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Management of high-risk pulmonary embolism in the emergency department: A narrative review

Samuel G. Rouleau [a], Scott D. Casey [b,c], Christopher Kabrhel [d], David R. Vinson [b,e], Brit Long [f,*]

[a] Department of Emergency Medicine, UC Davis Health, University of California, Davis, Sacramento, CA, United States of America
[b] Kaiser Permanente Northern California Division of Research, The Permanente Medical Group, Oakland, CA, United States of America
[c] Department of Emergency Medicine, Kaiser Permanente Vallejo Medical Center, Vallejo, CA, United States of America
[d] Department of Emergency Medicine, Center for Vascular Emergencies, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States of America
[e] Department of Emergency Medicine, Kaiser Permanente Roseville Medical Center, Roseville, CA, United States of America
[f] Department of Emergency Medicine, Brooke Army Medical Center, Fort Sam Houston, TX, United States of America

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ABSTRACT

Background: High-risk pulmonary embolism (PE) is a complex, life-threatening condition, and emergency clinicians must be ready to resuscitate and rapidly pursue primary reperfusion therapy. The first-line reperfusion therapy for patients with high-risk PE is systemic thrombolytics (ST). Despite consensus guidelines, only a fraction of eligible patients receive ST for high-risk PE.
Objective: This review provides emergency clinicians with a comprehensive overview of the current evidence regarding the management of high-risk PE with an emphasis on ST and other reperfusion therapies to address the gap between practice and guideline recommendations.
Discussion: High-risk PE is defined as PE that causes hemodynamic instability. The high mortality rate and dynamic pathophysiology of high-risk PE make it challenging to manage. Initial stabilization of the decompensating patient includes vasopressor administration and supplemental oxygen or high-flow nasal cannula. Primary reperfusion therapy should be pursued for those with high-risk PE, and consensus guidelines recommend the use of ST for high-risk PE based on studies demonstrating benefit. Other options for reperfusion include surgical embolectomy and catheter directed interventions.
Conclusions: Emergency clinicians must possess an understanding of high-risk PE including the clinical assessment, pathophysiology, management of hemodynamic instability and respiratory failure, and primary reperfusion therapies.

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1. Introduction

1.1. Background

High-risk pulmonary embolism (PE), also referred to as massive PE, represents 5–10% of all PE cases [1-4]. This diagnosis carries a mortality rate of 30–40% at 30 days, with an in-hospital mortality rate ranging from 22 to 32% [3,5-7]. While high-risk PE makes up a small proportion of all PE, it has a disproportionate effect on total deaths from PE. In the United States, PE is estimated to cause up to 300,000 deaths per year and is the third most frequent cause of mortality among cardiovascular diseases [8-10].

For this review, we adopt the European Society of Cardiology (ESC) guidelines nomenclature for PE (high-risk, intermediate-high and intermediate-low risk, and low-risk PE) in lieu of alternative nomenclature (massive, submassive) (Table 1) [11]. The ESC guidelines define high-risk PE as hemodynamic instability due to PE delineated by one of the following: 1) cardiac arrest; 2) presence of obstructive shock, which is defined as a systolic blood pressure (BP) < 90 mmHg or the use of vasopressors to maintain a systolic BP ≥ 90 mmHg and evidence of end-organ ischemia (altered mental status, cool skin, oliguria/anuria, increased serum lactate); 3) persistent hypotension, defined as a systolic BP < 90 mmHg or a drop ≥40 mmHg for longer than 15 min not explained by an alternative cause (hypovolemia, sepsis, arrhythmia) [11].

* Corresponding author at: 3551 Roger Brooke Dr, Fort Sam Houston, TX 78234, United States of America.
E-mail addresses: srouleau@ucdavis.edu (S.G. Rouleau), scott.d.casey@kp.org, scasey@mail.einstein.yu.edu (S.D. Casey), ckabrhel@mgb.org (C. Kabrhel), drvinson@ucdavis.edu (D.R. Vinson), Brit.long@yahoo.com (B. Long).
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Table 1
Pulmonary embolism definitions by the European Society of Cardiology Guidelines and American Heart Association Guidelines [11-14].

ESC guideline categories	Definitions
High-risk PE	Hemodynamic instability as defined by any of the following criteria: 1) Cardiac arrest 2) Obstructive shock defined as systolic BP < 90 mmHg or the use of vasopressors to maintain BP ≥ 90 mmHg despite adequate filling status *AND* evidence of end-organ ischemia[a] 3) persistent hypotension, defined as a systolic BP < 90 mmHg or a drop ≥40 mmHg for longer than 15 min which is not explained by an alternative cause[b]
Intermediate-high risk PE	Hemodynamically stable and meet both criteria below: 1) Elevated cardiac troponin level *AND* evidence of RV strain on imaging (CTPA or TTE) 2) PESI Class III-V or sPESI ≥ 1[c]
Intermediate-low risk PE	Hemodynamically stable with: 1) Elevated cardiac troponin level *OR* evidence of RV strain on imaging (CTPA or TTE) 2) PESI Class III-V or sPESI ≥1
Low-risk PE	Hemodynamically stable and meet both criteria below: 1) No evidence of RV strain on imaging *AND* cardiac troponin level normal (if measured) 2) PESI Class I-II or sPESI score 0
AHA guideline categories	**Definitions**
Massive PE	Hemodynamic instability as defined by: 1) Sustained hypotension defined as systolic BP < 90 mmHg for at least 15 min or requiring inotropic support not due to an alternative cause[d] 2) Drop of systolic BP > 40 mmHg for at least 15 min 3) Pulselessness
Submassive PE	Hemodynamically stable and meet the criterion below: 1) The presence of RV dysfunction *OR* myocardial necrosis[e]
Low-risk PE	Do not meet criteria for submassive PE

AHA, American Heart Association; BP, blood pressure; CTPA, computed tomography pulmonary angiography; ESC, European Society of Cardiology; PE, pulmonary embolism; PESI, PE Severity Index; sPESI, simplified PESI; RV, right ventricle; TTE, transthoracic echocardiogram.
[a] End-organ ischemia is defined by altered mental status, cool skin, oliguria/anuria, or increased serum lactate.
[b] Alternative cause is defined as hypovolemia, sepsis, or new onset cardiac arrhythmia.
[c] Refer to Table 3 for PESI and sPESI definitions.
[d] AHA guidelines define alternative causes as: arrhythmia, hypovolemia, sepsis, left ventricular dysfunction.
[e] RV dysfunction is defined as follows: RV dilation or RV systolic dysfunction on echocardiography, RV dilation on CT, elevation on brain natriuretic peptide (BNP) > 90 pg/mL, elevation of N-terminal pro-BNP > 500 pg/mL, electrocardiographic changes of new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion. Myocardial necrosis is defined as troponin *I* > 0.4 ng/mL or troponin *T* > 0.1 ng/mL.

1.2. Importance

Despite the life-threatening nature of high-risk PE, widespread implementation of best practices is lacking. Unfortunately, many patients eligible for primary reperfusion with systemic thrombolytics (ST) do not receive it, despite clear consensus guidelines [10,11,15]. While multidisciplinary PE Response Teams (PERTs) have been associated with increased use of reperfusion therapy in appropriate patients, many emergency clinicians do not have access to these teams and must independently manage patients with high-risk PE [16].

1.3. Goals of this investigation

This narrative review discusses the essential aspects of managing high-risk PE with an emphasis on the emergency clinician, including clinical assessment, pathophysiology of right ventricular failure, management of hemodynamic instability, airway management, and reperfusion therapies. We focus on ST as the mainstay of treatment for high-risk PE. While pursuing primary reperfusion therapy, emergency clinicians must understand and manage the life-threatening clinical manifestations of high-risk PE.

2. Methods

The authors searched PubMed and Google Scholar for articles using a combination of the keywords “high-risk” or “massive” and “pulmonary embolism” or “PE” or “pulmonary embolus”. The search was conducted from the database's inception to October 1, 2023. PubMed yielded over 800 articles. The first 200 articles in Google Scholar were also searched. Authors evaluated case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, and other narrative reviews. Authors also reviewed guidelines and supporting citations of included articles. The literature search was restricted to studies published in English, with focus on the emergency medicine and critical care literature. Authors decided which studies to include for the review by consensus. When available, systematic reviews and meta-analyses were preferentially selected. These were followed sequentially by randomized controlled trials (RCTs), prospective studies, retrospective studies, case reports, and other narrative reviews when alternate data were not available. A total of 147 articles were selected for inclusion in this narrative review.

3. Discussion

3.1. Clinical assessment

High-risk PE is a clinical definition based on clinician assessment. The presentation and pathophysiology of PE is dynamic, and there is a wide spectrum of disease severity. Even among patients with high-risk PE, the presentation varies significantly from hypotension to severe shock and cardiac arrest. Some literature refers to a PE that causes refractory shock or cardiac arrest as “catastrophic PE,” though this definition is not widespread or well-studied [17]. Emergency clinicians should be familiar with risk stratification of patients with PE who have, or may go on to develop, high-risk PE.

If there is elevated clinical concern for high-risk PE, we recommend forgoing D-dimer testing and proceeding directly to computed tomography pulmonary angiography (CTPA). If a patient is too unstable for CTPA, then the clinician should evaluate and exclude other causes of shock and perform point-of-care ultrasound (POCUS) with an emphasis on echocardiography [18]. Although laboratory values have a minimal role in diagnosing patients with high-risk PE because the diagnosis is clinical, we recommend the following diagnostic studies be obtained concurrently with emergent CTPA. While there are no validated values or cut-offs, several diagnostic tests have been shown to be related to risk for deterioration or mortality in patients with PE, including electrocardiogram (EKG), troponin, B-type natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide, and echocardiography (Table 2).

There are no risk scores designed specifically for predicting clinical outcomes among patients with high-risk PE. The PE Severity Index (PESI) classification system and simplified PESI (sPESI) score predict 30-day mortality in all patients with PE (Table 3) [13,14]. These scores may help estimate the risk of further decompensation, though their use specifically in high-risk patients has not been studied. Other scores such as the Bova, SHIeLD, and TELOS scores are under investigation to predict deterioration in normotensive PE [30-33]. However, like PESI/sPESI, no score has been developed specifically for patients with high-risk PE.

Table 2
Clinical assessment of patients with high-risk PE [13,19-29].

Assessment	Finding	Risk for decompensation or mortality
Syncope	Presence of syncope[a]	OR 2.00, 95% CI 1.11–3.60 (30-day PE-related decompensation)
EKG	Atrial fibrillation	OR 1.75, 95% CI 1.15–2.66[b] (30-day decompensation)
	Complete RBBB	OR 2.67, 95% CI 1.81–4.95
	S1Q3T3	OR 2.06, 95% CI 1.23–3.45
	Sinus tachycardia	OR 4.46, 95% CI 1.68–11.84
	ST elevation in lead aVR	OR 5.24, 95% CI 3.98–6.91
	T-wave inversions in	
	Lead V1	OR 2.63, 95% CI 1.47–4.73
	Lead V2	OR 6.94, 95% CI 2.41–19.96
	Lead V3	OR 7.07, 95% CI 1.13–44.22
Lab Values	Elevated troponin[cd]	OR 5.24, 95% CI 3.28–8.38 (in-hospital or 30-day mortality)
	Elevated BNP, NT-proBNP	OR 3.71, 95% CI 0.81–17.02 (in-hospital or 30-day mortality)
CTPA[e]	RV/LV ratio > 1.0	OR, 5.0; 95% CI, 2.7–9.2 (PE-related mortality with median follow-up at 30 days)
Echocardiography[f]	TAPSE <17 mm	HR 4.4; 95% CI 1.3–15.3

BNP, brain-type natriuretic peptide; CI, confidence interval; CTPA, computed tomography pulmonary angiography; EKG, electrocardiogram; HR, hazard ratio; LV, left ventricle; mm, millimeters; NT-proBNP, N-terminal pro B-type natriuretic peptide; OR, odds ratio; PE, pulmonary embolism; RBBB, right bundle branch block; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

[a] Syncope is a potential indication of high-risk PE in the appropriate setting. In the absence of syncope, emergency clinicians should evaluate for presyncopal symptoms, as presyncope may be an independent risk factor for intensive care unit admission in patients with PE.

[b] Several EKG findings are associated with an increased risk of hemodynamic stability in patients with PE. The EKG is normal in up to 25% of patients with PE, and thus repeat EKG is recommended in those with change in hemodynamic status or symptoms.

[c] Data prior to introduction of high-sensitivity troponins. Generally, the cut-offs were defined as exceeding the 99th percentile of healthy subjects in individual trials. Elevated troponins were associated with higher mortality.

[d] There are no guideline recommendations for BNP or NT-proBNP thresholds.

[e] CTPA is not reliable for identifying RV strain. Transthoracic echocardiography is the standard for RV function.

[f] There are quantitative and qualitative methods to assess for RV strain on TTE. We recommend emergency clinicians use TAPSE to quantitatively assess for RV strain. This is done by using m-mode over the lateral tricuspid annulus and measuring the displacement during end-diastole and systole. If this value is <17 mm, there is decreased systolic function of the RV. Qualitatively, RV should be less than two-thirds of the size of the left ventricle (LV) in both parasternal long and apical 4-chamber views. McConnel's sign, a regional wall motion abnormality created by akinesis of the free wall and normal motion of the apex, is not pathognomonic for PE. Of note, RV dysfunction on echocardiography may represent a chronic finding in the setting of chronic obstructive pulmonary disease, pulmonary hypertension, interstitial lung disease, and several other conditions.

Table 3
Definitions of the Pulmonary Index Severity Index and Simplified Pulmonary Severity Index [13,14].

Variables	PESI score	sPESI score
Age, years	+ Age in years	1 (1 point if age > 80 years)
History of cancer	+ 30	1
History of chronic lung disease[a]	+ 10	1
History of heart failure	+ 20	
Heart rate ≥ 110 bpm	+ 20	1
Systolic BP < 100 mmHg	+ 30	1
Oxygen saturation < 90%	+ 20	1
Respiratory rate ≥ 30 breath/min	+ 20	–
Altered mental status	+ 60	–
Temperature < 36 degrees C	+ 20	–
Male sex	+ 10	–

Bpm, beats per minute; BP, blood pressure; PESI, Pulmonary Embolism Severity Index; sPESI, simplified PESI.
The PESI is an 11-variable risk stratification score that categorizes patients into 5 distinct risk categories with ascending 30-day mortality, with class I (≤65 points) defined as very low risk, class II (66–85 points) as low risk, class III (86–105 points) as intermediate risk, class IV (106–125 points) as high risk, and class V (≥ 126 points) as very high risk. The sPESI is a 6-variable score with a score of 0 corresponding to low risk for 30-day mortality and a score ≥ 1 considered high risk for 30-day mortality.
If using the sPESI, emergency clinicians should be aware that the sPESI underperforms the PESI classifications system when predicting clinical deterioration at 5 days. The sPESI also misclassifies a significant number of low-mortality patients as higher risk.

[a] The sPESI combined the categories of chronic lung disease and heart failure into one category, termed "history of chronic cardiopulmonary disease."

3.2. Pathophysiology of right ventricular failure

Right ventricle (RV) anatomy differs from that of the left ventricle (LV). The RV's thin wall of myofibrils make it sensitive to increases in afterload. A healthy RV cannot acutely generate a systolic pressure > 40 mmHg [34,35]. Hemodynamic instability in high-risk PE occurs because the increase in pulmonary artery pressure (PAP) caused by the embolus surpasses the compensatory mechanisms of the RV, resulting in a drop in RV cardiac output (CO) [35,36]. As the RV is unable to compensate for the increase in PAP, the RV distends, resulting in myocardial stretching and impaired contractility [36-38]. Stretching of the tricuspid annulus also results in tricuspid regurgitation, further degrading RV CO [37]. Additionally, the distention of the RV shifts the interventricular septum towards the LV and decreases the volume of the LV, which is a phenomenon referred to as ventricular interdependence [39]. Eventually, the reduction of LV preload secondary to RV failure and ventricular interdependence leads to decreased LV CO. When systemic hypotension occurs, the RV wall becomes ischemic. In contrast to the LV, coronary artery perfusion for the RV is greatest during systole when the pressure gradient is largest [35,37]. RV ischemia then exacerbates the cycle and causes further deterioration, a process colloquially referred to as the "PE death spiral" (Fig. 1).

3.3. Management of hemodynamic instability

Management of RV failure reflects the underlying pathophysiology. As RV over-distention is the inciting event for decompensation in patients with high-risk PE, excessive volume resuscitation is likely to hasten cardiovascular compromise rather than improve hemodynamics [37,38]. However, hypotension in the setting of high-risk PE may warrant some attempt at volume resuscitation to improve preload. Clinicians should use their judgment in patients with high-risk PE, employing tools such as pulse variability, stroke volume variation, and

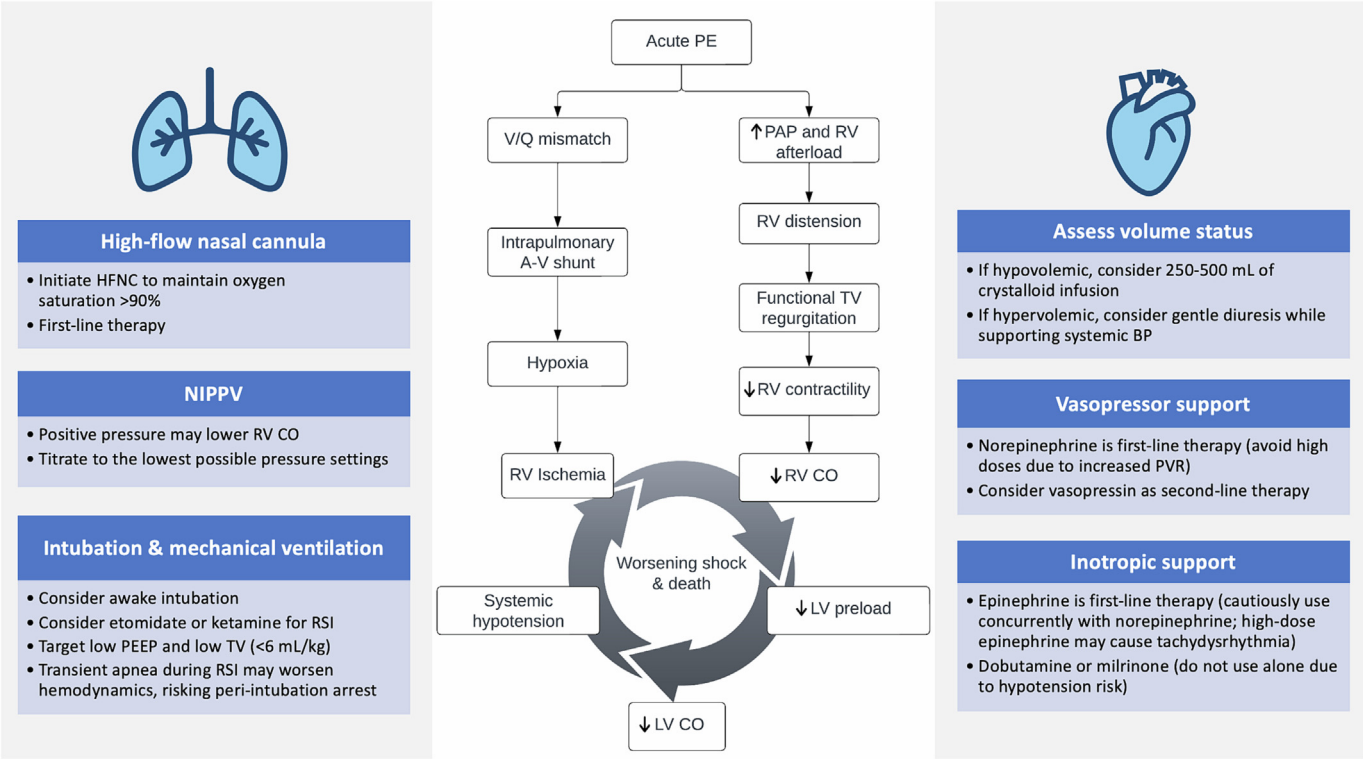


Fig. 1. Pathophysiology and Management of Hemodynamic Instability and Respiratory Failure. Abbreviations: *A-V shunt, arteriovenous shunt; BP, blood pressure; CO, cardiac output; HFNC, high-flow nasal cannula; LV, left ventricle; mL, milliliters; NIPPV, non-invasive positive pressure ventilation; PAP, pulmonary artery pressure; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; PVR, pulmonary vascular resistance; RV, right ventricle; TV, tricuspid valve; TV, tidal volume; V/Q, ventilation/perfusion.*

straight leg raise to assess volume status [40]. A straight leg raise is performed by placing the patient flat and lifting the legs to 45 degrees. If there is an increase in stroke volume or CO, then the patient's hemodynamics may improve with fluids [41]. If the decision is made to trial a crystalloid bolus, we recommend a cautious bolus of 250–500 mL and repeat assessments. There is one randomized trial of patients with intermediate-high risk PE that demonstrated diuresis with furosemide may reduce RV wall stress and prevent RV dysfunction [42]. In patients with high-risk PE, who by definition are hemodynamically unstable, diuresis has not been studied and may further reduce end organ perfusion.

Vasopressors should be administered in patients with high-risk PE as a temporary means of supporting a patient to primary reperfusion therapy (Fig. 1) [35,37]. Emergency clinicians are generally comfortable with norepinephrine, which is a reasonable first-line vasopressor in high-risk PE. Norepinephrine causes veno- and vasoconstriction, supporting blood pressure without disproportionately increasing pulmonary vascular resistance (PVR). However, high doses of norepinephrine may increase PVR and worsen RV dysfunction [43]. If hypotension is not resolved with the initiation of norepinephrine, vasopressin can be used to support blood pressure and may decrease PVR [44]. Phenylephrine should be avoided as it supports only systemic afterload [45]; in a study of patients with chronic pulmonary hypertension with RV dysfunction during surgery, norepinephrine outperformed phenylephrine [46].

Inotropic support should be considered concurrently with vasopressor initiation. Epinephrine is also a reasonable first-line vasopressor and inotrope in patients with high-risk PE [47]. The main concern with epinephrine is tachyarrhythmias, and emergency clinicians should consider another vasopressor in patients with significant tachycardia. Dobutamine, a phosphodiesterase inhibitor, exerts positive inotropy on the RV without increasing PVR and lowers filling pressure [48]. Dobutamine can precipitate worsening hypotension and should not be started without additional vasopressor support in patients with high-risk PE. We recommend initiating dobutamine with either norepinephrine or vasopressin concurrently. Due to the independent risk of tachyarrhythmia with epinephrine and dobutamine, they should not be used concurrently. Milrinone is another phosphodiesterase inhibitor that can be employed for inotropic support [35]. It is useful in patients on chronic beta-blockers, as its mechanism bypasses beta-1 receptors. In contrast to the 2-min half-life of dobutamine, milrinone's half-life is 2–4 h, making it more difficult to titrate [35]. Comparative studies of milrinone and dobutamine in patients with congestive heart failure exacerbation suggest similar effectiveness [35]. Others have explored intravenous pulmonary vasodilators in acute PE, but there is limited evidence to suggest they reliably improve RV function in the acute setting [49].

3.4. Airway management

The primary goal of treating hypoxia in patients with high-risk PE is to improve oxygen saturation without increasing intrathoracic pressure. Hypoxia in the setting of PE is typically caused by ventilation/perfusion (V/Q) mismatch secondary to clot burden and right-to-left shunting. Hypercapnia occurs secondary to increased dead space [40]. Therapy should be directed to maintain oxygen saturation above 90% [11]. High-flow nasal cannula (HFNC) has a vital role in improving oxygenation without significantly increasing intrathoracic pressure in patients with high-risk PE [35,49,50].

Both non-invasive positive pressure ventilation and intubation should be avoided if possible, as they can worsen RV hemodynamics and may result in cardiac arrest. The positive pressure from mechanical ventilation increases intrathoracic pressure, reduces venous return, and lowers RV CO [35,37,38]. The peri-intubation period is also dangerous, and emergency clinicians should ensure adequate intravenous access, such as a central line, and consider placement of an arterial line for hemodynamic monitoring. A retrospective study found that 20% of

patients with PE had either immediate hypotension or cardiac arrest directly after induction of general anesthesia in the operating room for emergent surgical embolectomy [51]. Prior to rapid sequence intubation in patients with high-risk PE, vasopressor infusion should be initiated, and push-dose pressors, preferably epinephrine, should be available. In general, fluids are ineffective at preventing and treating peri-intubation hypotension [52].

Transient apnea between induction and intubation can worsen hypoxia and hypercapnia. Both of these effects can further precipitate RV failure and may cause cardiac arrest [53]. If intubation is unavoidable, we recommend using hemodynamically neutral medications, such as ketamine, for rapid sequence intubation. An awake intubation approach can also be considered [53]. Once intubated, ventilator parameters should target low positive end-expiratory pressure (PEEP) and tidal volumes (TV) around 6 mL/kg to avoid hypoxia and hypercarbia [43]. High PEEP and large TV will worsen RV preload and CO, contributing to shock [54].

For refractory hypoxia, inhaled pulmonary vasodilators such as inhaled nitric oxide (iNO) and epoprostenol can be considered as they decrease PVR, improve oxygenation, and reduce V/Q mismatch [53]. Limited evidence suggests iNO may improve hypoxia and hemodynamics [55]. A multicenter randomized controlled trial (RCT) of iNO in patients with intermediate-risk PE showed no improvement in complete RV recovery, though there was an improvement in RV hypokinesis [56]. For emergency clinicians without access to iNO, there are case reports of making an iNO equivalent with sublingual nitroglycerin or intravenous nitroglycerin [57], though this is not routine care.

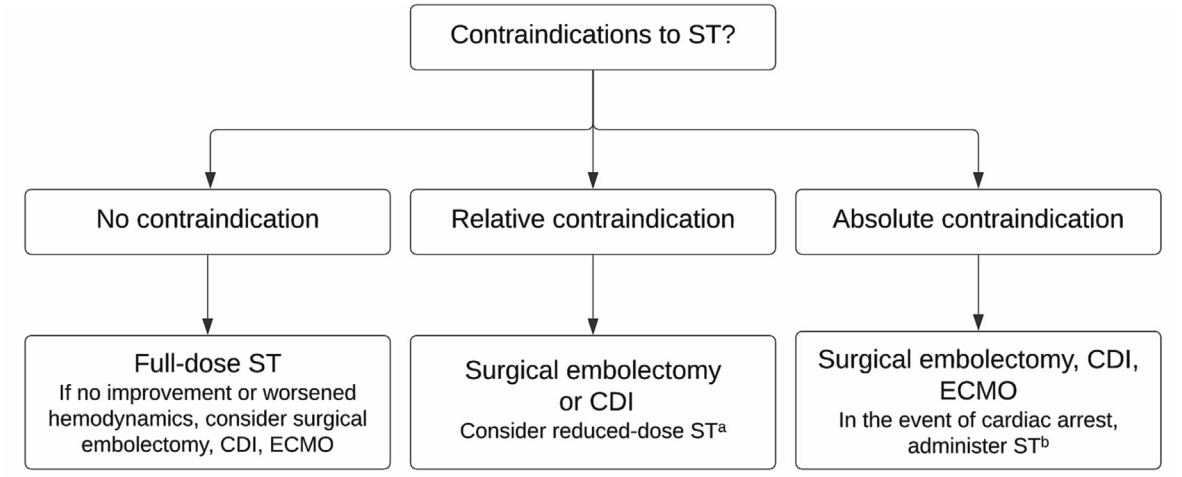
3.5. Primary reperfusion therapies

While considering primary reperfusion therapies, including ST, surgical embolectomy (SE), or catheter-directed intervention (CDI) (Fig. 2), emergency clinicians should administer anticoagulation to patients with high-risk PE unless absolutely contraindicated. If the emergency clinician has a high pretest probability that an unstable patient has PE, presumptive anticoagulation is indicated [58-61]. For unstable patients, the anticoagulant of choice is unfractionated heparin due to its short-half life and titratability, which does not exclude any of the primary reperfusion therapies [11]. However, studies have shown that many patients with severe PE fail to reach therapeutic anticoagulation with unfractionated heparin [62], so close monitoring is required. Direct-oral anticoagulants have not been studied in high-risk PE and should not be employed.

3.6. Systemic thrombolytics

There is a consensus among international guidelines that standard-dose ST is the first-line reperfusion therapy for high-risk PE [11,63]. Whereas anticoagulants allow for passive reduction of the thromboembolism, thrombolytic agents including tissue plasminogen activator (tPA) and tenecteplase (TNK) directly dissolve the thrombus by hydrolyzing fibrin molecules [64]. Thrombolytics can rapidly dissolve clots, decrease PAP, improve hemodynamics, and reduce mortality [65,66]. However, studies demonstrate that only 1 in 3 patients with high-risk PE who are eligible for ST actually receive it [67,68]. Additionally, patients with high-risk PE require specialized care but are less likely to receive thrombolytics when indicated at rural hospitals [69], so they may benefit from transfer to high-volume centers that offer the entire spectrum of reperfusion therapies [70]. Prior to transferring a patient with high-risk PE, emergency clinicians should consider administering ST if there are no contraindications. If a patient has confirmed high-risk PE and there are no contraindications to ST, emergency clinicians should pursue this therapy based on current guidelines and literature.

Early studies evaluating ST for high-risk PE found significant benefit. One of the first randomized trials of ST in patients with PE was the 1970 urokinase PE trial (UPET), which randomized patients with PE to urokinase bolus and 12-h heparin infusion versus heparin alone [67]. Of the study group, approximately 9% were classified as massive PE. Although there was no mortality benefit in the urokinase group, there was a subgroup of patients with poor cardiac index demonstrating improved



CDI, catheter-directed intervention; ECMO, extracorporeal membrane oxygenation; ST, systemic thrombolysis

[a] If no access to CDI or surgical embolectomy, consider reduced dose thrombolysis. Even with access to CDI or surgical embolectomy, considered reduced dose thrombolysis while consulting proceduralists.
[b] Unless ECLS is readily available at your institution.

Fig. 2. Primary Reperfusion Strategies for High-Risk PE, Stratified by Contraindications to ST.

cardiac function after ST, suggesting that those at highest risk may benefit from thrombolytics [67]. Based on this inference, an RCT was designed to compare the efficacy of streptokinase and heparin versus heparin alone for 40 patients with massive PE. An interim analysis conducted following enrollment of 8 patients found that the 4 patients randomized to receive only heparin died within 3 h of hospitalization; while the 4 patients randomized to the streptokinase and heparin group all survived, leading to early termination of the trial [71].

Since then, there have been no RCTs comparing ST to anticoagulation alone for high-risk PE. However, there have been multiple systematic reviews and meta-analyses seeking to answer this question. These are limited by the lack of recent clinical trials of ST in high-risk PE, resulting in meta-analysis cohorts with fewer patients with high-risk PE than desirable. Nevertheless, data from these meta-analyses suggest ST is beneficial. One meta-analysis from 2015 included over 2000 patients, many of whom were not high-risk, with only 4 of the 15 studies including high-risk PE [72]. Authors did not separately analyze the high-risk PE sub-group. This meta-analysis found that patients who received ST had a two-thirds reduction in early mortality or worsened hemodynamic instability compared to patients who received anticoagulation alone (odds ratio [OR] 0.34, 95% confidence interval [CI] 0.22–0.52), lower all-cause mortality (OR 0.59, 95% CI 0.36–0.96), lower PE-related mortality (OR 0.29, 95% CI 0.14–0.60), and decreased recurrent PE (OR 0.50, 95% CI 0.27–0.94) [72]. After excluding studies that included high-risk PE, the mortality reduction disappeared, suggesting that the improved mortality of patients with high-risk PE who received ST was the driving factor for the improved mortality. An earlier meta-analysis from 2004 of 11 randomized trials including patients across the PE-risk spectrum found a composite reduction in recurrent PE or death in patients with hemodynamic instability from PE who received ST compared to heparin alone (OR 0.45, 95% CI 0.22–0.92) and reported a number needed to treat (NNT) of 10 [73]. A smaller meta-analysis of 1500 patients focused on patients with high-risk PE and found that ST was associated with lower short-term mortality (OR 0.69, 95% CI 0.49–0.95) and PE-related mortality (OR 0.66, 95% CI 0.45–0.97) [74]. Additionally, a 10-year retrospective study demonstrated a lower in-hospital mortality rate in patients with PE and hemodynamic instability who received ST when controlling for age, sex, and comorbidities (OR 0.42, 95% CI 0.37–0.48) [7]. In addition to a reduction in mortality, multiple studies show that patients receiving ST had improvement in pulmonary blood flow by 30–35% within the first 24 h compared to those who received heparin alone [75-77]. Predictably, when analyzing the impact of ST on patients with all types of PE, the benefit of ST compared to anticoagulation becomes less marked [78]. When evaluating the PE literature, it is therefore important for emergency clinicians to distinguish outcomes of ST in study cohorts that focused on patients with high-risk PE from those that focused on non-high-risk patients. Overall, the recent literature on ST in high-risk PE is limited due to study design, possible confounders, and lack of randomized trials. However, until further trials are completed, ST remains the first-line reperfusion therapy for patients with high-risk PE.

In contrast to the clear time window for reperfusion therapy for myocardial infarction and ischemic stroke, there is no established timeframe for ST in patients with high-risk PE. No RCTs have investigated the timing of ST in high-risk PE [15], though literature suggests that patients with high-risk PE who receive ST earlier have better outcomes [79]. Earlier reperfusion with ST is associated with a decreased requirement for inotropic and respiratory support, and those who receive ST after 24 h from symptom onset demonstrate higher mortality (OR 5.67, 95% CI 2.64–10.67) [80]. One observational study concluded that administration of ST 8.5 h or later after symptom onset was associated with a higher risk of 30-day cardiovascular death (hazards ratio 7.81, 95% CI 1.84–33.5) and a higher incidence of bleeding events compared to those who received ST within 8.5 h of symptom onset [81]. Another small cohort study reported a survival rate at 24 h of 94% of high-risk PE patients who received ST within 1 h from ED arrival [82]. However, because these studies that sought to address timing of ST in high-risk PE are retrospective in nature, there is potential for bias and unmeasured confounders. Nevertheless, based on current evidence, ST is associated with improved outcomes in patients with high-risk PE, and outcomes are improved with more rapid administration of ST.

Table 4
Absolute and relative contraindications to systemic thrombolysis [11,65,83-85].

Absolute contraindications	Relative contraindications
- History of hemorrhagic stroke[a] - Ischemic stroke within 6 months - Central nervous system malignancy or structural intracranial disease - Major trauma, surgery - Suspected aortic dissection - Significant head injury in prior 3 weeks defined as skull fracture or brain injury - Bleeding diathesis	- Transient ischemic attack within 6 months - Age > 75 years[b] - Oral anticoagulation - Pregnancy or post-partum within one week of delivery[c] - Non-compressible vascular puncture sites - Traumatic resuscitation or cardiopulmonary resuscitation for longer than 10 min - Hypertension: systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg - Advanced liver disease or acute liver failure - Infective endocarditis - Known peptic ulcer - Pericarditis or known pericardial effusion - Recent internal bleeding within 2–4 weeks

This table is a compilation of absolute and relative contraindications to systemic thrombolysis per American Heart Association, American College of Chest Physicians, and European Society of Cardiology guidelines.

[a] Per the ESC guidelines, a stroke of unknown origin cannot be excluded as a hemorrhagic stroke.

[b] CHEST and the AHA list age >75 years of age as a relative contraindication, while ESC does not list age.

[c] Pregnancy is a relative contraindication to systemic thrombolysis. PE is the fifth cause for pregnancy-related deaths in the United States. There are not many cases published in the literature; however, a systematic review found 83 pregnant patients with high-risk PE who underwent systemic thrombolysis with a survival rate of 94% (95% CI 86–98). Fetal deaths related to PE or thrombolysis occurred in 12% of the cases with an 88% survival rate.

The most concerning adverse effect of thrombolytics is major bleeding. Prior to administering ST, emergency clinicians should assess for absolute and relative contraindications (Table 4) [11,65,83-85]. The estimates for frequency of major bleeding events after ST differ across studies. Among patients enrolled in the PEITHO trial, an RCT of patients with intermediate-risk PE comparing a single bolus of TNK plus heparin to heparin alone, the 7-day incidence of hemorrhagic stroke was 2.4% in the TNK group and 0.2% in the heparin-only group [86]. Seven-day extracranial bleeding occurred in 6.3% of the TNK group and 1.2% of the heparin-only group. Importantly, the risk of bleeding was lower in patients <75 years of age in the PEITHO trial, and of the 12 patients who suffered a stroke after receiving TNK, only one patient was under the age of 65. A large meta-analysis found a higher frequency of major hemorrhage (OR 2.91, 95% CI 1.95–4.36) and fatal or intracranial bleeding (OR 3.18, 95% CI 1.25–8.11) associated with ST [72]. However, the MAPPET-3 trial, a trial of 256 patients with intermediate-risk PE randomized to tPA plus heparin compared to heparin alone, had no cases of hemorrhagic stroke or fatal bleeding [87]. The TOPCOAT trial, an RCT of 83 patients with intermediate-risk PE randomized to TNK plus low-molecular weight heparin or low-molecular weight heparin alone, had no increase in the rate of bleeding events in the TNK group [88]. However, the published study was not powered to evaluate this endpoint. In a systematic review and Bayesian network meta-analysis evaluating mortality and bleeding risk in intermediate-risk PE, researchers found no difference in major bleeding among patients who received ST compared to those who received anticoagulation alone (relative risk [RR] 0.95, 95% credible interval [CrI] 0.31–2.42), though there

was a slightly increased risk of minor bleeding in the those who received ST (RR 1.95, 95% CrI 1.03–3.63) [89].

Bleeding risk can also be estimated with scores such as the BACS score and the PE-CH score [90,91], the latter of which focuses on risk of intracranial hemorrhage specifically. Pragmatically, we recommend that emergency clinicians review a checklist of absolute and relative contraindications before administering ST. However, in a truly life-threatening situation, we agree with the ESC guidelines which conclude "most contraindications to thrombolysis should be considered relative in patients with life-threatening, high-risk PE" [11,92].

The two most commonly employed modern thrombolytic medications are TNK and tPA. For tPA, the most studied dosing strategies include a bolus of 100 mg or 0.6 mg/kg intravenous (IV) infusion over 2 h [10]. In a peri-arrest scenario, the full-dose of tPA can be infused over 15 min or as a bolus, though these uses are not approved by the U.S. Food and Drug Administration (FDA) [93]. TNK is administered as a bolus dose ranging from 30 to 50 mg depending on the patient's weight over 5–10 s [94]. There is no evidence to suggest a benefit with using TNK instead of tPA [95]. The weight-based dosing of TNK is advantageous in elderly patients and those with low body weight [94,95]. While emergency clinicians should be familiar with both TNK and tPA, most institutions typically rely on one thrombolytic agent.

The risk of hemorrhage after ST has led to the development of reduced-dose infusion regimens for thrombolytics. The rationale of reduced-dose thrombolysis is related to the first-pass effect, whereby the total administered dose of thrombolytic is delivered to the lungs. This is in contrast to thrombolysis in ischemic stroke and myocardial infarction where the amount of thrombolytic delivered to the area of clot is less than the full dose [96].

The trial results for reduced-dose thrombolytics are conflicting. An RCT from 2010 compared half-dose tPA, 50 mg over 2 h, to full dose tPA, 100 mg over 2 h, in 118 patients with acute PE and hemodynamic instability or "massive pulmonary artery obstruction" [97]. This study found that half-dose tPA had a similar effect, measured by improvement in RV function on echocardiography and clot burden on V/Q scans or CTPA, when compared to the full-dose tPA group. Also, the half-dose tPA group had a significantly lower 14-day incidence of bleeding (3%) compared to the full-dose group (10%) [97]. On the other hand, a retrospective, propensity-matched study of 3768 patients with acute PE in the intensive care unit (ICU) compared half-dose to full dose tPA and found that those who received half-dose tPA were more likely to require treatment escalation, defined as secondary thrombolysis or CDI [98]. There was no significant decrease in intracranial bleeding or major bleeding in the half-dose tPA group, and mortality outcomes were similar in each group [98].

Reviews have also reached different conclusions regarding reduced-dose thrombolysis. A systematic review of trials comparing full-dose and half-dose tPA found a 33% reduction in bleeding risk with half-dose tPA with similar clinical efficacy [99]. A separate review concluded that trials on reduced-dose thrombolysis do not consistently illustrate functional improvement equivalent to full-dose thrombolysis and have not been appropriately powered [100].

In addition to the protocols studied above, new regimens for reduced-dose ST are being studied; an experimental study from 2023 of 37 patients with high-risk PE evaluated tPA 25 mg IV instilled over 6 h, though this protocol needs further investigation [101]. The PEITHO-3 trial, an RCT comparing half-dose to full-dose tPA for intermediate-high risk PE, will hopefully provide more information [102]. Although the current body of evidence has mixed results, emergency clinicians can still consider reduced-dose thrombolysis in patients with relative contraindications to ST. This is consistent with the 2019 PERT Consortium Consensus [103].

If there are contraindications to ST [83-85], emergency clinicians should consider alternative reperfusion therapies, such as SE or CDI. However, there are no data stating which contraindications to ST should also be applied to CDI. Cardiopulmonary support with extracorporeal membrane oxygenation (ECMO) may also be used as a bridge to reperfusion therapy. If a patient receives ST and continues to decompensate, emergency clinicians should not give additional doses of ST, but should instead consider surgical embolectomy or CDI, including ECMO [104].

3.7. Surgical embolectomy

SE (or thrombectomy) for patients with high-risk PE should be considered in patients who have failed thrombolysis, have absolute contraindication to ST, or when there is a thrombus in-situ in the right atrium or RV, especially in the presence of a patent foramen ovale and impending paradoxical embolism [105]. The 2019 ESC guidelines recommend SE for those with high-risk PE who have failed ST or have contraindications for ST with a class IC recommendation, which is a higher grade recommendation than given to CDI (class IIC) [11]. Of patients who undergo SE for high-risk PE, approximately 40% have a contraindication to ST and 20% have failed ST or CDI [106]. In a retrospective cohort study of 170,000 patients with acute PE, 257 patients underwent SE as a first-line reperfusion strategy [107]. When compared to the 1854 patients who underwent ST as first-line reperfusion therapy, there was no significant difference in 30-day mortality (15% versus 13%, OR 1.12, 95% CI 0.72–1.73) or 5-year survival. Those who received ST had a higher risk of 30-day stroke (1.9% versus 0.8%, OR 4.70, 95% CI 0.72–1.73) and were more likely to undergo additional intervention for PE within 30 days (3.8% versus 1.2%, OR 7.16, 95% CI 2.17–23.62) [107]. A smaller cohort of 80 patients with high-risk PE also demonstrated similar in-hospital mortality outcomes in those who received SE versus ST with significantly higher bleeding rates in the ST group [108].

SE is generally well-tolerated, especially at high-volume centers, with 1-year survival rates approximating 90% for patients with high-risk PE [109]. A retrospective study of 214 patients with acute PE who underwent SE had a post-operative mortality rate of 11.7%, though this study had higher illness severity and included 28 patients who had suffered cardiac arrest [110]. Mortality rates may be higher if a patient fails ST before SE rather than proceeding directly to surgery [104,111]. Another benefit of SE is that it may decrease the risk for chronic pulmonary hypertension [112]. Emergency clinicians should be aware that SE is a well-studied intervention for high-risk PE, understand when it is indicated, and be familiar with how to facilitate SE.

3.8. Catheter-directed intervention

Percutaneous CDI involves placement of a catheter into the pulmonary artery to deliver directed thrombolytics, mechanical clot fragmentation, or clot retrieval. The ESC 2019 guidelines and AHA 2011 guidelines recommend CDI in patients with high-risk PE who have failed or have a contraindication to ST as a class IIa, level C recommendation [10,11]. Studies comparing CDI to ST are lacking [2].

CDI offers the theoretical benefit of lower bleeding compared to ST [113], but there is insufficient evidence recommending CDI over ST for high-risk PE [114], nor is there clear evidence that suggests one method of CDI outperforms another. Interest in CDI for PE dates to the 1980s when an early trial randomized patients to catheter-infused tPA or ST and included high-risk PE [115]. The recently published FLAME study is the first modern study of CDI in patients with high-risk PE [116]. This was a nonrandomized, prospective study that compared mechanical thrombectomy to "other contemporary therapies," which were mainly ST (69%) and anticoagulation alone (23%). Those who underwent mechanical thrombectomy had an in-hospital mortality rate of 1.9% (95% CI 0.0–10.1%), and those who received "other contemporary strategies" had a mortality rate of 29.5% (95% CI 18.5–42.6%). No patients suffered from intracranial hemorrhage in the mechanical thrombectomy group, and 2 of the 42 (4.8%) patients who received ST had intracranial hemorrhage [116]. Other than the FLAME study, the evidence of CDI in high-risk PE is generally limited to case reports and

series in patients who either failed ST or have contraindications to ST [117]. Besides this initial study published in 1988 and the FLAME study [115,116], other prospective trials evaluating CDI in those with intermediate-risk PE have shown improvement in RV function and hemodynamics with CDI [118,119]. One of the weaknesses of these CDI trials is that their outcomes focus on RV function and hemodynamics rather than mortality. The several meta-analyses and systematic reviews of CDI for intermediate-risk PE do not provide evidence to support widespread adoption of CDI for high-risk PE [2,120,121]. There are currently two anticipated randomized trials investigating CDI in patients with intermediate-high risk PE (HI-PEITHO and PE-TRACT) [122,123]. Emergency clinicians should be aware of the indications of CDI in high-risk PE but understand the limitations of the available evidence for CDI in high-risk PE.

3.9. Extracorporeal membrane oxygenation

ECMO should be considered in patients with high-risk PE with rapid circulatory collapse, refractory shock, or cardiac arrest [40]. Patients with high-risk PE who receive ECMO generally receive venoarterial-ECMO (VA-ECMO) as venovenous-ECMO (VV-ECMO) does not offload the RV, and VA-ECMO minimizes RV preload and afterload [105,106,124]. VA-ECMO should be conceptualized as a bridge to intervention, typically with SE [105,124]. However, there are cases of patients placed on ECMO for high-risk PE who respond to anticoagulation alone while on ECMO without other intervention [125]. Those who receive ECMO for high-risk PE have mortality rates that reach 60% [104,126]. In-hospital and out-of-hospital survival with good neurological outcome widely varies with significant heterogeneity between studies, and there are no large prospective trials [127]. A recent single center retrospective study found only 22 patients who underwent VA-ECMO for high-risk PE over 7 years; the 30-day mortality was 59% and 1-year survival was 50% [128]. A systematic review evaluating 128 patients with high-risk PE on VA-ECMO found that 43% received ST before ECMO and 37.5% had received CDI before ECMO [129]. This systematic review had a 30-day survival rate of 78% [129]. When compared to other studies with higher mortality rates, the studies with higher mortality rates were more likely to use ECMO as a last resort [130-132]. One of the important factors in outcomes may be early initiation of ECMO prior to cardiac arrest [124,133]. Emergency clinicians should be aware of the indications for ECMO in patients with high-risk PE and be familiar with their institutions' ECMO protocols.

3.10. Cardiac arrest

Cardiac arrest is the most severe presentation of high-risk PE. If a patient with known diagnosis of PE suffers cardiac arrest, CPR is ineffective, as the clot burden decreases pulmonary blood flow, thereby reducing LV filling and compromising LV CO even under ideal CPR [106]. Multiple studies indicate that patients with cardiac arrest secondary to PE have better outcomes if they receive ST [134-137]. In a cohort of patients with in-hospital cardiac arrest secondary to PE, those who achieved ROSC received ST significantly earlier (13.6 versus 24.6 min) [137]. Based on current literature, the benefits of ST in patients in cardiac arrest secondary to PE likely outweighs risks such as bleeding. Guidelines vary on how long to continue cardiopulmonary resuscitation (CPR) after administering ST in those with cardiac arrest and range from 15 to 90 min [138,139,140]. We recommend continuing ACLS-guided CPR for at least 30 min following administration of ST.

In many cases, it is uncertain if PE is the cause of cardiac arrest. PE is estimated to cause 2–5% of all out-of-hospital cardiac arrests, though this may be an underestimation [141]. In this scenario, the emergency clinician should determine the likelihood that PE is the cause of cardiac arrest and consider ST if appropriate. Ongoing CPR makes history difficult to ascertain, although approximately 25–50% of patients with a first-time PE have no risk factors [142]. A proximal deep vein thrombosis found on POCUS could indicate PE as the cause of cardiac arrest, and it is reasonable to give ST in this situation. POCUS echocardiography may be difficult to perform during CPR. Markers of RV strain during cardiac arrest are non-specific for PE, and RV strain on echocardiography during CPR should not be used in isolation to justify ST [132]. PEA is the most common rhythm, perhaps due to profound hypotension [135]. In a prospective study, those with cardiac arrest secondary to PE were more likely to present with a non-shockable rhythm (50% versus 6%, OR 12.4, 95% CI 4.9–31) and have a prior venous thromboembolism (VTE) (23% versus 3%, OR 10.4, 95% CI 5.6–19.4) [143]. In this study, the presence of a shockable rhythm and absence of prior VTE had a negative predictive value of 98% for excluding PE as the cause of cardiac arrest. If the emergency clinician has a low suspicion of PE as the cause of cardiac arrest, then ST should not be administered, as empiric ST in patients with undifferentiated cardiac arrest is not associated with improved outcomes [144-146].

Lastly, emergency clinicians may consider the initiation of ECMO-enhanced CPR (ECLS) for patients with cardiac arrest secondary to PE. Similar to ST, the decision to cannulate should be made quickly, as outcomes worsen as time elapses before intervention. The evidence of ECLS as a routine intervention for PE with cardiac arrest is insufficient [131,132,147].

4. Conclusion

High-risk PE is a complex, challenging, life-threatening condition that emergency clinicians must be prepared to diagnose and treat. Clinicians must manage hemodynamics while rapidly pursuing ST in patients without contraindications. Other options include SE and CDI, as well as ECMO for select patients.

CRediT authorship contribution statement

Samuel G. Rouleau: Writing – review & editing, Writing – original draft, Validation, Resources, Conceptualization. **Scott D. Casey:** Writing – review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization. **Christopher Kabrhel:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Formal analysis, Data curation, Conceptualization. **David R. Vinson:** Writing – review & editing, Visualization, Validation, Supervision, Formal analysis. **Brit Long:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Formal analysis, Conceptualization.

Declaration of competing Interest

None of the authors have submitted a review on this topic or published previously on this topic.

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References

[1] Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353(9162):1386–9. https://doi.org/10.1016/s0140-6736(98)07534-5.

[2] Harvey JJ, Huang S, Uberoi R. Catheter-directed therapies for the treatment of high risk (massive) and intermediate risk (submassive) acute pulmonary embolism. Cochrane Database Syst Rev. 2022;8(8). https://doi.org/10.1002/14651858.CD013083.pub2. CD013083. Published 2022 Aug 8.

[3] Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. Eur Respir J. 2016;48(3):780–6. https://doi.org/10.1183/13993003.00024-2016.

[4] Laporte S, Mismetti P, Décousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry. Circulation. 2008;117(13):1711–6. https://doi.org/10.1161/CIRCULATIONAHA.107.726232.

[5] Barco S, Konstantinides SV. Medical management of pulmonary embolism. In: Chaar C, editor. Current Management of Venous Diseases. Springer; 2017. p. 371–87. https://doi.org/10.1007/978-3-319-65226-9_29.

[6] Casazza F, Becattini C, Bongarzoni A, et al. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER). Thromb Res. 2012;130(6):847–52. https://doi.org/10.1016/j.thromres.2012.08.292.

[7] Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J. 2020;41(4):522–9. https://doi.org/10.1093/eurheartj/ehz236.

[8] Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res. 2016;118(9):1340–7. https://doi.org/10.1161/CIRCRESAHA.115.306841.

[9] Sadeghi A, Brevetti GR, Kim S, et al. Acute massive pulmonary embolism: role of the cardiac surgeon. Tex Heart Inst J. 2005;32(3):430–3.

[10] Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2012 Aug 14;126(7):e104] [published correction appears in *Circulation*. 2012 Mar 20;125(11):e495]. Circulation. 2011;123(16):1788–830. https://doi.org/10.1161/CIR.0b013e318214914f.

[11] Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543–603. https://doi.org/10.1093/eurheartj/ehz405.

[12] Giri J, Sista AK, Weinberg I, et al. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. Circulation. 2019 Nov 12;140(20):e774–801. https://doi.org/10.1161/CIR.0000000000000707.

[13] Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172(8):1041–6. https://doi.org/10.1164/rccm.200506-862OC.

[14] Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383–9. https://doi.org/10.1001/archinternmed.2010.199.

[15] Zuin M, Piazza G, Barco S, et al. Time-based reperfusion in hemodynamically unstable pulmonary embolism patients: does early reperfusion therapy improve survival? [published online ahead of print, 2023 Jul 8]. Eur Heart J Acute Cardiovasc Care. 2023. https://doi.org/10.1093/ehjacc/zuad080. zuad080.

[16] Schultz J, Giordano N, Zheng H, et al. EXPRESS: a multidisciplinary pulmonary embolism response team (PERT) – experience from a national multicenter consortium [published online ahead of print, 2019 Jan 11]. Pulm Circ. 2019;9(3). https://doi.org/10.1177/2045894018824563. 2045894018824563.

[17] Roy PM, Douillet D, Penaloza A. Contemporary management of acute pulmonary embolism. Trends Cardiovasc Med. 2022;32(5):259–68. https://doi.org/10.1016/j.tcm.2021.06.002.

[18] Gjonbrataj E, Kim JN, Gjonbrataj J, et al. Risk factors associated with provoked pulmonary embolism. Korean J Intern Med. 2017;32(1):95–101. https://doi.org/10.3904/kjim.2015.118.

[19] Barco S, Ende-Verhaar YM, Becattini C, et al. Differential impact of syncope on the prognosis of patients with acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2018;39(47):4186–95. https://doi.org/10.1093/eurheartj/ehy631.

[20] Vinson DR, Engelhart DC, Bahl D, et al. Presyncope is associated with intensive care unit admission in emergency department patients with acute pulmonary embolism. West J Emerg Med. 2020;21(3):703–13. Published 2020 Apr 13. https://doi.org/10.5811/westjem.2020.2.45028.

[21] Shopp JD, Stewart LK, Emmett TW, Kline JA. Findings from 12-lead electrocardiography that predict circulatory shock from pulmonary embolism: systematic review and meta-analysis. Acad Emerg Med. 2015;22(10):1127–37. https://doi.org/10.1111/acem.12769.

[22] Thomson D, Kourounis G, Trenear R, et al. ECG in suspected pulmonary embolism. Postgrad Med J. 2019;95(1119):12–7. https://doi.org/10.1136/postgradmedj-2018-136178.

[23] Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation. 2007;116:427–33.

[24] Barco S, Mahmoudpour SH, Planquette B, et al. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2019;40:902–10.

[25] Meinel FG, Nance Jr JW, Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. Am J Med. 2015 Jul;128(7). https://doi.org/10.1016/j.amjmed.2015.01.023. 747–59.e2.

[26] Lyhne MD, Giordano N, Dudzinski D, et al. Low concordance between CTPA and echocardiography in identification of right ventricular strain in PERT patients with acute pulmonary embolism. Emerg Radiol. 2023;30(3):325–31. https://doi.org/10.1007/s10140-023-02130-z.

[27] Lobo JL, Holley A, Tapson V, et al. Prognostic significance of tricuspid annular displacement innormotensive patients with acute symptomatic pulmonary embolism. J Thromb Haemost. 2014;12(7):1020–7. https://doi.org/10.1111/jth.12589.

[28] Bleeker GB, Steendijk P, Holman ER, et al. Assessing right ventricular function: the role of echocardiography and complementary technologies. Heart. 2006 Apr;92(Suppl. 1):i19–26. https://doi.org/10.1136/hrt.2005.082503.

[29] Vaid U, Singer E, Marhefka GD, et al. Poor positive predictive value of McConnell's sign on transthoracic echocardiography for the diagnosis of acute pulmonary embolism. Hosp Pract (1995). 2013;41(3):23–7. https://doi.org/10.3810/hp.2013.08.1065.

[30] Bova C, Vanni S, Prandoni P, et al. A prospective validation of the Bova score in normotensive patients with acute pulmonary embolism. Thromb Res. 2018;165:107–11. https://doi.org/10.1016/j.thromres.2018.04.002.

[31] Freitas P, Santos AR, Ferreira AM, et al. Derivation and external validation of the SHIeLD score for predicting outcome in normotensive pulmonary embolism. Int J Cardiol. 2019;281:119–24. https://doi.org/10.1016/j.ijcard.2018.12.062.

[32] Vanni S, Jiménez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax. 2015;70(4):333–8. https://doi.org/10.1136/thoraxjnl-2014-206300.

[33] Vanni S, Nazerian P, Bova C, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate-high risk of adverse clinical outcome: the prognostic role of plasma lactate. Intern Emerg Med. 2017;12(5):657–65. https://doi.org/10.1007/s11739-016-1487-6.

[34] Matthews JC, McLaughlin V. Acute right ventricular failure in the setting of acute pulmonary embolism or chronic pulmonary hypertension: a detailed review of the pathophysiology, diagnosis, and management. Curr Cardiol Rev. 2008;4(1):49–59. https://doi.org/10.2174/157340308783565384.

[35] Kostura M, Smalley C, Koyfman A, Long B. Right heart failure: a narrative review for emergency clinicians. Am J Emerg Med. 2022 Aug;58:106–13. https://doi.org/10.1016/j.ajem.2022.05.030.

[36] Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and emerging clinical perspectives. J Am Coll Cardiol. 2017;69(13):1718–34. https://doi.org/10.1016/j.jacc.2017.01.051.

[37] Crager SE, Humphreys C. Right ventricular failure and pulmonary hypertension. Emerg Med Clin North Am. 2022;40(3):519–37. https://doi.org/10.1016/j.emc.2022.05.006.

[38] Green EM, Givertz MM. Management of acute right ventricular failure in the intensive care unit. Curr Heart Fail Rep. 2012;9(3):228–35. https://doi.org/10.1007/s11897-012-0104-x.

[39] Naeije R, Badagliacca R. The overloaded right heart and ventricular interdependence. Cardiovasc Res. 2017;113(12):1474–85. https://doi.org/10.1093/cvr/cvx160.

[40] Piazza G. Advanced management of intermediate- and high-risk pulmonary embolism: JACC Focus Seminar. J Am Coll Cardiol. 2020;76(18):2117–27. https://doi.org/10.1016/j.jacc.2020.05.028.

[41] Assadi F. Passive leg raising: simple and reliable technique to prevent fluid overload in critically ill patients. Int J Prev Med. 2017;8:48. Published 2017 Jul 4. https://doi.org/10.4103/ijpvm.IJPVM_11_17.

[42] Schouver ED, Chiche O, Bouvier P, et al. Diuretics versus volume expansion in acute submassive pulmonary embolism. Arch Cardiovasc Dis. 2017;110(11):616–25. https://doi.org/10.1016/j.acvd.2017.01.016.

[43] Tapson VF, Weinberg AS. Overview of management of intermediate- and high-risk pulmonary embolism. Crit Care Clin. 2020;36(3):449–63. https://doi.org/10.1016/j.ccc.2020.02.003.

[44] Currigan DA, Hughes RJ, Wright CE, et al. Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries: an in vitro study. Anesthesiology. 2014;121(5):930–6. https://doi.org/10.1097/ALN.0000000000000430.

[45] Hirsch LJ, Rooney MW, Wat SS, et al. Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. Chest. 1991;100(3):796–801. https://doi.org/10.1378/chest.100.3.796.

[46] Kwak YL, Lee CS, Park YH, et al. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension. Anaesthesia. 2002;57(1):9–14. https://doi.org/10.1046/j.1365-2044.2002.02324.x.

[47] Layish DT, Tapson VF. Pharmacologic hemodynamic support in massive pulmonary embolism. Chest. 1997;111(1):218–24. https://doi.org/10.1378/chest.111.1.218.

[48] Manier G, Castaing Y. Influence of cardiac output on oxygen exchange in acute pulmonary embolism. Am Rev Respir Dis. 1992;145(1):130–6. https://doi.org/10.1164/ajrccm/145.1.130.

[49] Kooter AJ, Ijzerman RG, Kamp O, et al. No effect of epoprostenol on right ventricular diameter in patients with acute pulmonary embolism: a randomized controlled

trial. BMC Pulm Med. 2010;10:18. Published 2010 Mar 30. https://doi.org/10.1186/1471-2466-10-18.
[50] Messika J, Goutorbe P, Hajage D, et al. Severe pulmonary embolism managed with high-flow nasal cannula oxygen therapy. Eur J Emerg Med. 2017;24(3):230–2. https://doi.org/10.1097/MEJ.0000000000000420.
[51] Rosenberger P, Shernan SK, Shekar PS, et al. Acute hemodynamic collapse after induction of general anesthesia for emergent pulmonary embolectomy. Anesth Analg. 2006;102(5):1311–5. https://doi.org/10.1213/01.ane.0000208970.14762.7f.
[52] Janz DR, Casey JD, Semler MW, et al. Effect of a fluid bolus on cardiovascular collapse among critically ill adults undergoing tracheal intubation (PrePARE): a randomised controlled trial. Lancet Respir Med. 2019;7(12):1039–47. https://doi.org/10.1016/S2213-2600(19)30246-2.
[53] Zhao S, Friedman O. Management of right ventricular failure in pulmonary embolism. Crit Care Clin. 2020;36(3):505–15. https://doi.org/10.1016/j.ccc.2020.02.006.
[54] Lentz S, Grossman A, Koyfman A, et al. High-risk airway management in the emergency department. Part I: diseases and approaches. J Emerg Med. 2020;59(1):84–95. https://doi.org/10.1016/j.jemermed.2020.05.008.
[55] Bhat T, Neuman A, Tantary M, et al. Inhaled nitric oxide in acute pulmonary embolism: a systematic review. Rev Cardiovasc Med. 2015;16(1):1–8. https://doi.org/10.3909/ricm0718.
[56] Kline JA, Puskarich MA, Jones AE, et al. Inhaled nitric oxide to treat intermediate risk pulmonary embolism: a multicenter randomized controlled trial. Nitric Oxide. 2019;84:60–8. https://doi.org/10.1016/j.niox.2019.01.006.
[57] Daxon BT, Lark E, Matzek LJ, et al. Nebulized nitroglycerin for coronavirus disease 2019-associated acute respiratory distress syndrome: a case report. A a Pract. 2021;15(2):e01376 Published 2021 Feb 5. https://doi.org/10.1213/XAA.0000000000001376.
[58] Kline JA, Marchick MR, Kabrhel C, et al. Prospective study of the frequency and outcomes of patients with suspected pulmonary embolism administered heparin prior to confirmatory imaging. Thromb Res. 2012;129(4):e25–8. https://doi.org/10.1016/j.thromres.2012.01.005.
[59] Woo C, Sun W, Thein P, et al. Preemptive anticoagulation of pulmonary embolism [published online ahead of print, 2023 Jul 25]. Intern Med J. 2023. https://doi.org/10.1111/imj.16174.
[60] Willoughby L, Adams DM, Evans RS, et al. Preemptive anticoagulation in patients with a high pretest probability of pulmonary embolism: are guidelines followed? Chest. 2018;153(5):1153–9. https://doi.org/10.1016/j.chest.2017.11.007.
[61] Soh S, Kim JM, Park JH, et al. Delayed anticoagulation is associated with poor outcomes in high-risk acute pulmonary embolism. J Crit Care. 2016;32:21–5. https://doi.org/10.1016/j.jcrc.2015.11.024.
[62] Prucnal CK, Jansson PS, Deadmon E, et al. Analysis of partial thromboplastin Ttmes in patients with pulmonary embolism during the first 48 hours of anticoagulation with unfractionated heparin. Acad Emerg Med. 2020;27(2):117–27. https://doi.org/10.1111/acem.13872.
[63] Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report [published correction appears in Chest. 2016 Oct;150(4):988]. Chest. 2016;149(2):315–52. https://doi.org/10.1016/j.chest.2015.11.026.
[64] Bell WR. Present-day thrombolytic therapy: therapeutic agents: pharmacokinetics and pharmacodynamics. Rev Cardiovasc Med. 2002;3(Suppl. 2):S34–44.
[65] Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. JAMA. 1970;214:2163–72.
[66] Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. J Am Coll Cardiol. 1992;20(3):520–6. https://doi.org/10.1016/0735-1097(92)90002-5.
[67] Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused [published correction appears in Am J Med. 2012 Jul;125(7):e13]. Am J Med. 2012;125(5):465–70. https://doi.org/10.1016/j.amjmed.2011.10.015.
[68] Zuin M, Rigatelli G, Zuliani G, et al. Thrombolysis in hemodynamically unstable patients: still underused: a review based on multicenter prospective registries on acute pulmonary embolism. J Thromb Thrombolysis. 2019;48(2):323–30. https://doi.org/10.1007/s11239-019-01867-0.
[69] Rush B, Wiskar K, Berger L, et al. The use of thrombolysis for acute pulmonary embolism in the United States: national trends and patient characteristics from 2006 to 2011. J Emerg Med. 2017;52(5):615–21. https://doi.org/10.1016/j.jemermed.2016.10.044.
[70] Rali P, Sacher D, Rivera-Lebron B, et al. Interhospital transfer of patients with acute pulmonary embolism: challenges and opportunities. Chest. 2021;160(5):1844–52. https://doi.org/10.1016/j.chest.2021.07.013.
[71] Jerjes-Sanchez C, Ramírez-Rivera A, de Lourdes García M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. J Thromb Thrombolysis. 1995;2(3):227–9. https://doi.org/10.1007/BF01062714.
[72] Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2015;36(10):605–14. https://doi.org/10.1093/eurheartj/ehu218.
[73] Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004;110(6):744–9. https://doi.org/10.1161/01.CIR.0000137826.09715.9C.
[74] Quezada CA, Bikdeli B, Barrios D, et al. Meta-analysis of prevalence and short-term prognosis of hemodynamically unstable patients with symptomatic acute pulmonary embolism. Am J Cardiol. 2019;123(4):684–9. https://doi.org/10.1016/j.amjcard.2018.11.009.
[75] Tibbutt DA, Davies JA, Anderson JA, et al. Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonay embolism. Br Med J. 1974;1(5904):343–7. https://doi.org/10.1136/bmj.1.5904.343.
[76] PIOPED Investigators. Tissue plasminogen activator for the treatment of acute pulmonary embolism: a collaborative study by the PIOPED Investigators. Chest. 1990;97(3):528–33. https://doi.org/10.1378/chest.97.3.528.
[77] Konstantinides S, Tiede N, Geibel A, et al. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. Am J Cardiol. 1998;82(8):966–70. https://doi.org/10.1016/s0002-9149(98)00513-x.
[78] Kulka HC, Zeller A, Fornaro J, et al. Acute pulmonary embolism–its diagnosis and treatment from a multidisciplinary viewpoint. Dtsch Arztebl Int. 2021;118(37):618–28. https://doi.org/10.3238/arztebl.m2021.0226.
[79] Daniels LB, Parker JA, Patel SR, et al. Relation of duration of symptoms with response to thrombolytic therapy in pulmonary embolism. Am J Cardiol. 1997;80(2):184–8. https://doi.org/10.1016/s0002-9149(97)00315-9.
[80] Keskin M, Dogan S, Kaya A, et al. The prognostic value of time from symptom onset to thrombolysis in patients with pulmonary embolism. Int J Cardiol. 2022;352:131–6. https://doi.org/10.1016/j.ijcard.2022.01.006.
[81] Zuin M, Rigatelli G, Carraro M, et al. Systemic thrombolysis in haemodynamically unstable pulmonary embolism: the earlier the better? Thromb Res. 2019;173:117–23. https://doi.org/10.1016/j.thromres.2018.11.029.
[82] Beydilli İ, Yılmaz F, Sönmez BM, et al. Thrombolytic therapy delay is independent predictor of mortality in acute pulmonary embolism at emergency service. Kaohsiung J Med Sci. 2016;32(11):572–8. https://doi.org/10.1016/j.kjms.2016.09.004.
[83] Ochani RK, Aibani R, Jatoi HN, et al. Evolving paradigm of thrombolysis in pulmonary embolism: comprehensive review of clinical manifestations, indications, recent advances and guideline. World J Clin Cases. 2023;11(8):1702–11. https://doi.org/10.12998/wjcc.v11.i8.1702.
[84] Kaplovitch E, Shaw JR, Douketis J. Thrombolysis in pulmonary embolism: an evidence-based approach to treating life-threatening pulmonary emboli. Crit Care Clin. 2020;36(3):465–80. https://doi.org/10.1016/j.ccc.2020.02.004.
[85] Martillotti G, Boehlen F, Robert-Ebadi H, et al. Treatment options for severe pulmonary embolism during pregnancy and the postpartum period: a systematic review. J Thromb Haemost. 2017;15(10):1942–50. https://doi.org/10.1111/jth.13802.
[86] Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370(15):1402–11. https://doi.org/10.1056/NEJMoa1302097.
[87] Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347(15):1143–50. https://doi.org/10.1056/NEJMoa021274.
[88] Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost. 2014;12(4):459–68. https://doi.org/10.1111/jth.12521.
[89] Mathew D, Kim J, Kosuru BP, et al. Mortality and bleeding associated with the management of sub-massive pulmonary embolism: a systematic review and Bayesian network meta-analysis. Sci Rep. 2023;13(1):7169. Published 2023 May 3. https://doi.org/10.1038/s41598-023-34348-9.
[90] Jara-Palomares L, Jiménez D, Bikdeli B, et al. Derivation and validation of a clinical prediction rule for thrombolysis-associated major bleeding in patients with acute pulmonary embolism: the BACS score [published online ahead of print, 2020 Jul 23]. Eur Respir J. 2020:2002336. https://doi.org/10.1183/13993003.02336-2020.
[91] Chatterjee S, Weinberg I, Yeh RW, et al. Risk factors for intracranial haemorrhage in patients with pulmonary embolism treated with thrombolytic therapy Development of the PE-CH Score. Thromb Haemost. 2017;117(2):246–51. https://doi.org/10.1160/TH16-07-0588.
[92] Konstantinides SV, Torbicki A, Agnelli G, et al. ESC guidelines on the diagnosis and management of acute pulmonary embolism [published correction appears in Eur Heart J. 2015 Oct 14;36(39):2666] [published correction appears in Eur Heart J. 2015 Oct 14;36(39):2642]. Eur Heart J. 2014;35(43):3033–3069k. https://doi.org/10.1093/eurheartj/ehu283.
[93] Chopard R, Behr J, Vidoni C, et al. An update on the management of acute high-risk pulmonary embolism. J Clin Med. 2022;11(16):4807. Published 2022 Aug 17. https://doi.org/10.3390/jcm11164807.
[94] Kahn SR, de Wit K. Pulmonary Embolism. N Engl J Med. 2022;387(1):45–57. https://doi.org/10.1056/NEJMcp2116489.
[95] Zhang Z, Xi L, Zhang S, et al. Tenecteplase in pulmonary embolism patients: a meta-analysis and systematic review. Front Med (Lausanne). 2022;9:860565. Published 2022 Mar 31. https://doi.org/10.3389/fmed.2022.860565.
[96] Murguia AR, Mukherjee D, Ojha C, et al. Reduced-dose thrombolysis in acute pulmonary embolism a systematic review [published online ahead of print, 2023 Apr 15]. Angiology. 2023. https://doi.org/10.1177/00033197231167062.33197231167062.
[97] Wang C, Zhai Z, Yang Y, et al. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. Chest. 2010;137(2):254–62. https://doi.org/10.1378/chest.09-0765.
[98] Kiser TH, Burnham EL, Clark B, et al. Half-dose versus full-dose alteplase for treatment of pulmonary embolism. Crit Care Med. 2018;46(10):1617–25. https://doi.org/10.1097/CCM.0000000000003288.
[99] Zhang Z, Zhai ZG, Liang LR, et al. Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. Thromb Res. 2014;133(3):357–63. https://doi.org/10.1016/j.thromres.2013.12.026.

[100] Götzinger F, Lauder L, Sharp ASP, et al. Interventional therapies for pulmonary embolism. Nat Rev Cardiol. 2023;20(10):670–84. https://doi.org/10.1038/s41569-023-00876-0.
[101] Aykan AÇ, Gökdeniz T, Gül İ, et al. Reduced-dose systemic fibrinolysis in massive pulmonary embolism: a pilot study. Clin Exp Emerg Med. 2023;10(3):280–6. https://doi.org/10.15441/ceem.23.015.
[102] Sanchez O, Charles-Nelson A, Ageno W, et al. Reduced-dose intravenous thrombolysis for acute intermediate-high-risk pulmonary embolism: rationale and design of the Pulmonary Embolism International THrOmbolysis (PEITHO)-3 trial. Thromb Haemost. 2022;122(5):857–66. https://doi.org/10.1055/a-1653-4699.
[103] Rivera-Lebron B, McDaniel M, Ahrar K, et al. Diagnosis, treatment and follow up of acute pulmonary embolism: consensus practice from the PERT Consortium. Clin Appl Thromb Hemost. 2019;25. https://doi.org/10.1177/1076029619853037. 1076029619853037.
[104] Meneveau N, Séronde MF, Blonde MC, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. Chest. 2006;129(4):1043–50. https://doi.org/10.1378/chest.129.4.1043.
[105] de Perrot M. Role of extracorporeal membrane oxygenation and surgical embolectomy in acute pulmonary embolism. Curr Opin Pulm Med. 2022;28(5):384–90. https://doi.org/10.1097/MCP.0000000000000897.
[106] Goldberg JB, Giri J, Kobayashi T, et al. Surgical management and mechanical circulatory support in high-risk pulmonary embolisms: historical context, current status, and future directions: a scientific statement from the american heart association. Circulation. 2023;147(9):e628–47. https://doi.org/10.1161/CIR.0000000000001117.
[107] Lee T, Itagaki S, Chiang YP, et al. Survival and recurrence after acute pulmonary embolism treated with pulmonary embolectomy or thrombolysis in New York State, 1999 to 2013. J Thorac Cardiovasc Surg. 2018;155(3):1084–1090.e12. https://doi.org/10.1016/j.jtcvs.2017.07.074.
[108] Aymard T, Kadner A, Widmer A, et al. Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy – should surgical indications be revisited? Eur J Cardiothorac Surg. 2013;43(1):90–4. https://doi.org/10.1093/ejcts/ezs123.
[109] Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg. 2005;129(5):1018–23. https://doi.org/10.1016/j.jtcvs.2004.10.023.
[110] Keeling WB, Sundt T, Leacche M, et al. Outcomes after surgical pulmonary embolectomy for acute pulmonary embolus: a multi-institutional study. Ann Thorac Surg. 2016;102(5):1498–502. https://doi.org/10.1016/j.athoracsur.2016.05.004.
[111] Azari A, Beheshti AT, Moravvej Z, et al. Surgical embolectomy versus thrombolytic therapy in the management of acute massive pulmonary embolism: short and long-term prognosis. Heart Lung. 2015;44(4):335–9. https://doi.org/10.1016/j.hrtlng.2015.04.008.
[112] Deas DS, Keeling B. Surgical pulmonary embolectomy. Crit Care Clin. 2020;36(3):497–504. https://doi.org/10.1016/j.ccc.2020.02.009.
[113] Planer D, Yanko S, Matok I, et al. Catheter-directed thrombolysis compared with systemic thrombolysis and anticoagulation in patients with intermediate- or high-risk pulmonary embolism: systematic review and network meta-analysis. CMAJ. 2023;195(24):E833–43. https://doi.org/10.1503/cmaj.220960.
[114] Serebriakoff P, Cafferkey J, de Wit K, et al. Pulmonary embolism management in the emergency department: part 2. Emerg Med J. 2023;40(1):69–75. https://doi.org/10.1136/emermed-2021-212001.
[115] Verstraete M, Miller GA, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation. 1988;77(2):353–60. https://doi.org/10.1161/01.cir.77.2.353.
[116] Silver MJ, Gibson CM, Giri J, et al. Outcomes in high-risk pulmonary embolism patients undergoing FlowTriever mechanical thrombectomy or other contemporary therapies: results from the FLAME study. Circ Cardiovasc Interv. 2023;16(10):e013406. https://doi.org/10.1161/CIRCINTERVENTIONS.123.013406.
[117] He J, Clayton B, Kurdi H, et al. Massive pulmonary embolism in patients with extreme bleeding risk: a case series on the successful use of ultrasound-assisted, catheter directed thrombolysis in a district general hospital. J Thromb Thrombolysis. 2021;51(4):1120–6. https://doi.org/10.1007/s11239-020-02258-6.
[118] Ruohoniemi DM, Sista AK. Interventional radiology therapy: inferior vena cava filter and catheter-based therapies. Crit Care Clin. 2020;36(3):481–95. https://doi.org/10.1016/j.ccc.2020.02.005.
[119] Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. JACC Cardiovasc Interv. 2015;8(10):1382–92. https://doi.org/10.1016/j.jcin.2015.04.020.
[120] Pietrasik A, Gąsecka A, Szarpak Ł, et al. Catheter-based therapies decrease mortality in patients with intermediate and high-risk pulmonary embolism: evidence from meta-analysis of 65,589 patients. Front Cardiovasc Med. 2022;9:861307 Published 2022 Jun 16. https://doi.org/10.3389/fcvm.2022.861307.
[121] Milioglou I, Farmakis I, Wazirali M, et al. Percutaneous thrombectomy in patients with intermediate- and high-risk pulmonary embolism and contraindications to thrombolytics: a systematic review and meta-analysis. J Thromb Thrombolysis. 2023;55(2):228–42. https://doi.org/10.1007/s11239-022-02750-1.
[122] Klok FA, Piazza G, Sharp ASP, et al. Ultrasound-facilitated, catheter-directed thrombolysis vs anticoagulation alone for acute intermediate-high-risk pulmonary embolism: rationale and design of the HI-PEITHO study. Am Heart J. 2022;251:43–53. https://doi.org/10.1016/j.ahj.2022.05.011.
[123] Pulmonary embolism – Thrombus removal with catheter-directed therapy (PETRACT). ClinicalTrials.gov ID NCT05591118. Last update posted 28 July 2023. Available at. https://clinicaltrials.gov/study/NCT05591118. Accessed 02 October 2023.
[124] Kmiec L, Philipp A, Floerchinger B, et al. Extracorporeal membrane oxygenation for massive pulmonary embolism as bridge to therapy. ASAIO J. 2020;66(2):146–52. https://doi.org/10.1097/MAT.0000000000000953.
[125] Ghoreishi M, DiChiacchio L, Pasrija C, et al. Predictors of recovery in patients supported with venoarterial extracorporeal membrane oxygenation for acute massive pulmonary embolism. Ann Thorac Surg. 2020;110(1):70–5. https://doi.org/10.1016/j.athoracsur.2019.10.053.
[126] Elbadawi A, Mentias A, Elgendy IY, et al. National trends and outcomes for extracorporeal membrane oxygenation use in high-risk pulmonary embolism. Vasc Med. 2019;24(3):230–3. https://doi.org/10.1177/1358863X18824650.
[127] Pozzi M, Metge A, Martelin A, et al. Efficacy and safety of extracorporeal membrane oxygenation for high-risk pulmonary embolism: a systematic review and meta-analysis. Vasc Med. 2020;25(5):460–7. https://doi.org/10.1177/1358863X20944469.
[128] Kelty CE, Berjaoui W, Shrestha NK, et al. Veno-arterial extracorporeal membrane oxygenation versus standard medical management for massive pulmonary embolism [published online ahead of print, 2023 Jun 7]. Perfusion. 2023. https://doi.org/10.1177/02676591231182247. 2676591231182247.
[129] O'Malley TJ, Choi JH, Maynes EJ, et al. Outcomes of extracorporeal life support for the treatment of acute massive pulmonary embolism: a systematic review. Resuscitation. 2020;146:132–7. https://doi.org/10.1016/j.resuscitation.2019.11.018.
[130] Kaso ER, Pan JA, Salerno M, et al. Venoarterial extracorporeal membrane oxygenation for aAcute massive pulmonary embolism: a meta-analysis and call to action. J Cardiovasc Transl Res. 2022;15(2):258–67. https://doi.org/10.1007/s12265-021-10158-0.
[131] George B, Parazino M, Omar HR, et al. A retrospective comparison of survivors and non-survivors of massive pulmonary embolism receiving veno-arterial extracorporeal membrane oxygenation support. Resuscitation. 2018;122:1–5. https://doi.org/10.1016/j.resuscitation.2017.11.034.
[132] Kjaergaard B, Kristensen JH, Sindby JE, et al. Extracorporeal membrane oxygenation in life-threatening massive pulmonary embolism. Perfusion. 2019;34(6):467–74. https://doi.org/10.1177/0267659119830014.
[133] Bazan VM, Rodgers-Fischl P, Zwischenberger JB. Supportive therapy: extracorporeal membrane oxygenation. Crit Care Clin. 2020;36(3):517–29. https://doi.org/10.1016/j.ccc.2020.02.007.
[134] Javaudin F, Lascarrou JB, Le Bastard Q, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest caused by pulmonary embolism increases 30-day survival: findings from the French national cardiac arrest registry. Chest. 2019;156(6):1167–75. https://doi.org/10.1016/j.chest.2019.07.015.
[135] Kürkciyan I, Meron G, Sterz F, et al. Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. Arch Intern Med. 2000;160(10):1529–35. https://doi.org/10.1001/archinte.160.10.1529.
[136] Sharifi M, Berger J, Beeston P, et al. Pulseless electrical activity in pulmonary embolism treated with thrombolysis (from the "PEAPETT" study). Am J Emerg Med. 2016;34(10):1963–7. https://doi.org/10.1016/j.ajem.2016.06.094.
[137] Er F, Nia AM, Gassanov N, et al. Impact of rescue-thrombolysis during cardiopulmonary resuscitation in patients with pulmonary embolism. PloS One. 2009;4(12). https://doi.org/10.1371/journal.pone.0008323. e8323. Published 2009 Dec 15.
[138] Stewart LK, Kline JA. Fibrinolytics for the treatment of pulmonary embolism. Transl Res. 2020;225:82–94. https://doi.org/10.1016/j.trsl.2020.05.003.
[139] Truhlář A, Deakin CD, Soar J, et al. European resuscitation council guidelines for resuscitation 2015: section 4. Cardiac arrest in special circumstances. Resuscitation. 2015;95:148–201. https://doi.org/10.1016/j.resuscitation.2015.07.017.
[140] Reynolds JC, Frisch A, Rittenberger JC, et al. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? Circulation. 2013;128(23):2488–94. https://doi.org/10.1161/CIRCULATIONAHA.113.002408.
[141] Bougouin W, Marijon E, Planquette B, et al. Pulmonary embolism related sudden cardiac arrest admitted alive at hospital: management and outcomes. Resuscitation. 2017;115:135–40. https://doi.org/10.1016/j.resuscitation.2017.04.019.
[142] White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I4–8. https://doi.org/10.1161/01.CIR.0000078468.11849.66.
[143] Bougouin W, Marijon E, Planquette B, et al. Factors associated with pulmonary embolism-related sudden cardiac arrest. Circulation. 2016;134(25):2125–7. https://doi.org/10.1161/CIRCULATIONAHA.116.024746.
[144] Abu-Laban RB, Christenson JM, Innes GD, et al. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity [published correction appears in N Engl J Med. 2003 Oct 9;349(15):1487]. N Engl J Med. 2002;346(20):1522–8. https://doi.org/10.1056/NEJMoa012885.
[145] Wang Y, Wang M, Ni Y, et al. Can systemic thrombolysis improve prognosis of cardiac arrest patients during cardiopulmonary resuscitation? A systematic review and Meta-analysis. J Emerg Med. 2019 Oct;57(4):478–87. https://doi.org/10.1016/j.jemermed.2019.07.011.
[146] Böttiger BW, Arntz HR, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. N Engl J Med. 2008;359(25):2651–62. https://doi.org/10.1056/NEJMoa070570.
[147] Sakuma M, Nakamura M, Yamada N, et al. Percutaneous cardiopulmonary support for the treatment of acute pulmonary embolism: summarized review of the literature in Japan including our own experience. Ann Vasc Dis. 2009;2(1):7–16. https://doi.org/10.3400/avd.AVDrev07017.