Submassive & Massive PE

September 5, 2019 by Josh Farkas

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https://emcrit.org/ibcc/pe/
PE is a humbling disease. This is a highly heterogeneous disease, spanning the gamut from patients who are doing pretty well to patients who are profoundly ill. To complicate matters further, patients can evolve rapidly in one direction or the other.

Given that PE is a heterogeneous and emergent condition, it should come as no surprise that our evidence basis is far from complete. This is a prime example of the lumping-vs-splitting paradox common in researching many critical illnesses:

- If we lump patients with different severity together, then results become difficult to interpret (perhaps the study intervention is helping some patients within the cohort, but not others).
- If we split patients apart on the basis of severity, then it becomes difficult to recruit a large enough population to study with statistical power.

Recently, multidisciplinary PE response teams (PERT teams) have become popular as a strategy to handle this disorder. PERT teams offer the patient prompt access to numerous different services and the opinions of a diverse group of specialists. A formalized team-based approach is also ideal for collecting data and following patients longitudinally. Where available this is an excellent strategy, but most hospitals lack the resources for this approach.

Controversy abounds regarding pulmonary embolism, and will likely persist into the foreseeable future. This chapter includes schemas to provide direction for how these patients might be managed (and which are largely consistent with the PERT consortium consensus practices)(https://www.ncbi.nlm.nih.gov/pubmed/31185730). However, individual patients are quite heterogeneous, so these concepts need to be adapted to the specifics of each patient (including patient preferences).

### is PE driving the patient’s instability?

Lots of unstable patients have PE, but in some cases they may have multifactorial instability (e.g. PE plus sepsis plus hypovolemia). Thrombolysis is beneficial only if PE is causing the patient's instability. Factors to consider are:

- (1) Clot burden on the CT scan
  - In order to blame the patient's instability on PE, there should be a moderate to large clot burden on the CT scan.
  - The precise amount of clot on the scan may not be useful (e.g. whether the patient has a "saddle" PE). However, if there is only a small amount of clot, PE probably isn't causing the instability. For example, a patient with right ventricular dilation and small clot burden may have chronic pulmonary hypertension.
- (2) Global hemodynamic assessment with echocardiography
  - Patients who are unstable due to PE should have at a minimum a dilated inferior vena cava and a dilated right ventricle.
● If the inferior vena cava and right ventricle aren’t dilated, consider whether another process is causing the patient's instability (e.g. hypovolemic shock plus small PE).

Ultimately, clinical judgement is necessary to determine whether a patient's instability is caused by the pulmonary embolism. For more information on the investigation of shock, see the shock chapter (https://emcrit.org/bcc/shock).

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**initial evaluation to guide risk stratification & management**

Once a (sub)massive PE is known or strongly suspected, it is useful to immediately obtain the following panel of studies. Given the rapidity of this disease process, it's generally best to get a full panel of labs up-front.

### Evaluation to risk stratify (sub)massive PE

#### History & Physical
- Medication review – Focus on anticoagulants & anti-platelet medications.
- Vital signs & general appearance.
- Duration of symptoms.

#### Labs
- CBC with differential
- Complete coags: INR, PTT, Fibrinogen, D-dimer
- Lactate
- Troponin

#### Imaging
- EKG
- CT angiogram chest
- Bedside echocardiogram
- Bedside ultrasonography to evaluate for DVT

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(1) This workup certainly doesn't need to be done for every patient with PE. It may be helpful for patients with imaging evidence of RV dilation, or other features of severe PE. -Internet Book of Critical Care, by @PulmCrit

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**risk stratification: primary factors**

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Risk stratification in PE is extraordinarily challenging. Being thorough is good, but it is also important to avoid "counting" the same risk factor multiple times (e.g. if the right ventricle is severely dilated on CT and also dilated on echocardiogram, then echocardiogram doesn't really provide any new prognostic information).

**history**

- **Syncope or near-syncope** are concerning (revealing an absence of hemodynamic reserve).
  - However, these features may be an independent risk factor when other variables are accounted for (30339253). (https://www.ncbi.nlm.nih.gov/pubmed/30339253).

- **Symptom duration** is important:
  - Having symptoms >10-14 days suggests a more chronic thrombus (over time, clots organize and become less responsive to thrombolysis).
  - Having stable symptoms for several days reduces the likelihood of sudden deterioration.
  - Recent-onset or accelerating symptoms are worrisome.

**general appearance**

- (0) A sense of impending doom is concerning. If the patient volunteers a sensation that they are dying, they're often right.
- (1) Diaphoresis is very worrisome (this reflects endogenous epinephrine secretion keeping the patient alive).
- (2) Signs of hypoperfusion are the most worrisome.
Mottling (especially diffuse mottling)
Cool extremities
Confusion, agitation

**vital signs**

- **Bradycardia** is the most worrisome
  - May be a harbinger of impending brady-asystolic arrest (often how these patients die).
- **Tachycardia** is also worrisome
  - A shock index (heart rate / systolic blood pressure) greater than one suggests poor hemodynamic reserve and a worse prognosis
    - (30638984, 27800569, 27742425, 27107684, 25743032, 24973834, 23168283, 19649996, 18308025, 17804446, 12581684).
- **Hypotension** is traditionally the main parameter used to define massive PE. Any of the following criteria would generally be defined as a massive PE:
  - (i) Systolic blood pressure < 90 mm for 15 minutes
  - (ii) Fall in systolic blood pressure by >40 mm for 15 minutes
  - (iii) Requirement for vasopressors.
- Hypertension is generally reassuring – but not always.
  - A small subset of patients with PE have an exuberant release of epinephrine which leads to hypertension (essentially overcompensating for their PE). These patients are hypertensive, but they look and feel awful (e.g. diaphoretic, tachycardic, clammy) and often have elevated lactate. These patients should probably be classified as high-risk submassive PE.
- **Tachypnea**
  - In general, respiratory rate is an excellent predictor of occult critical illness and subsequent deterioration (18513176).
  - Severely elevated respiratory rate (e.g. >30 breaths/minute) has been correlated with worse outcomes (27800569, 23168283).

**troponin**

- Elevated troponin correlates with mortality risk (with an odds ratio of ~5) (25976228).
- Studies have used a broad range of troponin cutoff values (25976228). Considering the available body of literature, reasonable cutoff values might be Troponin I >0.1 ng/ml or Troponin T >0.03 ng/ml (16018861, 17606843).
  - However, it must be borne in mind that values close to these cutoffs may actually represent a grey zone. Such values don't truly contribute any useful information (they neither increase nor decrease the patient's risk substantially).

**lactate**
Lactate is a strong predictor of mortality. Overall, it is probably underutilized in risk stratification.

An elevated lactate generally reflects aerobic hyperlactatemia due to endogenous epinephrine production. This reveals that the patient is under occult hemodynamic stress, and is trying to compensate for that stress through increased sympathetic outflow.

- Lactate essentially functions as a marker of endogenous sympathetic tone.

**right ventricular dilation & strain**

- **EKG signs of RV strain**
  - Right-sided precordial and inferior lead T-wave inversion suggests pulmonary hypertension.
  - ST elevation in lead aVR with STE/STD elsewhere (https://emcrit.org/pulmcrit/two-ekg-patterns-of-pulmonary-embolism-which-mimic-mi/) may be even worse.

- **CT signs**
  - [1] RV dilation (isolated mild RV dilation doesn't have a great specificity for true RV dilation on echocardiogram)(21835376, 27664798). If RV dilation on CT is equivocal, additional signs of RV dysfunction should be sought either on CT scan or echocardiography.
  - [2] Bowing of the RV into the LV. This may be best observed in a coronal CT projection (as with echocardiography, evaluation of the heart in multiple planes may improve diagnostic accuracy).
  - [3] Contrast reflux into the inferior vena cava and hepatic veins.

- **Echocardiographic signs**
  - [1] RV dilation.
  - [2] RV systolic failure (reduced tricuspid valve annular systolic excursion). McConnel's signs (hypokinesis of the RV free wall) may also be noted, but the amount of independent information that this provides is unclear. Contrary to popular belief, McConnel's sign isn't entirely specific for PE, but may also be seen in right ventricular myocardial infarction.

- **Interpretation of RV dysfunction**
  - RV dilation is generally a pre-requisite for either submassive or massive PE. Alternatively, lack of RV dilation suggests that hemodynamic instability may be caused by another problem (e.g. small PE plus septic shock).
  - When possible, comparison should be made to archival echocardiograms or CT scans. This may help differentiate chronic vs. acute right ventricular failure.
    - Chronic right ventricular dysfunction is common in patients with COPD or obesity hypoventilation syndrome, so this shouldn't be misinterpreted as evidence of a (sub)massive PE.
PE exists on a spectrum of disease severity. Thus, divisions are somewhat arbitrary. Nonetheless, it is useful to divide PE into roughly five categories:

- **Low-risk PE**: Patients at the lowest risk of dying. Some may be able to be discharged home (a topic beyond the scope of this chapter).
- **Low-risk submassive PE**: Patients with RV dilation, but who are at low risk of dying and don’t require intensive care.
- **High-risk submassive PE**: Hemodynamically stable patients who nonetheless have elevated mortality. They merit ICU admission and consideration for advanced therapies.
- **Non-crashing massive PE**: Patients with hypotension who stabilize well on low-dose vasopressor. These patients need ICU admission and advanced therapies.
- **Crashing massive PE**: Patients with hypotension and persistent features of instability, who are at the greatest risk for immediate death.
**patients who defy immediate risk stratification**

- Some patients don’t fit neatly into one of the above categories. This is most clinically relevant for patients with submassive PE who are sitting on the borderline between low-risk submassive versus high-risk submassive PE.
- As with all things, clinical judgement is required (potentially taking into account additional features such as exertional capacity, neutrophil to lymphocyte ratio, and lower extremity clot burden as discussed further below).
- For patients who are really on the borderline of low-risk submassive vs. high-risk submassive PE, consider:
  - Admission to intensive care.
  - Monitoring serial vital signs, lactate level, and troponin level.
  - If patients remain stable with low troponin and lactate levels, then they may be categorized into low-risk submassive PE. Alternatively, evidence of hemodynamic instability or rising biomarkers may push patients into a high-risk submassive or even massive PE category.

**persistent large DVT**

- A large clot burden poses the risk of additional emboli. This is an independent risk factor for mortality.

**neutrophil / lymphocyte ratio (NLR)**

- **Neutrophil/Lymphocyte ratio** is a measurement of occult physiologic stress (because endogenous cortisol will increase the neutrophil count and reduce the lymphocyte count, thereby increasing the ratio).
- Meta-analysis suggests that elevated NLR may be an even stronger prognostic indication than troponin, as shown in the figure below.
- Studies have used different NLR cutoffs, creating a grey zone. Based on available data, NLR may be interpreted in the context of acute PE as follows:
  - NLR <5.5 suggests low mortality risk (~2.7%)
  - NLR 5.5-9.2 is a grey zone (NLR in this range is nonspecific and adds no useful information)
  - NLR >9.2 suggests high mortality risk (~26%)
- NLR may be useful as an early indicator of severe PE, because it will often become available early (e.g. before lactate or troponin levels have been ordered).

Caveat: NLR may be elevated by any cause of physiologic stress. Therefore, this test will be predictive of PE-related mortality only in patients with isolated PE (no other active medical problems). This is a bit like lactate, in that it's a global reflection of physiologic stress.

**walking challenge test**

- Some patients will report pre-syncpe or syncpe, or dyspnea with minimal exertion.
- If the history is unclear, this can be clarified a bit by asking the patient to walk (with assistance, to ensure against falling).
- The key parameter to follow is the way the patient looks and feels when walking. If patients become (pre)syncopal or severely dyspneic with minimal exertion, this implies a significant strain on the right ventricle with low physiologic reserve.
- May be used in a serial fashion to assess the patient's evolution over time and responsiveness to various therapies.

**prognostic features which don't add much**

The main challenge in prognostication is integrating lots of information in a non-redundant fashion. If the list of factors to consider is too long, then we will get lost in it.

**Brain natriuretic peptide (BNP) or NT-BNP**

- This is used in some prognostic systems, but seems to be dropping out of favor.
- BNP doesn't distinguish between failure of the right or left ventricle. Additionally, NT-BNP is elevated in renal dysfunction. Overall, this makes the test nonspecific for diagnosis of acute right ventricular failure.
- Inclusion may cause patients with chronic heart failure to be classified incorrectly.

**BOVA score**

- This is a four-component risk-stratification system for PE. It's good, but not perfect.
- The BOVA score doesn't ensure that instability is due to pulmonary embolism (specifically, it doesn't require RV dysfunction).
- Patient with mild tachycardia (HR > 110 b/m) and elevated troponin would be classified as intermediate-risk (7% risk of PE-related mortality), even with a completely normal right ventricle. This doesn't make a lot of sense, as it would tend to suggest an alternative etiology of the
patient's instability.

**PESI (Pulmonary Embolism Severity Index) score & Simplified PESI score (sPESI score)**

- These are designed to predict all-cause 30-day mortality. This frankly is *not* what we need to know when risk-stratifying a PE patient (we need to know the *short-term* risk of PE-related hemodynamic collapse).
- As a subacute mortality-prediction tool, PESI focuses excessively on baseline epidemiological features of the patient (rather than the patient’s acute hemodynamic status). Elderly patients with many comorbidities will be categorized as "high risk" even if they have a tiny pulmonary embolism.
- Patients with high-risk submassive PE may (incorrectly) receive a low-risk PESI score. This is a well-known problem with the score. According to the 2019 ESC guidelines, "Signs of RV dysfunction or elevated cardiac biomarker levels may be present, despite a calculated PESI of I-II or an sPESI of 0. Until the implications of such discrepancies for the management of PE are fully understood, these patients should be classified into the intermediate-risk category."

![Diagram showing the PESI score and simplified PESI score](https://emcrit.org/ibcc/pe/

**Examples of how the PESI score fails in acute prognosis of PE**

- **Left panel:** PESI may categorize elderly patients with comorbidities as "very high risk" - even if they have a tiny pulmonary embolism and have no acute physiologic abnormality at all.
- **Right panel:** PESI may categorize young patients without comorbidities as "low risk" - even if they have hemodynamic instability.

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**risk stratification & lysis without a CT scan**

**failing to get a CT scan is a common mistake in (sub)massive PE management**

- CT scans are commonly avoided due to fear that they may cause renal failure from "contrast nephropathy."
- "Contrast nephropathy" from venous contrast for CT scans probably *doesn't exist* (https://emcrit.org/ibcc/contrast/).
- If you truly believe that the patient may have a submassive or massive PE and the patient has renal dysfunction, get a STAT CT scan.
  - The risk of dying from PE is more real and greater than whatever theoretical risk might exist from IV contrast.

**empiric lysis in patient with crashing, massive PE**

- Occasionally, it will be appropriate to proceed directly to thrombolysis in a patient with crashing, massive PE who is too unstable to be transported to the CT scanner.
- This should be done only if there is extremely high suspicion of massive PE, for example:
  - i) Bedside ultrasound shows a DVT, RV dilation, and all other clinical features that are consistent with PE.
  - ii) Patient presents in severe shock following discharge home from orthopedic surgery. Echocardiography and EKG show RV dilation with strain, and there is no evidence of a competing diagnosis.

https://emcrit.org/ibcc/pe/
Beware that empiric thrombolysis without CT scan can create an extremely confusing picture if the patient doesn't improve or starts bleeding (because the initial diagnosis is unclear, and further complexity is piled onto that).

**physiology**

Below is the physiology of sudden death due to PE. This is a vicious cycle, which may rapidly spiral out of control. The cyclical nature of this explains why patients may be stable one minute, but crash the next minute. The remainder of this chapter focuses on how to interrupt this process.

![Pulmonary Embolism Death Spiral](image)

**avoid procedures if possible**

**avoid unnecessary lines & ABGs**

Patients with massive PE will often require thrombolysis. Minor vascular trauma that occurs when placing an arterial or venous line may become a real problem after giving thrombolytics. Thus, unnecessary lines or ABG sticks should be avoided. Peripheral lines are fine for short-term use of vasoressors (especially [epinephrine](https://emcrit.org/pulmcrit/phenylephrine-epinephrine-central-access/)). An ABG or VBG is exceedingly unlikely to change management.

If lines do need to be placed, they should be inserted with extreme care by the most experienced operator with extreme care. For example, a central line should ideally be placed on the first entry into the vessel (rather than by going through the vessel and then pulling back, injuring the back wall of the vessel in the process).

**avoid intubation**

Intubation often precipitates cardiac arrest for several reasons:

- Sedatives may drop the blood pressure.
- Positive pressure within the chest reduces the preload.
- Over-distension of the lungs may compress pulmonary capillaries, increasing the pulmonary vascular resistance.

Whenever possible, intubation should be avoided or delayed:

https://emcrit.org/ibcc/pe/
• High-flow nasal cannula may be used for dyspneic or hypoxic patients to avoid or delay intubation. This may be combined with inhaled pulmonary vasodilators (more on this below).

• If thrombolytics are ordered, try to give the thrombolytics first and then intubate later (or ideally never, if the patient responds to thrombolysis). Unless the patient has lost their mental status or has developed respiratory exhaustion, intubation won’t be beneficial.

If you can’t avoid intubation, the following measures can reduce the risk of cardiac arrest:

• Before intubation, try to increase the systolic blood pressure to ~130-140 mm, usually with an epinephrine infusion. This will give you a margin of error to work with, if the pressure falls following intubation.

• Be prepared with push-dose epinephrine (https://emcrit.org/emcrit/bolus-dose-pressors/) to support the blood pressure after intubation. Have a low threshold for using this for hypotension or worsening bradycardia.

• Consider getting inhaled pulmonary vasopressors at the bedside and ready to be given through the ventilator circuit as soon as the patient is intubated. Administration of a milrinone dose through the endotracheal tube may also be utilized, if this is available.

• Use meticulous pre-oxygenation and apneic oxygenation, paired with intubation by the most experienced operator present. These patients will respond very poorly to hypoxemia or hypercarbia.

• Use sedatives that are hemodynamically stable (e.g. ketamine).

• Following intubation, don’t over-distend the lungs (this will increase pulmonary vascular resistance). Avoid over-vigorous bag ventilation, which will cause excessive intrathoracic pressures.

• Pay extreme attention to the patient’s hemodynamics and oxygenation in the first 10 minutes after intubation, as this is when they are most likely to arrest.
  • The point of greatest risk might be ~5 minutes after intubation, which is often when people stop paying close attention to the patient. Patients may take a little while to slide into the death spiral.
  • The ideal way to achieve this is Weingart’s hemodynamically neutral intubation (https://emcrit.org/emcrit/hemodynamically-neutral-intubation/), but this is a bit involved and may not be possible in many scenarios.

fluid only if clear evidence of hypovolemia (back to contents/ATHE)

ideal fluid balance in massive PE?

• Excess preload may exacerbate RV dilation, which impairs cardiac function.

• The vast majority of patients dying from massive PE will already have elevated filling pressures (due to backup of blood behind a failing right ventricle). The potential risk of fluid generally outweighs the potential benefit in these patients.

general approach

• Evaluate with ultrasound.

• If there is clear evidence of hypovolemia (e.g. small IVC with respirophasic variation), give fluid judiciously and in small amounts.
  • Note that a small IVC should rarely or almost never occur in massive PE. This could conceivably occur if the patient is volume depleted and also has a massive PE. Thus, if you do see a small IVC, think carefully about whether the patient truly has a massive PE.

• If the IVC is dilated, don’t give fluid. Bear in mind that massive PE generally isn’t a fluid-depleted state, so most patients won’t benefit from fluid.

• If the patient has already received a substantial volume of fluid, consider diuresis.

inotropes & vasopressors (back to contents/ATHE)

epinephrine is generally the front-line agent

• Epinephrine may be the front-line agent here, for several reasons (8325096 (https://www.ncbi.nlm.nih.gov/pubmed/8325096)):
  • (a) Beta-agonist activity from epinephrine may cause pulmonary vasodilation.
  • (b) Massive PE causes death due to failure of the right ventricle (it’s fundamentally a form of cardiogenic shock). Beta-agonist stimulation may improve contractility of the right ventricle, thereby improving cardiac output.
• (c) The most common final terminal pathway of pulmonary embolism is often brady-asystolic arrest. The positive chronotropic effects of epinephrine may act to block this event.
• Establishing an adequate mean arterial pressure (e.g. >65 mm) will help ensure adequate perfusion of the right coronary artery and thereby support right ventricular function.
• There is no specific "maximal" dose of epinephrine for use in the patient with massive pulmonary embolism. High doses may be necessary.

Triple action of epinephrine to support cardiac function?

Lactate is widely feared due to its correlation with mortality. However, lactate may serve as a beneficial source of fuel to the myocardium (prospective studies show that infusion of sodium lactate improves cardiac function). Therefore, lactate generation from epinephrine isn’t a bug – it’s a feature. Epinephrine may also be more powerful than dobutamine due to stimulation of cardiac beta-2 receptors. Overall, there are probably good reasons that humans evolved to secrete epinephrine in the face of physiologic stress.

— The Internet Book of Critical Care, by @PulmCrit

**vasopressin may be used as a second-line agent**

• Vasopressin causes systemic vasoconstriction, while simultaneously causing pulmonary vasodilation. Beneficial effects on the pulmonary vasculature make vasopressin a good choice in pulmonary hypertension.
• The typical dose range might be similar to a sepsis dose (e.g. 0–0.06 U/min)(27483065). (https://www.ncbi.nlm.nih.gov/pubmed/27483065)
• Vasopressin is generally used as a second-line agent because it’s not tremendously powerful and it is difficult to titrate (with a half-life of ~20 minutes, its onset and offset are sluggish).

**inhaled pulmonary vasodilators**

(back to contents/atri)

**why inhaled pulmonary vasodilators may be helpful:**

• May improve oxygenation by improving ventilation-perfusion matching.
• May improve hemodynamics (afterload-reduction of the right ventricle compensates for obstruction due to clot).
  • Much of the hemodynamic deterioration due to PE isn’t due to the clot itself, but rather to pulmonary vasoconstrictors which are released in response to the clot. Pulmonary vasodilators are a rational approach to combat this.

**evidentiary basis for pulmonary vasodilators**

• The iNOPE trial randomized 76 patients with submassive PE to placebo vs. inhaled nitric oxide at 50 ppm for 24 hours. Inhaled nitric oxide increased the likelihood of having a normal-sized right ventricle. It was well tolerated without any adverse events (more discussion of this study here).

**choice of nitric oxide vs. epoprostanol**

• There isn’t strong evidence comparing one agent to the other. Overall, available evidence generally finds no huge differences between the two agents.
  • In practice, the best agent is whatever you can get to the patient’s bedside fastest.
  • Both agents can be given to non-intubated patients or to intubated patients.
• If you don’t have access to pulmonary vasodilators, keep in mind that oxygen causes pulmonary vasodilation as well.
  • High FiO2 oxygen is a poor-person’s pulmonary vasodilator.
Nitric oxide and epoprostanol act via different mechanisms, so they can be used together in attempts to target synergistic pulmonary vasodilation.

**anticoagulation (heparin)**

### background on heparin

- Heparin prevents additional clot from forming, but it doesn't break down existing clot.
- Heparin started being used prior to the era of evidence-based medicine. Consequently, there is essentially no high-quality evidence regarding the use of heparin in PE.
- Retrospective time-to-intervention studies suggest that early heparin has a huge mortality benefit. These studies are likely flawed (https://emcrit.org/pulmcrit/the-fallacy-of-time-to-intervention-studies/), and overall are extremely dubious.
- For patients with (sub)massive PE who are receiving tPA or who will immediately receive tPA, heparin increases the risk of bleeding without providing any proven benefit.

### unfractionated heparin is preferred in sub(massive) PE

- For *most* pulmonary emboli, low molecular-weight heparin has been shown to have a lower risk of bleeding. Thus low molecular-weight heparin is usually the preferred form of heparin for low-risk pulmonary emboli.
- For (sub)massive PE, unfractionated heparin is generally preferred for the following reasons (31185730 https://www.ncbi.nlm.nih.gov/pubmed/31185730):
  - (a) Can be stopped if the patient begins hemorrhaging.
  - (b) Can be paused or down-titrated in anticipation of thrombolysis or procedures.

### approach to anticoagulation in (sub)massive PE

- Below is my preferred strategy for anticoagulation.

![Anticoagulation strategy in (sub)massive PE](https://emcrit.org/wp-content/uploads/2019/09/anticoastrat.png)

**thrombolysis: evidentiary basis**

The use of thrombolysis for *massive PE* is widely accepted as the standard of care. This has been shown to reduce mortality and PE recurrence compared to anticoagulation alone (30325344 https://www.ncbi.nlm.nih.gov/pubmed/30325344), 15262836 https://www.ncbi.nlm.nih.gov/pubmed/15262836, 22325236 https://www.ncbi.nlm.nih.gov/pubmed/22325236). The controversial bit is the use of thrombolysis for *submassive* PE, which is explored further below.
For a while, it was believed that thrombolysis would reduce the risk of chronic thromboembolic pulmonary hypertension and thereby improve long-term functional endpoints. The long-term results of the PEITHO trial convincingly disproved this (https://www.ncbi.nlm.nih.gov/pubmed/28335835). This simplifies matters considerably. Currently the primary reason to use thrombolysis is to reduce the risk of cardiac arrest.

Unfortunately, the evidence on thrombolysis remains murky for the following reasons:

1. Studies usually include a heterogeneous group of patients with a range of PE severity and age. This tends to cause large studies to have a neutral outcome.
2. The absolute magnitude of benefit is relatively small, which causes many studies and meta-analyses to be underpowered.
3. Studies often overlap thrombolysis and heparin anticoagulation in a dangerous fashion, with subsequent attribution of bleeding events to the thrombolytic agent.
4. Studies involve different thrombolytic drugs and at varying dosages, which limits generalizability between studies.

For the above reasons, there is no large, multi-center RCT which has unequivocally proven the benefit of thrombolysis in submassive PE. Meta-analyses have suggested that thrombolysis reduces all-cause mortality in submassive PE, but this finding is not robust; see figure below (29175415; 24938564). In order to construct a logical argument regarding the use of thrombolysis in submassive PE, we need to extrapolate the results from numerous studies as below.

**Figure 3. Odds of Mortality in Patients With Intermediate-Risk Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation**

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>No. of Patients</th>
<th>No. of Patients</th>
<th>OR (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
<th>Weight, %</th>
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<td>35</td>
<td>0.11 (0.02-0.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOPETT, 2012</td>
<td>1</td>
<td>61</td>
<td>3</td>
<td>60</td>
<td>0.35 (0.03-2.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ULTIMA, 2013</td>
<td>0</td>
<td>30</td>
<td>1</td>
<td>29</td>
<td>0.13 (0.00-6.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOPCAT, 2014</td>
<td>1</td>
<td>40</td>
<td>1</td>
<td>43</td>
<td>0.98 (0.77-1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEITHO, 2014</td>
<td>6</td>
<td>596</td>
<td>9</td>
<td>499</td>
<td>0.66 (0.24-1.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>866</td>
<td>26</td>
<td>889</td>
<td>0.48 (0.23-0.93)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meta-analyses disagree about whether thrombolysis improves mortality in sub-massive PE. This analysis in JAMA found a mortality benefit, but other meta-analyses have not (Chatterjee S et al. JAMA 311:2414). Any evidence of benefit here (whether or not statistically significant) suggests that benefit exists for patients with high-risk submassive PE (because patients in the high-risk subgroup would be expected to have greater benefit than the entire pool of patients with both low-risk submassive PE and high-risk submassive PE).

**principle #1: thrombolysis reduces the risk of cardiovascular collapse**

Thrombolysis has been shown in several studies to cause an immediate reduction in pulmonary vascular resistance and thus an immediate improvement in right ventricular function. This relieves RV strain, and reduces the risk of acute RV failure.

- Two multi-center RCTs have shown that thrombolysis decreases the risk of hemodynamic deterioration (MAPPET and PEITHO).
- Overall, numerous studies support the concept that thrombolysis will considerably reduce the likelihood of cardiovascular collapse (by ~50%)(30560579).

**principle #2: thrombolysis with alteplase is safer than is usually thought**

- It is widely believed that alteplase carries a high risk of intracranial hemorrhage. However, this is not supported by high-quality prospective evidence.
- The risk of intracranial hemorrhage due to alteplase in prospective RCTs is shown in the table below. Available studies are underpowered to clearly define the risk of intracranial hemorrhage, but it seems to be low. Particularly for reduced-dose regimens of alteplase (e.g. 50 mg), the risk is likely <1%.
- This risk may be minimized by avoiding simultaneous exposure to alteplase and heparin (more on this below).
A patient is actively dying from PE and there aren’t good options, it may be necessary to use thrombolysis despite the presence of an absolute contraindication. For example, CNS neoplasm is listed as an "absolute" contraindication, but case reports do exist of such patients receiving thrombolysis. If the patient has a >5% risk of cardiac arrest due to PE, then they should benefit from thrombolysis:

- Added risk of intracranial hemorrhage = 1%
- Reduction in rate of cardiac arrest = (>5%)/(>50%) = >2.5%
- The exact numbers here are debatable. However, overall, a patient at real risk from dying of PE (e.g., with a short-term mortality of >5%) is likely to benefit from thrombolysis.
- Of course, benefit is best assessed on a patient-by-patient basis, weighing the risk of death from PE versus the risk of bleeding due to thrombolysis.

---

### Complication rates of placebo-controlled RCTs involving thrombolysis for PE

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Regimen</th>
<th>ICH rate, Heparin + Placebo</th>
<th>ICH rate, Heparin + Alteplase</th>
<th>Major hemorrhage, Heparin + Placebo</th>
<th>Major hemorrhage, Heparin + Alteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICPED 1990</td>
<td>40-80 mg alteplase</td>
<td>0/4</td>
<td>0/9</td>
<td>0/4</td>
<td>1/9</td>
</tr>
<tr>
<td>Levine 1990</td>
<td>0.6 mg/kg alteplase</td>
<td>0/25</td>
<td>0/33</td>
<td>3/25</td>
<td>3/33</td>
</tr>
<tr>
<td>Dalla-Volta 1992</td>
<td>100 mg alteplase</td>
<td>0/16</td>
<td>1/20</td>
<td>2/16</td>
<td>3/20</td>
</tr>
<tr>
<td>Konstantinides 2002 (PURIT)</td>
<td>100 mg alteplase</td>
<td>0/138</td>
<td>0/118</td>
<td>5/138</td>
<td>1/118</td>
</tr>
<tr>
<td>Passo 2011</td>
<td>100 mg alteplase</td>
<td>0/35</td>
<td>0/37</td>
<td>1/35</td>
<td>2/37</td>
</tr>
<tr>
<td>Sharp 2012 (HOPIT)</td>
<td>50 mg alteplase</td>
<td>0/60</td>
<td>0/61</td>
<td>0/60</td>
<td>0/61</td>
</tr>
</tbody>
</table>

All Alteplase vs. placebo trials: 0/278 (0.4%) 1/278 (0.4%) 11/278 (4.0%) 10/278 (3.6%)

### Tenecteplase versus placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>ICH rate, Heparin + Placebo</th>
<th>Major hemorrhage, Heparin + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boccati 2010</td>
<td>0/30</td>
<td>1/28</td>
</tr>
<tr>
<td>Mayer 2014 (PEITHO)</td>
<td>1/499</td>
<td>10/506</td>
</tr>
<tr>
<td>Klene 2014 (TOPCAT)</td>
<td>0/43</td>
<td>1/40</td>
</tr>
</tbody>
</table>

All Tenecteplase vs. placebo: 1/572 (0.2%) 12/574 (2.1%) 12/572 (2.3%) 61/574 (11%)

---

**principle #3: complete resolution of clot isn’t necessary**

- The goal of lytic therapy isn’t to normalize the pulmonary pressures, but rather merely to cut back pressure sufficiently to prevent sudden cardiac death.
- A moderate reduction in pulmonary pressure may be achievable with a lower dose of thrombolytic than has been used traditionally (e.g. 12-50 mg alteplase). This may carry a lower risk of hemorrhage, thereby improving the overall risk/benefit ratio.

### risk-benefit calculus

- Let’s approximate the risk of systemic thrombolysis as a 1% risk of intracranial hemorrhage. This is probably higher than the true risk (especially if reduced doses are used with avoidance of simultaneous heparin use).
- If a patient has a >5% risk of cardiac arrest due to PE, then they should benefit from thrombolysis:
  - Added risk of intracranial hemorrhage = 1%
  - Reduction in rate of cardiac arrest = (>5%)/(>50%) = >2.5%
- The exact numbers here are debatable. However, overall, a patient at real risk from dying of PE (e.g., with a short-term mortality of >5%) is likely to benefit from thrombolysis.
  - Of course, benefit is best assessed on a patient-by-patient basis, weighing the risk of death from PE versus the risk of bleeding due to thrombolysis.

---

**thrombolysis: contraindications**

- Start by reviewing the patient’s medications, history, and coagulation labs.
- Contraindications are traditionally divided into “relative” and “absolute” contraindications, but this must be taken into clinical context. For example, CNS neoplasm is listed as an “absolute” contraindication, but case reports do exist of such patients receiving thrombolysis. If the patient is actively dying from PE and there aren’t good options, it may be necessary to use thrombolysis despite the presence of an “absolute” contraindication.
  - Please note that some “absolute contraindications” to thrombolysis in PE (e.g. ischemic stroke) are actually indications for thrombolysis in other situations! So these aren’t truly “absolute” contraindications.

### contraindications to thrombolysis: a primer

- Start by reviewing the patient’s medications, history, and coagulation labs.
- Contraindications are traditionally divided into “relative” and “absolute” contraindications, but this must be taken into clinical context. For example, CNS neoplasm is listed as an “absolute” contraindication, but case reports do exist of such patients receiving thrombolysis. If the patient is actively dying from PE and there aren’t good options, it may be necessary to use thrombolysis despite the presence of an “absolute” contraindication.
  - Please note that some “absolute contraindications” to thrombolysis in PE (e.g. ischemic stroke) are actually indications for thrombolysis in other situations! So these aren’t truly “absolute” contraindications.
Brain/spinal cord pathology
- Hemorrhagic CVA (absolute)
- Ischemic CVA (absolute if within 3 months; otherwise relative)
- Known vascular lesion, e.g. arteriovenous malformation (absolute)
- Brain or spinal surgery (absolute if recent)
- CNS tumor (relative)
- Diabetic retinopathy (relative)

Trauma/surgery/procedure
- Recent head trauma with fracture or brain injury within three weeks (absolute).
  - Minor head trauma due to syncope isn’t necessarily a barrier to fibrinolysis (AHA/ACC 2011).
- Major non-CNS surgery within 2-3 weeks (relative)
- Recent puncture of non-compressible vessel (relative)

Bleeding history
- Serious active bleeding, excluding menses (absolute)
- Recent internal bleeding within 4 weeks (relative)
- Known coagulopathy

Coagulation studies
- Platelets < 100,000 (relative)
- Warfarin use with INR > 1.7 (relative)
- Fibrinogen < 150 mg/dL (relative; usually don’t delay treatment in massive PE if fibrinogen is unknown)

Anticoagulants
- Oral anticoagulation (relative)
- Multiple anticoagulants, e.g. anti-platelet agents (relative)

HTN
- History of chronic, severe, poorly controlled HTN (relative)
- Blood pressure on presentation > 180 systolic or > 110 diastolic (relative)

Age
- > 75 years old (relative)
- Dementia (relative)

Specific situations
- Pregnancy or first week post-partum (relative)
- Infectious endocarditis (relative)
- Advanced cirrhosis (relative)

PE-CH score
- Tool to predict risk of intracranial hemorrhage during thrombolysis for PE (27882375). This was generated and validated using a large dataset from community hospitals in the United States.

Tally points for the patient:
- Peripheral vascular disease = 1 point
- Age > 65YO = 1 point
- Prior cerebrovascular accident with residual deficit = 5 points
- Prior myocardial infarction = 1 point

Risk of intracranial hemorrhage following systemic thrombolysis:
- 0 points = 1.2%
- 1 point = 2.9%
- 2 points = 3.4%
- 5 points or more = 18%

This was based on retrospective data, with attribution of every intracranial hemorrhage to thrombolysis (as opposed to heparin, or other causes). As such, it will inevitably over-estimate the risk of intracranial hemorrhage caused by thrombolysis. However, this may remain a reasonable tool to roughly gauge relative risk. The key point is that patients with vascular disease anywhere in their bodies (e.g. coronary arteries, peripheral arteries) are at risk of occult cerebrovascular disease which will lead to an increased risk of intracranial hemorrhage.
Thrombolysis for PE is used far less often than thrombolysis for ischemic stroke or myocardial infarction. This has led many of our practices regarding PE thrombolysis to be borrowed from thrombolysis for stroke or for myocardial infarction. For example, the list of absolute and relative contraindications above seems to be adapted from the literature on myocardial infarction and stroke.

One aspect of thrombolysis borrowed from the MI and stroke literature seems to be the dose. Full-dose alteplase for pulmonary embolism (100 mg alteplase) is very similar to regimens used for myocardial infarction (maximal dose 100 mg) and stroke (maximal dose 90 mg). This was probably a big mistake.

**why PE requires lower doses of alteplase than MI or stroke:**

- 100% of the infused dose of alteplase will go to the pulmonary arteries (as opposed to, for example, ~5% of the blood flow going to the coronary arteries in myocardial infarction).
- The half-life of alteplase is ~4 minutes, meaning that each molecule of alteplase will pass through the lungs about five times.
- 100% of the occlusion in PE is due to clot formation. Compare this, for example, to a coronary artery which may be partially occluded due to plaque with a moderate contribution due to acute clot formation.
  - The greater the amount of vessel occlusion that is due to clot, the greater the efficacy of thrombolysis (and thus a lower dose is required).
- We don't need complete resolution of the clot – all that is required to improve patient outcomes is a partial improvement.
  - Immediately opening some pulmonary arteries (while other pulmonary arteries remain occluded) may be adequate to produce an excellent clinical outcome.

**evidence that surprisingly low doses of alteplase are effective:**

- The literature contains numerous case reports and case series describing the use of extremely low doses of alteplase (e.g. 4 mg) in PE used for patients with contraindication to higher doses. These reports aren't definitive, but suggest that small doses of alteplase may be much more effective than we believe, particularly for fresh thrombus (21127275).
- The OPTALYSE PE trial was a prospective trial comparing different regimens of alteplase administered via catheter-directed thrombolysis. There was no apparent difference in efficacy between doses of ~8 mg and ~24 mg. This suggests that low doses of alteplase may be much more effective than we realize (further discussion of this study here).
- Aykan 2014 published a case series describing the use of 25 mg alteplase infusions over 6 hours in high-risk PE patients with contraindications to higher doses of thrombolytic. This relatively low dose of alteplase caused a dramatic drop in pulmonary artery systolic pressure (from 57 mm to 34 mm) – essentially identical to effects that might be expected from 50-100 mg alteplase. The dose was well tolerated, with no serious hemorrhagic complications (despite use in patients at increased risk of bleeding). This, again, indicates that low doses of alteplase may be entirely adequate to cause clinical improvement.
“half-dose” thrombolysis

- Typical regimen based on the MOPETT trial:
  - Alteplase dose = 0.5 mg/kg up to a maximal dose of 50 mg (https://www.ncbi.nlm.nih.gov/pubmed/23102885).
  - First 10 mg infused as a bolus, followed by remainder over 2 hours.
- 50 mg alteplase has been shown to have identical efficacy compared to 100 mg alteplase, with fewer bleeding complications (figure below) (19741062, https://www.ncbi.nlm.nih.gov/pubmed/19741062). These same results have been found in other studies and meta-analyses as well (30068253, https://www.ncbi.nlm.nih.gov/pubmed/30068253).

“full-dose” thrombolysis

- 100 mg IV alteplase (TPA) over 2 hours has traditionally been considered as “full dose” thrombolysis, for use in massive pulmonary embolism.
- This dose was selected in an arbitrary fashion. There is no evidence supporting the use of this dose, as compared to a lower dose.
  - 100 mg is probably an excessive dose for almost all patients.
- For patients with crashing massive PE, the initial ~20 mg may be given as an IV push (with the remaining medication infused over two hours).

Examples of balancing risk vs. benefit of lytic therapy

<table>
<thead>
<tr>
<th>Low-Risk PE</th>
<th>No lytic contraindication (including &lt;65 YO)</th>
<th>Relative lytic contraindication</th>
<th>Absolute lytic contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation alone</td>
<td>Anticoagulation alone</td>
<td>Anticoagulation alone</td>
<td></td>
</tr>
</tbody>
</table>

| Low-risk Submassive PE | Anticoagulation alone | Anticoagulation alone | Anticoagulation alone |

| High-risk Submassive PE | 0.5 mg/kg up to max dose of 50 mg TPA (over 2 hours) | 25 mg TPA as slow infusion (peripheral IV vs. catheter-directed thrombolysis) | Anticoagulation alone +/- IR dot removal |

| Non-crashing Massive PE | 100 mg TPA over 2 hours (Repeat PRN) | IR dot removal or surgical embolectomy |

| Crashing Massive PE | 100 mg TPA over 2 hours (give initial ~20 mg as bolus) | 100 mg TPA over 2 hours (give initial ~20 mg as bolus) | IR dot removal or surgical embolectomy |

The dose-response curve for alteplase in PE remains almost entirely unknown. The fact that such a simple question remains unanswered is a scientific embarrassment (and a reflection of research priorities which largely reflect marketable devices rather than medical therapy). My guess is that it might look something like this.
“quarter-dose” thrombolysis (25 mg alteplase)

- The ideal dose of alteplase in PE remains unknown. As discussed above, the optimal dose is probably lower than generally used (e.g. perhaps in the range of 15-40 mg).
- The most evidence-based approach to using quarter-dose thrombolysis is to provide this as a slow infusion (e.g. 1 mg/hour). This is identical to the use of alteplase in catheter-directed thrombolysis for PE or DVT (except that drug is infused into a peripheral vein). The safety of this regimen has been established by dozens of studies over many years, with a risk of intracranial hemorrhage on par with a standard heparin infusion. Its efficacy in PE is less well established in the literature, but it does seem to work.
  - This is an alternative to catheter-directed thrombolysis, depending on availability and local norms.
- One protocol for this is shown below. An essential component of this strategy is close monitoring for hemorrhage or excess coagulopathy, with the ability to immediately stop the alteplase infusion if necessary.
- More discussion of this strategy here (https://emcrit.org/pulmcrit/ultrasound-assisted-thrombolysis-pulmonary-embolism-alteplase/).
**Fallacy of using fixed doses of alteplase**

- Nearly all studies of thrombolysis in PE are based on using specific dosing regimens across an entire population of patients. However, this strategy is deeply flawed because the balance of fibrinolysis vs. fibrin generation is extremely complex and variable between patients. Therefore, different patients may respond to the same dose of thrombolytic in **dramatically** different ways.
- For a patient who isn't actively dying, the most sensible approach could be to provide titrated doses of fibrinolytic, while closely monitoring coagulation parameters (especially fibrinogen). There are roughly two ways to do this:
  - (a) Administration of fibrinolytic as a continuous slow infusion, with monitoring of coagulation parameters over time (commonly done in interventional radiology and also described immediately above).
  - (b) Intermittent administration of reduced doses of thrombolytic (e.g. 10-25 mg alteplase) with re-evaluation of clinical and coagulation parameters prior to the administration of each dose.

**Coordination of heparin & tPA**

*How to coordinate the use of heparin and thrombolysis remains a largely evidence-free zone. Available evidence regarding this is explored in detail in a prior blog [here](https://emcrit.org/pulmcrit/fibrinogen_pe/).*

**Before thrombolysis: ideally stop heparin and allow it wear off**

- Heparin anticoagulation and thrombolysis can be performed simultaneously, but this is generally not preferred.
  - The MOPPETT trial combined full-dose anticoagulation with enoxaparin (1 mg/kg q12hr) with half-dose tPA.
  - The PEITHO trial combined full-dose anticoagulation with heparin and thrombolysis (which is probably why they had a very high rate of intracranial hemorrhage).
  - So, a patient who is anticoagulated (e.g. with enoxaparin) and develops hemodynamic instability can receive thrombolysis.
- For a patient undergoing systemic thrombolysis, heparin increases the risk of bleeding without providing any proven additional benefit.
- Ideally, heparin will be stopped and allowed to clear from the patient prior to systemic thrombolysis. This may be possible for hemodynamically stable patients with submassive pulmonary embolism, but not for patients with massive pulmonary embolism.

**After thrombolysis: when to resume heparin?**

- Although tPA has a short half-life, it causes several persistent abnormalities in the coagulation system, including:
  - (1) Reduced fibrinogen levels.
  - (2) Fibrinogen degradation coagulopathy (degraded bits of fibrinogen actually exert anticoagulant effects!).
  - (3) Reduced platelet function (due to cleavage of glycoprotein Ib receptors on the platelet surface) [30474416](https://www.ncbi.nlm.nih.gov/pubmed/30474416).
- The traditional approach has been to resume heparin (without a bolus) when the PTT is below 1.5-2 times normal.
- Checking a fibrinogen level prior to heparin resumption makes sense, given that tPA may have unpredictable effects on fibrinogen levels. It may be reasonable to avoid resumption of heparin infusion until fibrinogen is over ~100-150 mg/dL.
- Overall, if the patient has a favorable response to thrombolysis (clinical improvement, weaning off vasopressors), then waiting longer before resumption of heparin may increase safety and reduce the likelihood of hemorrhage.

**Illustration of what happens when heparin and alteplase are combined in a suboptimal fashion:**
tenecteplase

As shown in the following table, tenecteplase has been associated with a higher rate of bleeding than alteplase (25457585)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Regimen</th>
<th>ICH rate, Heparin + Placebo</th>
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<td>0/9</td>
<td>0/4</td>
<td>1/9</td>
</tr>
<tr>
<td>Levine 1990</td>
<td>0.6 mg/kg alteplase</td>
<td>0/25</td>
<td>0/13</td>
<td>3/25</td>
<td>3/33</td>
</tr>
<tr>
<td>Dalla-Volta 1992</td>
<td>100 mg alteplase</td>
<td>0/16</td>
<td>1/20</td>
<td>2/16</td>
<td>3/20</td>
</tr>
<tr>
<td>Kontantinou 2002</td>
<td>100 mg alteplase</td>
<td>0/138</td>
<td>0/118</td>
<td>5/138</td>
<td>1/118</td>
</tr>
<tr>
<td>Tansio 2011</td>
<td>100 mg alteplase</td>
<td>0/35</td>
<td>0/37</td>
<td>1/35</td>
<td>2/37</td>
</tr>
<tr>
<td>Sharp 2012</td>
<td>Up to 100 mg alteplase</td>
<td>0/60</td>
<td>0/61</td>
<td>0/60</td>
<td>0/61</td>
</tr>
<tr>
<td><strong>All Alteplase vs. placebo trials</strong></td>
<td><strong>0/278</strong></td>
<td><strong>1/278 (0.4%)</strong></td>
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<td>1/30</td>
<td>2/28</td>
</tr>
<tr>
<td>Mayer 2014</td>
<td>(PEITHO)</td>
<td>1/499</td>
<td>10/506</td>
<td>12/499</td>
<td>58/506</td>
</tr>
<tr>
<td>Kliew 2014</td>
<td>(TOPCAT)</td>
<td>0/43</td>
<td>1/40</td>
<td>0/43</td>
<td>1/40</td>
</tr>
<tr>
<td><strong>All Tenecteplase versus placebo</strong></td>
<td><strong>1/572 (0.2%)</strong></td>
<td><strong>12/574 (2.1%)</strong></td>
<td><strong>13/572 (2.3%)</strong></td>
<td><strong>61/574 (11%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Review of this raw data leads to some interesting conclusions. First, tenecteplase leads to a higher hemorrhage risk than alteplase (so tenecteplase-based trials cannot be generalized to reach conclusions about alteplase). Second, the risk of bleeding from alteplase is relatively low. Only one intracranial hemorrhage is seen, in a trial involving 100 mg alteplase. Of course, bleeding rates of patients outside RCTs will be higher.

The reason that tenecteplase has been associated with more bleeding is unclear. It may relate to a dosing issue, wherein studies have generally used "full dose" tenecteplase (i.e. the same dose as is used for thrombolysis of STEMI). It could relate to the use of simultaneous boluses of tenecteplase and heparin in the PEITHO trial (which is a formula for disaster).

Based on the above data and overall greater breadth of experience using alteplase, the front-line lytic choice for PE is currently alteplase. If alteplase isn’t available, tenecteplase could certainly be used for massive PE. Tenecteplase is a bit easier to reconstitute, so it’s possible that tenecteplase might have an advantage in PE-induced cardiac arrest if it were quicker to access.

interventional radiology
catheter-directed thrombolysis

- This involves placement of bilateral catheters into the pulmonary arteries to directly infuse tPA in close proximity to the clot. (Occasional patients may have unilateral clot, but in most patients there is bilateral clot requiring bilateral catheters.)
- There is little theoretical or evidentiary support for why catheter-directed thrombolysis should be superior to administration of an identical dose of tPA via peripheral circulation (all tPA infused peripherally will be transported directly to the pulmonary circulation).
  - All available studies have been funded by pharma. These studies compared catheter-directed thrombolysis to either anticoagulation with heparin (which is a straw-person comparator) or performed a one-arm study with no comparator group at all. The unwillingness of pharma to fund a meaningful RCT comparing peripheral versus catheter-directed thrombolysis is conspicuous (24226805, 26315743).
  - One RCT is currently underway to finally attempt to clarify whether catheter-directed thrombolysis is any better than administration of an equal dose of tPA via peripheral vein (NCT03581877).
- Some catheters use ultrasound energy in efforts to break up the clot. Available data suggests that ultrasound energy has no benefit. Overall, the addition of ultrasound seems to be a worthless frill added by device companies in efforts to market an expensive catheter (25856269, 27630267).
- The main benefit of catheter-directed thrombolysis likely stems merely from the use of low-dose thrombolysis. This is a safe and effective treatment which may be very beneficial—especially in a hospital which is uncomfortable with the use of low dose peripheral thrombolytics (a common issue).
- Traditionally, the most common dose of tPA has been 0.5-1 mg/hour per catheter for a total dose of 12-24 mg delivered over a 24 hour period (31185730). The recent OPTALYSE trial suggested that tPA may be more effective than previously believed, such that the optimal dose might be ~8-12 mg total (30025734).
- The optimum dosing of unfractionated heparin during catheter-directed thrombolysis is unknown. The safest approach might be a fixed low-dose infusion at ~500-1,000 units/hour (31185730).

Ronald Winokur, MD, FSIR, RPVI
@RonaldWinokurMD

Amazing immediate results with @InariMedical. 12 mmHg pressure reduction and immediate symptomatic improvement @JeffersonRads. Hard to deny the immediate response and lack of tPA related bleeding risk. TBD on long term meaningful benefit @akhileshsistaMD
percutaneous mechanical thrombectomy

- The true benefit of interventional radiology probably lies in physical clot extraction.
- Potential indications:
  - Patients with high-risk submassive or massive PE with contraindication to thrombolysis.
  - Patients in whom thrombolysis has failed to be effective.
- The evidence basis for clot extraction is relatively sparse. Furthermore, this is an operator-dependent procedure, so evidence may not necessarily be generalizable from one center to another center. Results are likely to be superior at high-volume centers.
- Various devices are available, as follows:
  - **Inari FlowTriever system**
    - Device designed to remove clot from the pulmonary arteries (see video below).
    - FLARE study: Single-arm trial involving 106 patients with submassive PE treated with the FlowTriever. A substantial reduction in RV/LV ratio was achieved (from 1.56 to 1.15 over 48 hours, on average). Nearly all patients received no thrombolytic, so this was a true study of mechanical intervention. The rate of severe adverse events was low, at 4% ([31072507](https://www.ncbi.nlm.nih.gov/pubmed/31072507)).
    - Further evidence is needed to see how this device will work outside the confines of a clinical trial. However, available evidence looks very promising at this stage.
  - **Prenumbra Indigo embolectomy system**
    - Currently supported by case reports, with a prospective multi-center trial ongoing (NCT03218566).
  - **AngioVac**
    - Large (22F) catheter that removes emboli through a centrifugal pump with blood return (similar to cardiopulmonary bypass).
    - Best for clots in the inferior vena cava or right ventricle (accessing the pulmonary artery is difficult and may increase the complication rate) ([31185730](https://www.ncbi.nlm.nih.gov/pubmed/31185730)).
  - **AngioJet**
    - Device designed to break up clot within the vasculature.
    - Has earned a black box warning from the FDA by causing numerous adverse events (including bradycardia, massive hemoptysis, and renal failure). Available evidence doesn't support its use.

![](inari_flowtriever_retrieval_aspiration_system.png)

surgical thrombectomy

For many years, surgical thrombectomy was believed to be excessively dangerous and generally unhelpful. However, this procedure has made a resurgence over the past decade. Currently the mortality of the procedure is roughly 10%, which can be reasonable in selected patients at very high risk of death from PE ([31185730](https://www.ncbi.nlm.nih.gov/pubmed/31185730), [28942971](https://www.ncbi.nlm.nih.gov/pubmed/28942971), [27373187](https://www.ncbi.nlm.nih.gov/pubmed/27373187)).
potential indication for surgical thrombectomy

- Clot-in-transit which is lying across a patent foramen ovale (PFO). This situation carries a risk of immediate stroke if the clot breaks up and parts of it enter the systemic circulation. Therefore, surgery may be a front-line intervention in this rare scenario.
- Massive PE in a patient with absolute contraindication to thrombolysis.
- Massive PE with failure of other interventions (e.g. lytic failure).
  - ~10% of clots will not respond to thrombolysis (perhaps because they are chronic and have undergone organization).

surgical thrombectomy vs. interventional radiology clot extraction

- Currently no high-level evidence exists comparing these modalities.
- Advances in catheter embolectomy (e.g. Inari Flowtriever system) could make interventional radiology approaches superior in many cases. However, further study is needed.

Patients with (sub)massive PE may be excellent candidates for VA-ECMO if this therapy is available. Unless patients have suffered from severe anoxic brain injury (due to cardiac arrest) or have other active problems, they should generally improve if they can be supported. The role of VA-ECMO is largely defined by available resources, with some potential utilizations listed below.

Potential indications for ECMO may include the following:

- Massive PE in a patient with absolute contraindication to thrombolysis.
- Stabilization of a patient with massive PE prior to intubation.
- Patient with massive PE and persistent instability despite thrombolysis (lytic failure).
Potential roles for VA ECMO may include:

- Bridge to anticoagulation efficacy: Over time, patients will generally degrade clot on their own (with systemic anticoagulation to prevent additional thrombosis). Thus, ECMO alone may be sufficient to support the patient for several days to allow natural thrombolysis.
- Bridge to controlled thrombolysis: ECMO could be used to support a patient while undergoing gradual thrombolysis (e.g. 1-2 mg/hour tPA infusion either systemically or via catheter-directed lysis).
- Bridge to intervention: ECMO could be used as a bridge to other definitive therapies (e.g. catheter-directed thrombolysis or cardiothoracic surgery).

No high-level evidence exists regarding VA-ECMO in PE, nor is such evidence likely to emerge in the near future (given how rare this situation is). The main limitation of ECMO is that it is available only in a limited number of centers.

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**IVC filter**

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Potential clinical effects of an IVC filter include:

- Might intercept clots traveling to the lungs (thereby avoiding pulmonary embolism).
- Might increase stasis of blood in the legs (thereby increasing the risk of deep vein thrombosis).
- Might become thrombosed, leading to occlusion of blood in the inferior vena cava.
- Might cause a procedural complication (e.g. filter embolization or bleeding).
  - Penetration of the vena cava wall occurs in 19% of procedures! ([26169756](https://www.ncbi.nlm.nih.gov/pubmed/26169756)).

From a theoretical standpoint, an IVC filter is a bit of a wild card. It may cause both potential benefit and potential harm. There is no good evidentiary support for the IVC filter (previously discussed [here](https://emcrit.org/pulmcrit/what-is-the-evidence-behind-the-ivc-filter/)). The most relevant study with regards to submassive PE is PREPIC-2, which showed that IVC use in patients with large PE on anticoagulation caused a trend towards harm.

Traditionally, IVC filters have been utilized among patients with contraindication to anticoagulation. However, there is precisely zero evidence that IVC filters are beneficial for that situation. Inability to anti-coagulate may increase the risk of IVC filter thrombosis.

Overall, there is no good evidence that the theoretical benefits of IVC filters outweigh their numerous risks. The placement of thousands of IVC filters over decades is a case study in fear-based medical practice, reinforced by eminence-based guidelines ([23552611](https://www.ncbi.nlm.nih.gov/pubmed/23552611)). That being said, IVC filter placement might be reasonable if all the following criteria are met:

1. Inability to receive anticoagulation.
2. (Sub)massive PE with a low hemodynamic reserve.
3. Known DVT with large clot burden (especially large, free-floating, proximal DVT).

If an IVC filter is placed, a retrievable filter should be used. This should be removed at the first available opportunity. Unfortunately, it requires much less courage to insert a DVT filter than to remove it. Consequently, studies consistently show that most "retrievable" IVC filters are not in fact retrieved ([28123984](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5220200/)). Prolonged filter implantation increases the risk of retrieval failure, filter migration, IVC perforation, filter embolization, or filter thrombosis ([31185730](https://www.ncbi.nlm.nih.gov/pubmed/31185730)).

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**(sub)massive PE in a patient with hemoptysis**

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Hemoptysis from PE is a result of pulmonary infarction. This typically occurs somewhat later in the natural course of the PE (after the central clot breaks up and fragments migrate distally). As such, it's a bit unusual for a patient with submassive or massive PE to have hemoptysis. Hemoptysis is usually seen during a recovery phase, at which point the patient no longer has a large central clot burden.
Hemoptysis from PE reflects necrosis of lung tissue from infarction, which causes bleeding from pulmonary capillaries and veins. Since bleeding doesn't originate from the pulmonary arteries, the bleeding is generally minor. It is extremely unusual for a patient to have massive hemoptysis due to PE. As a rule, anticoagulation can be continued despite hemoptysis. Likewise, hemoptysis is only a relative contraindication to thrombolysis.

**key points**

- Hemoptysis from PE is generally minor, and almost never life-threatening.
- Hemoptysis *shouldn't* have a major impact on the treatment strategy for PE.
- Don't stop anticoagulation due to hemoptysis (unless the hemoptysis is unusually brisk).

**(sub)massive PE in a patient with ST elevation**

Pulmonary embolism is a *known cause* of ST elevation. More on the EKG manifestations of PE [here](https://emcrit.org/pulmcrit/two-ekg-patterns-of-pulmonary-embolism-which-mimic-mi/).

In cases of diagnostic uncertainty regarding ST elevation MI vs. PE, the best approach may be immediate bedside echocardiography.

- ST elevation MI should cause regional wall motion abnormalities involving the left ventricle and dysfunction of the left ventricle.
- Massive PE will cause RV dilation and usually an under-filled left ventricle (which is vigorously contracting).

**key points**

- If a patient with known submassive/massive PE develops ST elevation, this is most likely due to the PE itself.
- Treatment should generally focus on management of the PE.
- Don't make the mistake of assuming that all patients with ST elevation require a cardiac catheterization – in the context of known (sub)massive PE, sending the patient for cardiac catheterization would generally be an unwise maneuver.

**clot in transit**

Prominent Eustachian valve can be confused with the right atrial mass, esp when there is a clinical presentation to support it. #echofirst #POCUS #cardiotwitter

**diagnosis of clot-in-transit: exercise caution**

https://emcrit.org/ibcc/pe/
There are lots of things that can mimic clot-in-transit within the right ventricle (e.g. Eustacian valves or prominent trabeculations of the right ventricular moderator band).

A clinically significant clot-in-transit is generally fairly unmistakable (as a large, thick, highly mobile snake-like structure).

Therefore, if you are unsure about whether there is a clot in transit, be suspicious about whether this is a real finding and seek expert advice.

- Avoid assuming that any mobile structure in the right ventricle is a clot-in-transit.

Clot-in-transit can be broken down into roughly three distinct entities. Confusion arises because these are often lumped together in a single group.

**Level I clot in transit**

- Definition: Small clot-in-transit. This may appear similar to a vegetation from endocarditis, as a small structure stuck to the tricuspid valve.
- This is often a somewhat incidental finding in a patient who is otherwise doing OK.
- The significance of a small clot-in-transit is frankly unclear. This probably increases the risk of deterioration somewhat, but not tremendously. It shouldn’t necessarily have huge implications for treatment.

**Level II clot in transit**

- Definition: Large, mobile, snake-like clot in transit. This has a fairly unmistakable and obvious appearance on echocardiography.
- A large clot-in-transit poses a clear and present danger to the pulmonary circulation, as this is likely to break off at some point in the future.
  This will generally move the patient’s severity classification up by one class (e.g. a patient with an otherwise low-risk submassive PE who is found to have a large clot-in-transit would be re-classified as having a high-risk submassive PE).
- Treatment is similar to pulmonary embolism in general (with the increased severity classification taken into account).
  - Systemic thrombolysis is often adequate if there are no contraindications. Retrospective studies suggest an improved survival among patients treated with systemic thrombolysis (31185730).
  - Patients with contraindications to thrombolysis might benefit from IR clot extraction.

**Level III clot in transit**

- Definition: Clot-in-transit is wedged lying across a patent foramen ovale (PFO). This is essentially a paradoxical-embolism-in-transit (clot in the process of slipping from the venous system into arterial circulation).
- This is an enormous problem, because it poses a threat of arterial embolization (which could cause a stroke).
  - Thrombolysis is relatively contraindicated in this situation, to avoid causing the clot to break off within the arterial system and precipitate a stroke.
- Optimal treatment will often involve cardiothoracic surgery to directly remove it.

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kazi ferdous
@fazalalbul

Thrombus is going through the PFO courtesy- Vk Van

https://emcrit.org/ibcc/pe/
differential diagnosis: causes of hypoxemia refractory to ~100% FiO2

- Refractory hypoxemia always reflects some sort of shunt. The differential diagnosis here is pretty short.
- (1) Right-to-left shunting of blood through a patent foramen ovale (PFO) or atrial septal defect.
  - PE causes an elevation of right-sided pressures.
  - This causes right-to-left shunting of deoxygenated blood.
- (2) Another co-existent pulmonary process (e.g. pneumonia, mucus plugging, or pneumothorax).

evaluation

- Cardiopulmonary ultrasound with bedside bubble study to evaluate for shunting.
  - Injection of agitated saline while imaging the heart is the test of choice to evaluate for right-to-left shunting.
- Additional chest imaging (especially if the bubble study is negative) – such as chest X-ray and possibly CT chest.

treatment of PE-induced right-to-left shunting

- (1) High-flow nasal cannulae with 100% FiO2 is generally the first thing to try.
- (2) Pulmonary vasodilators may encourage blood to flow through the lungs (thereby decreasing the fraction of shunted blood).
- (3) Advanced PE therapies are indicated (e.g. thrombolytics or embolism extraction by interventional radiology).
  - Ultimately, any effective treatment of the PE will reduce the right-sided pressures and decrease the fraction of shunted blood.
- Note: Intubation generally won't improve oxygenation due to a right-to-left shunt; it may actually make matters worse (by increasing pulmonary vascular resistance, positive intra-thoracic pressure may merely increase the fraction of shunted blood).
Patients can survive and do well despite coding from a PE (with survival >50%). A few useful components to this:

- **Thrombolysis**
  - Regardless of the patient's contraindications, they should receive thrombolysis (unless immediate ECMO is an option).
  - The code dose of alteplase which is best evidence-supported seems to be a [50 mg IV bolus](https://www.ncbi.nlm.nih.gov/pubmed/27422214). However, if 100 mg is available, administering this entire dose may also be reasonable.
  - Tenecteplase may be faster to mix up, so that is another option.

- **Epinephrine**: If the patient regains a pulse after an epinephrine bolus, strongly consider immediately starting a high-dose epinephrine infusion (e.g. 20 mcg/min, then titrate based on blood pressure). These patients often seem to re-arrest after the epinephrine bolus wears off.

- **Limit airway pressures**, as discussed above (avoid over-aggressive bagging).

- **Inhaled pulmonary vasodilator** – Consider administration of any pulmonary vasodilator available via the endotracheal tube (e.g. nitric oxide, epoprostenol, or milrinone).

- **Provide time for thrombolytic to circulate** – Consider extended CPR (e.g. 60-90 minutes) to allow thrombolytic time to circulate.

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### coding a PE patient

- **Algorithm**

#### 1) crashing massive PE patient:

- **Massive PE – Initial resuscitation**
  - **Fluid-conservative strategy**
    - Rarely helpful (venous pressure generally already excessively high)
    - Don’t give fluid unless evidence of low filling pressure (e.g. small IVC or collapsed jugular veins)
  - **Pressor-aggressive strategy**
    - Epinephrine good front-line agent, titrate for MAP > 65 mm
    - Vasopressin as second-line agent
  - **Inhaled pulmonary vasodilators**
    - Epoprostenol or nitric oxide – whatever you can get fastest.
    - If refractory may consider combination of nitric oxide plus epoprostenol.
  - **Thrombolysis**
    - No contraindication: 100 mg alteplase.
    - Relative contraindication & actively dying: 100 mg alteplase.
    - Relative contraindication & stabilized: may start with 50 mg alteplase.
  - **Other PE-directed therapies (tPA failure/contraindication)**
    - Interventional radiology clot extraction (e.g. FlowTriever)
    - Cardiothoracic surgical extraction
    - VA ECMO

#### 2) non-crashing patient: risk stratification & tailored treatment

**Evaluation to risk stratify (sub)massive PE**

- **History & Physical**
  - Medication review – Focus on anticoagulants & anti-platelet medications.
  - Vital signs & general appearance.
  - Duration of symptoms.

- **Labs**
  - CBC with differential
  - Complete coags: INR, PTT, Fibrinogen, D-dimer
  - Lactate
  - Troponin

- **Imaging**
  - EKG
  - CT angiogram chest
  - Bedside echocardiogram
  - Bedside ultrasonography to evaluate for DVT

(1) This workup certainly doesn’t need to be done for every patient with PE. It may be helpful for patients with imaging evidence of RV dilation, or other features of severe PE.

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**PE risk stratification**

New PE diagnosis

- Are ALL THREE of the following criteria met?
  1. Large clot burden on CT scan
  2. RV dilation (on echo/CT)
  3. Euvolemic (e.g. IVC normal/dilated) & no alternative cause of hemodynamic instability

Low-risk PE

- Are any of the following criteria met?
  - SBP <90 mm for 15 minutes
  - SBP drops >40 mm from baseline for 15 minutes
  - Cardiac arrest
  - Persistent bradycardia (e.g. HR<40 with clinical features of shock)
  - Requirement for vasopressor to maintain Bp

Are patient hemodynamically unstable with evidence of hypovolemia (e.g. collapsed IVC and/or jugular veins)?

- Are any of the following criteria met?
  - Need for high-dose vasopressor (e.g. >>10 mcg/min epinephrine or norepinephrine)
  - Persistent bradycardia
  - Patient looks/feels severely ill (e.g. diaphoretic, mottled, confused, sensation of dying)
  - Status post cardiac arrest
  - Large clot-in-transit visualized in right ventricle

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**Examples of balancing risk vs. benefit of lytic therapy**

<table>
<thead>
<tr>
<th>Low-Risk PE</th>
<th>Relative lytic contraindication (including &lt;65 YO)</th>
<th>Absolute lytic contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Risk Submassive PE</td>
<td>Anticoagulation alone</td>
<td>Anticoagulation alone</td>
</tr>
<tr>
<td>High-risk Submassive PE</td>
<td>0.5 mg/kg up to max dose of 50 mg IFA (over 2 hours)</td>
<td>25 mg IFA as slow infusion (peripheral IV vs. catheter-directed thrombolysis)</td>
</tr>
<tr>
<td>Non-crashing Massive PE</td>
<td>100 mg IFA over 2 hours (Repeat PRN)</td>
<td>IR clot removal or surgical embolectomy</td>
</tr>
<tr>
<td>Crashing Massive PE</td>
<td>100 mg IFA over 2 hours (give initial –20 mg as bolus)</td>
<td>IR clot removal or surgical embolectomy</td>
</tr>
</tbody>
</table>

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Submassive PE:
The foundation of a successful approach is thoughtful risk-stratification and thorough evaluation for contraindications to thrombolysis. Be extremely careful when combining thrombolytics and heparin, especially heparin boluses (which may produce supratherapeutic levels). When in doubt, be conservative with the heparin (heparin prevents new clot from forming but has no immediate impact on the patient, so leaving the patient off heparin for a few hours is probably fine).

Massive PE:
Avoid volume administration unless there is definitive evidence of coexisting hypovolemia. Don't hesitate to initiate vasopressors as needed to stabilize the blood pressure (with epinephrine potentially as a front-line agent). Don't delay thrombolysis if this is an option. Thrombolysis is the only intervention which is evidence-supported to improve mortality in these cases. All other interventions (pressor, inhaled vasodilators, etc) are merely intended to stabilize the patient until thrombolysis can be performed.

Going further:
- Diagnosis: EKG patterns of PE that mimic MI
- IVC filters: where is the evidence?
- Thrombolysis: Fibrinolysis of Pulmonary Embolism with Jeffrey Kline (EMCrit Podcast 2011)
- Submassive PE 2014: PEITHO, MOPETT, ULTIMA, TOPCOAT
- 2016: Controlled thrombolysis I: deconstructing catheter-directed thrombolysis
- 2016: Controlled thrombolysis II: rationale & protocol
- Should we monitor fibrinogen during full/half-dose lysis? (https://emcrit.org/pulmcrit/fibrinogen_pe/)
- OPTALYSE-PE: We're dosing tPA wrong (https://emcrit.org/pulmcrit/pulmcrit-solving-the-optalyse-pe-riddle-were-dosing-tpa-wrong/)

- Resuscitation:
  - Eight pearls for the crashing PE patient (https://emcrit.org/pulmcrit/eight-pearls-for-the-crashing-patient-with-massive-pe/)
  - Hemodynamic management of massive PE (https://emcrit.org/emcrit/hemodynamic-management-massive-pulmonary-embolism-pe/) (Oren Friedman on EMCrit podcast)
  - Inhaled pulmonary vasodilators: iNope trial (https://emcrit.org/pulmcrit/inope/)
  - PERT team with Oren Friedman (https://emcrit.org/emcrit/pulmonary-embolism-treatment-team/), (EMCrit Podcast 2014)

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The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.