated as soon as possible. When contraindicated, an IVC filter should be placed. Timing of filter depends on urgency of other interventions and may be done in conjunction with these. If the patient is too unstable to move, a bedside IVC filter may be placed. [a] The minimum requirement to meet the definition of high-risk PE is systolic BP <90 mm Hg for ≥15 minutes. However, high-risk PE is heterogeneous, ranging from the latter to catastrophic PE with cardiovascular collapse and PEA arrest. Management and use of specific therapies may vary based on the severity of the high-risk PE and on available resources. [b] IV heparin or LMWH. LMWH administration is not a contraindication to thrombolysis. Standard UFH is often used in anticipation of thrombolysis based on its shorter half-life. [c] Specific measures depend on details of the case and resources available. Contraindications to thrombolysis should be carefully considered. Systemic thrombolysis may be given at full dose or half dose; no clear guidelines differentiate the indications for the 2 dosing strategies. Relative contraindications, age, and body weight may aid in this decision. Catheter-directed therapy may use thrombolysis, or not. When thrombolysis is contraindicated, then a nonthrombolytic procedure should be used. There is no proven advantage of measuring fibrinogen levels for the purpose of guiding thrombolytic dose. Before and during systemic thrombolytic infusion, the heparin infusion may be stopped or reduced substantially. After thrombolysis, heparin may be reinitiated several hours later without a bolus. [d] If resources are limited and thrombolysis contraindicated, "mild" high-risk PE may sometimes be closely observed in the ICU with anticoagulation and supportive therapy, particularly if trends suggest improvement. Few outcome data exist on safety of transfer to tertiary care center. ACLS, advanced cardiac life support; CDT, catheter-directed therapy; UFH, unfractionated heparin.

the low cardiac output state during CPR is far from an ideal setting for thrombolytic penetration into the emboli.

If thrombolysis is administered in catastrophic PE, it is generally given by bolus or very rapidly. Systemic thrombolysis may be given at full dose or half dose; no clear guidelines differentiate the indications for the 2 dosing strategies. Relative and absolute contraindications should be considered, and age and body weight may aid in this decision; elderly patients are more likely to suffer intracranial hemorrhage and major bleeding.[29,38]

There is no proven advantage of measuring fibrinogen levels for the purpose of guiding thrombolytic dose. Before and during systemic thrombolytic infusion, the heparin infusion may be stopped or reduced substantially. In actuality, IV tissue type-plasminogen activator , the most commonly used thrombolytic agent, outlasts its apparent half-life because of thrombin-binding and the prolonged effects and longer half-life of its product, plasmin; however, the pharmacokinetics do not warrant prolonged avoidance of therapeutic anticoagulation when clinically indicated. In a clinical trial comparing thrombolysis followed by immediate heparin to heparin alone, only 1 intracranial hemorrhage was observed, in a patient who had sustained head trauma.[39] After thrombolysis, heparin is generally restarted within a few hours without a bolus.

Catheter-directed therapy may use thrombolysis, or not. When thrombolysis is contraindicated, then a nonthrombolytic procedure should be used. In the setting of catastrophic PE, catheter-directed approaches are feasible but require experience, a very well-organized team effort, and available resources. Although several catheter-based techniques have been used and are being studied, these techniques as well as systemic thrombolysis are reviewed in a separate article.

Patients with catastrophic PE with impending or actual PEA arrest are potential candidates for venoarterial ECMO. As ECMO teams have become more commonplace and response times and technology have improved, ECMO has become increasingly useful in these patients. In such patients, when ECMO is available, the decision must be made as to whether to administer bolus IV thrombolysis or whether to immediately cannulate for ECMO. Although immediate systemic thrombolysis has the potential to reverse hemodynamic compromise, the bleeding risk may complicate cannulation and successful ECMO. Surgical embolectomy combined with ECMO should be considered in critical patients with PE particularly with impending PEA arrest or after CPR has been initiated. These decisions cannot easily be standardized based on the few available pieces of outcome data and the individual variation in clinical specifics, resources and timing. The authors believe that PERTs facilitate these decisions.

Survival of critically ill patients on ECMO has been described in several case series,[40] but randomized controlled trials are exceedingly difficult to accomplish. ECMO is associated with a high incidence of complications, and patient selection and experience of the medical center are of critical importance. A critical evaluation of ECMO as well as other RV support methods is offered in separate articles.

High-Risk Pulmonary Embolism: The "More Stable" Patient

Although high-risk patients have increased mortality, some patients are less critically ill without the appearance of impending arrest. Based on the definition of high-risk PE, 1 end of the spectrum is the patient with a systolic BP of approximately 90 mm Hg requiring no pressors or perhaps low-dose norepinephrine (eg, 2–4 μg/min) who is awake and alert and, for example, slightly improved over the prior hour. Such patients are nearly always tachycardic and have severely abnormal RV function unless there is an additional contributor to the hypotension. These patients should be carefully risk assessed and individualized for systemic thrombolysis or catheter-directed therapy.

Although the evidence base for these therapies in such patients is weak, it is generally considered the standard of care to proceed with one of these interventions if available, in patients meeting the definition of high-risk PE if there are no contraindications, even if the patient is not requiring substantial hemodynamic support.[1]

TREATMENT OF INTERMEDIATE-RISK PULMONARY EMBOLISM

Anticoagulation is the cornerstone of PE therapy and is sufficient for low-risk as well as many intermediate-risk patients.[1,16] Those intermediate-risk patients with more advanced features or who are deteriorating can be considered for more advanced therapy. Those who deteriorate on or before anticoagulation and are now *high-risk* PE are treated as such. Those intermediate-risk patients who have not progressed to high-risk status, but have very concerning features, can be considered for therapeutic options, including catheter-directed clot extraction, and catheter-directed thrombolysis, although again, the evidence base for these approaches is weaker and such patients should be individualized. Recognizing the heterogeneity of these patients is important. For example, the intermediate-high-risk patient with sPESI greater than 0, a mildly abnormal right ventricle, and elevated troponin is not *automatically* a candidate for more advanced therapy than anticoagulation, despite that the data that this group *as a whole* have a higher risk of mortality at 30 days.

It is critical that the clinician recognize that each of the parameters that used to gauge severity should be closely scrutinized. Tachycardia might be a heart rate of 100/min or 130/min. RV dysfunction may be mild or very severe. A troponin elevation may be just above the upper limit of normal, or it may be hundreds of times that.

The authors' opinion is that the intermediate-low-risk patient (sPESI >0, who has either normal RV function and normal RV biomarkers, or mild RV dysfunction, *or* a mildly elevated troponin) should nearly always be managed with anticoagulation alone. The intermediate-high-risk, normotensive patient who appears comfortable on room air, with a heart rate of 112/min, for example, mildly depressed RV function, and a mildly elevated troponin would be a reasonable candidate for close observation in a monitored bed (or ICU) on anticoagulation because of the risk of early hemodynamic decompensation.[29] If symptoms and tachycardia, for example, worsen, ICU admission and more aggressive therapy should be considered. Depending on the precise conditions and resources, a catheter-directed approach might be considered for some intermediate-high-risk patients at some centers, although it should be recognized that although the RV/LV ratio has been shown to improve with such interventions, clinical outcomes, including mortality, have not been demonstrated to improve in these patients, perhaps in part because of inadequate trial sample size. The authors believe that well-designed clinical trials are essential in this area and that medical centers with the interest and capability should make every effort to participate.

Clinical trends may be critically important in decision making. Appearance, vital signs, and all parameters should be considered. Guidelines generally support aggressive therapy, such as systemic thrombolysis, in the intermediate-risk patient with clear signs of deterioration (American College of Chest Physicians).[41] Catheter-directed approaches may be considered, and their use depends on experience and the rapidity with which resources can be mobilized.[42] If, for any reason, anticoagulation has been discontinued at any point, it should be resumed as soon as deemed safe. The general therapeutic approach to intermediate-risk PE is shown in **Fig. 2**.

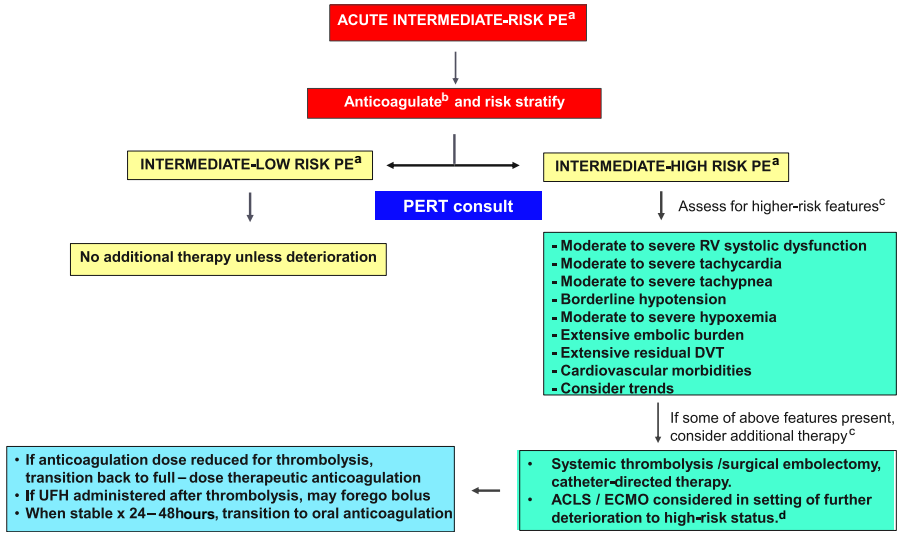

Fig. 2. Intermediate-risk acute PE: initial management. Intermediate-risk PE is a heterogeneous category with regard to severity. Anticoagulation should be initiated as soon as possible. When contraindicated, an IVC filter should be placed. [a] Intermediate-risk = sPESI greater than 0, and/or RV dysfunction and/or elevated troponin. Intermediate-low risk = any sPESI and RV dysfunction or elevated troponin. Intermediate-high-risk PE = any sPESI and RV dysfunction and elevated troponin. The definition of RV dysfunction varies and can be characterized echocardiographically based on RV wall motion, TAPSE, RV/LV ratio. Chest CTA can be used to indicate RV size, RV/LV ratio, furthermore, contrast reflux into the IVC/liver may indicate elevated PA pressure. Although intermediate-high-risk PE appears to have poorer outcomes than intermediate-low-risk PE, this distinction does not necessarily aid in treatment decisions. [b] IV heparin or LMWH unless contraindicated. [c] None of these higher-risk features clearly mandate more aggressive therapy but should be carefully taken into consideration. There is no particular number of, and no absolute cut-off values for, any of these measures that suggest the need for more aggressive therapy than anticoagulation. Use of a PERT with clinical expertise combined with gestalt, as well as clinical trends, should be considered. [d] Specific measures depend on details of the case and the resources available. Catheter-directed therapy may use thrombolysis, or not. When thrombolysis is deemed contraindicated, then a nonthrombolytic procedure should be used (see Fig. 1). CDT, catheter-directed therapy; PA, pulmonary arterial; TAPSE, tricuspid annular plane systolic excursion.

Finally, other clinical scenarios, such as clot-in-transit and paradoxic emboli, do not actually fit into the definitions of high-risk or intermediate-risk PE and are beyond the scope of this article but merit consideration.[43,44]

SUMMARY

Anticoagulation remains the best guarantee of reducing mortality in acute PE.[1,25,41] Patients with intermediate-risk (submassive) or high-risk (massive) PE have a higher mortality than low-risk patients. Patients with high-risk PE should be considered for more aggressive therapy. Both high- and intermediate-risk patients are heterogeneous, and this heterogeneity extends beyond the subdivision into intermediate-low and intermediate-high risk; more than simply categorizing a patient in this manner is required to guide therapy. Therapeutic approaches depend on a prompt, detailed

evaluation of all parameters and on expertise that may be provided by multidisciplinary PERTs. More clinical trial data are needed to guide clinicians in the management of patients with acute intermediate- and high-risk PE.

DISCLOSURE

Authors have nothing to disclose.

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