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"REVOLUTIONIZING ACUTE PULMONARY EMBOLISM MANAGEMENT: ADVANCEMENTS IN INTERVENTIONAL TREATMENT AND THE ROLE OF INTERDISCIPLINARY COLLABORATION"

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ABSTRACT Traditionally, catheter-based recanalization techniques have been the gold standard for treating myocardial infarction and stroke. However, interventional treatments for pulmonary embolism (PE) have often been relegated to second-line measures. While systemic thrombolysis has been shown to potentially halve the mortality risk in patients with high-risk PE, its application remains limited outside specialized medical facilities. Recent advancements in thrombectomy devices have significantly altered clinical practice, addressing a critical therapy gap for both intermediate and high-risk pulmonary emboli. To ensure these new therapies demonstrate safety and efficacy, current treatment paradigms must evolve; promising observational evidence is emerging, and randomized controlled trials are underway. Given their expertise in invasive procedures and diagnostic imaging, interventional radiologists are ideally positioned to play a pivotal role in interdisciplinary pulmonary embolism response teams, which are essential for delivering tailored therapies.

KEYWORDS :

INTRODUCTION

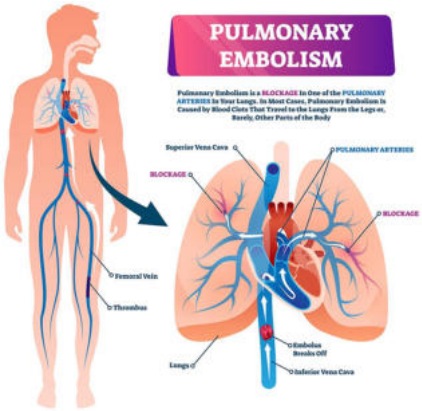
Acute pulmonary embolism is a leading cause of preventable mortality among hospitalized patients, ranking third after heart attacks and strokes. Although systemic thrombolysis is an effective treatment for high-risk PE, its associated risk of bleeding—particularly intracranial hemorrhage—limits its use outside specialized centers.[1,2] The emergence of innovative thrombectomy tools offers new avenues for managing patients at elevated risk of mortality. This review explores existing research on large-bore thrombectomy and its potential integration into acute PE treatment protocols.[3,4]

Epidemiology

A German registry analysis from 2020 found that the number of people with PE rose from 85.3 per 100,000 in 2005 to 108.7 in 2015 [4]. At the same time, the death rate in the hospital went down from 20.4% to 13.9%, and the number of patients with unstable blood flow stayed the same at roughly 9%. About 11% of hemodynamically stable patients died during the same hospital stay between 2005 and 2015. In the high-risk group, 78% died. Cardiovascular illness and being unable to move after trauma surgery are both risk factors. In addition to the high death rate, PE causes a lot of long-term health problems. About half of the patients have post-PE syndrome, which means they have symptoms including chest discomfort, shortness of breath, exhaustion, dizziness, or fainting for more than three months following an acute PE [5]. About 3–4% of these patients get chronic thromboembolic pulmonary hypertension (CTEPH), which is when the mean pulmonary arterial pressure is higher than 25 mmHg and the pulmonary artery occlusion pressure is 15 mmHg or less. They also have ventilation-perfusion defects and imaging shows confirmed thromboembolic changes after 3 months of effective anticoagulation [6].

Pathophysiology Of Pulmonary Artery Embolism

During acute PE, a blood clot that usually starts in the veins of the legs or pelvis gets into the lungs. When the pulmonary artery is blocked by more than 30–50%, the right ventricle's afterload suddenly goes up. This is made worse by neurohormonally induced vasoconstriction [7, 8]. This makes the thin-walled right ventricle expand, which raises the wall tension and oxygen demand because of inflammation of the heart muscle. The strain causes malperfusion and relative hypoxia, which lower contractility and the output of the right ventricle. The septum moves when the right ventricle balloons, which makes it harder for the left ventricle to fill, lowers output, and lowers systemic blood pressure, which makes coronary perfusion even worse. This makes the right ventricle even more deprived of oxygen, which could cause obstructive cardiogenic shock because of right heart failure [9] (Fig. 1).



Risk Stratification

We use clinical scores, test results, and imaging to sort people into different risk groups. The pulmonary embolism rule out criteria (PERC) are useful when the chance of having PE

before the test is low (≤ 15%). The revised Geneva Score gives a more objective measure of the risk of PE and helps support imaging tests. The simplified pulmonary embolism severity index (sPESI) can tell you how likely it is that a PE patient will die within 30 days [10,11,12]. In real life, the updated Geneva Score is most useful because it is meant to avoid or maybe start CT imaging for a definitive diagnosis and risk classification. The European Society of Cardiology (ESC) guidelines from 2019 put PE into three groups: low, intermediate-low, and intermediate-high, with high projected acute mortality risk from right heart failure (Table 1) [9]. This classification says that at least intermediate-risk PE has clinical features such a heart rate over 110 beats per minute, a systolic blood pressure below 100 mmHg, or an oxygen saturation below 90%. The intermediate-high-risk group also has higher levels of cardiac biomarkers and evidence of right ventricular dysfunction on echocardiography or CT angiography. Patients with an intermediate-low risk meet at least one of these criteria. Patients at high risk often need circulatory support because their blood flow is unstable. It's hard to treat PE with a high risk of complications since patients can abruptly get worse after being stable for a long time.

Treatment Recommendations According To Current Guidelines

When treating PE with a high risk of death, doctors should carefully give fluids, aggressively give oxygen, and treat hypercapnia, and they should have a low threshold for using vasopressors and inhaled pulmonary vasodilators for hypoxemia that doesn't respond to other treatments. Intubation should be avoided since it can cause temporary hypoxemia, low blood pressure, sedation-related inhibition of endogenous sympathetic activation, and the danger of making right ventricular afterload worse with positive pressure breathing [13, 14]. Unfractionated heparin should be given to all patients to prevent blood clots. The 2019 ESC guidelines say that systemic thrombolysis should be used for high-risk patients or patients who are at lower risk but showing signs of clinical deterioration (class 1b recommendation). Catheter-based procedures should only be used when thrombolysis is not possible or not working (class IIa) [9, 15,16,17]. (See Fig. 1.) A 2022 ESC consensus statement suggests that interventional strategies could be a good alternative to thrombolysis for patients with worsening intermediate-risk conditions, even if they don't have any thrombolytic contraindications. This is because novel thrombectomy devices have high procedural success rates and show signs of lower mortality and bleeding risks [18, 19]. Surgical embolectomy is only done when there is a lot of clot-in-transit or when less invasive options have failed. The 30-day death rate and 5-year survival rate are the same as those of thrombolysis in selected patients and experienced facilities [20, 21]. The implantation of cava filters to stop further embolization was one of the first treatments offered in PE

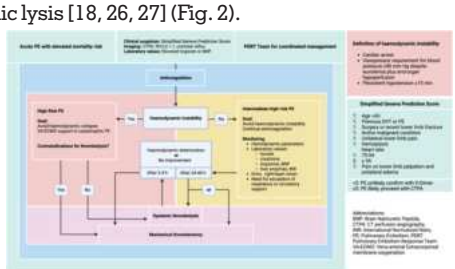
and is still used when anticoagulation is not possible or doesn't work [9]. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) can be used as a temporary fix for severe PE until a permanent solution is found.

Increasing Role Of Pulmonary Embolism Response Teams (PERTs)

The 2022 ESC consensus suggested setting up Pulmonary Embolism Response Teams (PERTs) to set treatment goals because there is more and more evidence that activating PERTs can lower short- and mid-term death rates and readmission rates [22, 23]. These teams of experts in cardiology, pulmonology, hematology, vascular medicine, intensive care, cardiothoracic surgery, or interventional radiology are meant to give specialized care to patients who are at a higher risk of dying and to set up a centralized, spoke-like referral system for healthcare providers in the area. At the very least, a PERT needs an intensive care department with people from different fields who are familiar with extracorporeal life support systems, a radiology department that is open 24 hours a day, seven days a week, and interventionalists who are available 24 hours a day, seven days a week, at least on an on-call basis. It helps to prevent structural redundancy and management inconsistencies to start with one intensive care unit, one interventional department, and one catheter-based procedure, respectively. Once a center has set up a common methodology for everything from activating PERT to discussing cases, getting input, managing individual cases, and following up, it's easy to add more local treatment teams and outside referrals to the system. Artificial intelligence solutions that have been approved by the FDA and CE for automatically interpreting images and integrating clinical data can help speed up PERT activation and cut down on the time it takes to consult. However, they also come with the risk of automation bias and notification fatigue if the false positive rates are not good enough [24, 25].

In addition to risk classification and procedural feasibility, a typical PERT conversation should also include how well the patient can handle lying on their back and breathing on their own during the procedure. It is quite dangerous to turn an intermediate-high-risk patient into a high-risk patient during a procedure or through elective intubation before the procedure. Patients whose hemodynamics

are getting worse should be quickly checked by the PERT team for reperfusion techniques before they go into full-blown cardiogenic shock. Because early therapies have better outcomes than delayed ones, a choice to do a thrombectomy should mean starting it within 60–90 minutes or 2–4 hours after systemic lysis [18, 26, 27] (Fig. 2).



Treatment algorithm for elevated pulmonary embolism

Intravenous Thrombolysis: Who Is Likely To Benefit?

Current guidelines say that giving alteplase (100 mg over 2 hours) quickly through an IV is better than giving first-generation thrombolytic agents like streptokinase and urokinase for a long time. These agents are less specific to fibrin and may require stopping heparin administration [9, 28]. Systemic thrombolysis cuts the risk of cardiovascular collapse in high-risk patients by roughly half. There is a 1.5% risk of bleeding in the brain, compared to an estimated 0.7% risk with anticoagulation alone [4, 15, 29, 30]. Patients who have had cerebrovascular episodes, cardiovascular illnesses, or are older are the most at risk [31]. It's not obvious what the benefits of thrombolysis are for people with intermediate risk, which is possibly why this group hasn't been treated as much in the past [32]. Thrombolysis lowers the risk of death and recurrent PE in the near term, but it has not been shown to

have any long-term effects on death rates or cardiovascular outcomes, such as the rate of pulmonary hypertension [30, 32]. Another thing to think about while giving thrombolysis is that how well it works depends on the age and make-up of the clot. For example, older thrombi with a lot of connective tissue are harder to break down, which explains why some treatments don't work [32, 33]. The 2020 registry study mentioned above looked at data from the German Federal Statistical Office

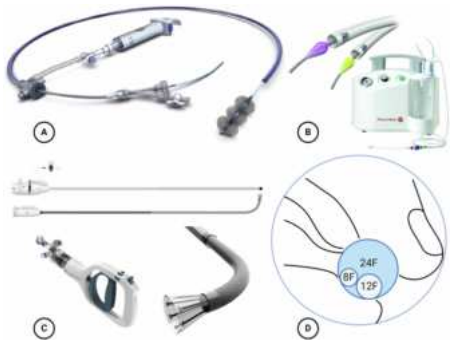
from 2005 to 2015 and included 885,806 patients. It found that thrombolysis cut the risk of death in the hospital by 60% in unstable patients who had not had any previous resuscitation events, which is in line with what has been found in the past [4]. Only about one-third of patients are predicted to have contraindications to thrombolysis, however it was only given to roughly 25% of patients who had been resuscitated and 15% of unstable patients who had not been resuscitated before [4, 34]. The fact that it is used much less often outside of experienced centers is probably due to the difficulties of risk stratification, fear of intracranial bleeding, uncertainty about individual effectiveness, and the absence of established "time is tissue" paradigms like those used in ischemic stroke or acute coronary syndrome. The recommended maximum doses for systemic thrombolysis in myocardial infarction, stroke, and PE are comparable. The dosing estimate for PE is based on what has been learned from the other two vascular areas, which only get a little amount of cardiac output [35]. It was shown that utilizing half or even a quarter of the normal dose was safe and successful, especially in people who had relative contraindications to thrombolysis and needed more research, such as in the ongoing PEITHO-3 experiment [29, 36, 37, 38].

Catheter-directed Thrombolysis

Local catheter-directed thrombolysis (CDT) tries to lower the risk of bleeding while maximizing the effectiveness of thrombolytics by employing lower dosages that are usually given across 24 hours. The 2018 OPTALYSE trial found that doses as low as 8–12 mg of alteplase might be enough [39]. The idea is to improve the effectiveness of thrombolysis by getting around the problem of pulmonary shunting, which moves systemically delivered thrombolysis to areas with reduced thrombus burden. A randomized controlled experiment (RCT) from the late 1980s indicated that giving 50 mg of alteplase directly into the pulmonary artery was not better than giving it through a peripheral vein. This was probably because the drug was shunted to the unblocked contralateral artery [40, 41]. Interest in CDT grew again when ultrasound-assisted CDT was used, as in vitro studies showed that ultrasound could help thrombolytics get deeper into clots [42]. But the recent SUNSET sPE experiment showed that both standard and ultrasound-assisted CDT reduced thrombus in the same way, which raises questions about the therapeutic usefulness of this mechanism [43]. A recent meta-analysis also didn't show that ultrasound help adds anything to standard CDT [44]. It is still not apparent if CDT without ultrasound help is better than peripheral thrombolysis with the same dose. A network metanalysis demonstrated that CDT was linked to lower rates of death and hemorrhage than systemic thrombolysis. However, the sole RCT included did not show a statistically significant difference [45]. A different meta-analysis from 2023 came to the same conclusions [46]. The problem is that most research look back in time or compare CDT with anticoagulation, which makes it hard to apply the results to other situations because of selection bias. Patients who have systemic thrombolysis frequently have worse problems, and clinics that perform CDT usually have more experience treating PE [47, 48]. It is likely that the first-pass effect of directly infusing thrombolytics into pulmonary thrombi has been overstated and that the benefits of CDT are actually more like the effects of low-dose systemic thrombolysis and second-pass re-circulation [49]. The ongoing Danish STRATIFY trial is the most promising study to clear up this confusion. It is projected to end by the end of 2024 [50]. This trial comprises 210 intermediate-risk patients and compares ultrasound-assisted CDT, peripheral thrombolysis with a lower dose of 20 mg rTPA, and anticoagulation alone. BETULA, PE-TRACT, and HI-PEITHO are other big RCTs that are looking at different types of CDT or CDT with anticoagulation over a period of 12 months [51,52,53].

Procedures For Mechanical Thrombectomy

In the 1990s, the first attempts at catheter-based fragmentation utilizing rotating and hydrodynamic catheters were made. These were followed by aspiration and ultrasound-guided local thrombolysis [26, 54]. The development of new aspiration catheters around 2019 was a major step forward in the treatment of PE. The AngioVac system (AngioDynamics) is a 24F aspiration catheter that reinfuses aspirated blood through an extracorporeal circuit. It has been used to aspirate thrombus in PE, however it is only approved to treat venous thrombosis. AlphaVac, a better follow-up device, no longer needs an extracorporeal circuit. It has a mechanical handle that acts as the engine and comes with 18F and 22F aspiration catheters (Fig. 3). AlphaVac is already approved in the US and is waiting for approval in Europe. It is currently being investigated for use in the lungs in the APEX-AV study [55]. The Inari FlowTriever System (Inari Medical) and the Lightning Indigo Aspiration System (Penumbra) (Fig. 3) are the two systems with the most evidence so far. They are both approved in the US and Europe.

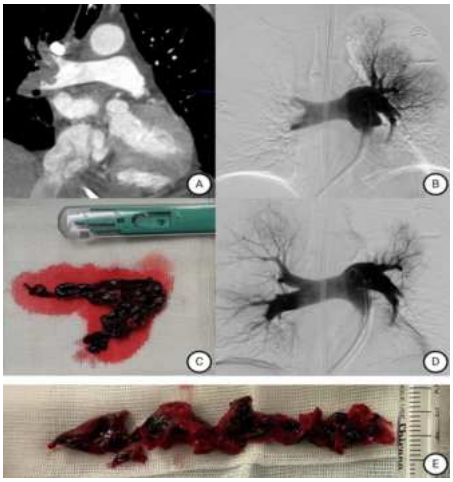


Modern devices for percutaneous thrombectomy. A The Inari FlowTriever system is a mechanical, large-bore aspiration catheter with diameters of 16F, 20F, and 24F. Sudden release of a 60 mL vacuum leads to aspiration of the thrombus into the connected syringe. A thrombus can be macerated or mobilized using self-expanding nitinol mesh discs prior to thrombectomy. **B** The Penumbra Lightning Indigo aspiration system is an electrically powered aspiration system with 6F, 8F, 12F and 16F (U.S.) catheter diameters. The continuous suction adapts automatically depending on the position in the thrombus or free vessel lumen in order to minimize blood loss. A so-called separator can be used coaxially to macerate thrombi. **C** The Angiodynamics AlphaVac System comes with a mechanical handle that works as the engine and offers 18F and 22F aspiration catheters. AlphaVac is already approved in the United States, with approval for Europe pending. **D** Illustration of different catheter sizes. The potential flow rate of a 24F system is eight times greater than that of a 12F system according to the Hagen–Poiseuille equation of fluid dynamics

Inari FlowTriever

The FlowTriever system is a large-bore aspiration catheter with diameters of 16F, 20F, and 24F. It works only mechanically. Using traditional angiographic methods, a rigid guidewire is put into a lower lobe artery. The catheter is then put in front of the clot, which can be broken up or moved if aspiration alone doesn't work. A 60 mL syringe makes a vacuum, and when it is suddenly released, it makes it easier to aspirate thrombus (Fig. 4). A filter can be used to manually reinfuse the aspirated blood. The system needs time to learn how to work best, since clots can get stuck and the whole catheter may need to be removed. The FlowTriever Pulmonary Embolectomy Clinical Study (FLARE) was a prospective, single-arm, multicenter study of 106 intermediate-risk patients with signs of right heart strain. It found that the right-to-left ventricular ratio (RV/LV ratio) went down by an average of 25.1%, and the rate of major adverse events was 3.8% [56]. The average length of stay in the intensive care unit (ICU) was 1.5 days. The FLASH study for patient safety and hemodynamics in 2023 had 800 patients in the US and 200 in Europe. It corroborated similar results [34].

In the US group, 92.1% were considered to be at intermediate-high risk, while 7.9% were considered to be at high risk. 32.1% of the patients could not get thrombolysis. The peri-interventional RV/LV ratio went down from 1.23 to 0.98 ($p<0.0001$), and the average pulmonary arterial pressure (PAP) went down from 48.9 mmHg to 38.8 mmHg ($p<0.0001$). The average length of stay in the hospital was three days, and almost two-thirds of the patients did not need to be watched in the ICU. 1.8% of people had serious adverse events at 48 hours, and 1.4% of those were related to major bleeding before the reinfusion filtration device was put in place. There were no deaths linked to the system or the procedure, and the 30-day death rate was 0.8%. The FLAME research, which was a prospective multicenter observational analysis of high-risk patients, found that there were fewer bad events than in groups that only had systemic lysis or anticoagulation [57]. The PEERLESS study, which was just published, was a randomized controlled trial (RCT) of 550 patients with intermediate-high risk PE. It looked at death rates, bad events, and ICU stays between CDT and aspiration thrombectomy. Aspiration thrombectomy had fewer cases of clinical deterioration or bailout therapy, as well as fewer admissions to the critical care unit, shorter hospital stays, and 30-day readmissions. There was no difference in mortality or bleeding [58]. PEERLESS 2 and PERSEVERE are also RCTs that are still going on. They are looking at thrombectomy versus anticoagulation in 1200 intermediate-high and 200 high-risk patients, respectively [59, 60].



Large-bore thrombectomy in high-risk pulmonary embolism. **A** Pre-treatment CT-Scan. **B** Digital subtraction angiography (DSA) before thrombectomy. **C** Macroscopic thrombus after removal. Histologic analysis revealed it to be mostly fresh with about 20% fibrin content. **D** Final DSA after thrombus removal. **E** Thrombus from another patient who needed to be intervened due to failure of thrombolysis. Fibrin content was 70% (yellow portions of the specimen)

Penumbra Lightning Indigo Aspiration System

The Indigo aspiration system is an electrically powered aspiration device that works with catheters that are 6F, 8F, 12F, and 16F in diameter. The continuous suction changes automatically according on where it is in the thrombus or free vessel lumen to reduce blood loss. The BOLT technology, which was added to the 7F system in 2023, adds pulsatile suction to help break up the clot. Because it has a lower profile, it's easier to handle and move around at the distal end than with the FlowTriever system. But the technique can't completely remove the thrombus with sudden convective force, and smaller catheters might make channels in the clot. The EXTRACT-PE trial, which used the 8F system on 119 patients with an intermediate risk level, found that the RV/LV ratio dropped by an average of 27±13% (from 1.47±0.30 before to 1.04±0.16 after) [61]. This is similar to what the FLARE study found with the FlowTriever system. The average decrease in systolic PAP was 4.3 mmHg (95% CI 2.6–5.9 mmHg, $p < 0.0001$). The average length of the surgery was 37 minutes (95% CI 23.5–60.0 minutes), and the patient stayed in the ICU for one day. Two individuals had severe bleeding, and two more had damage to their pulmonary arteries. The overall prevalence of adverse events was 1.7%. The 12F system is still being tested in the prospective STRIKE-PE observational trial to see how safe and effective it is [62]. In 2024, an interim analysis of 150 patients treated with the 12F system showed a big drop in pulmonary artery pressure and RV/LV ratio, a median thrombectomy time of 33.5 minutes, a composite major adverse event rate of 2.7%, and big improvements in functional and quality of life outcomes after 90 days [63]. The STORM-PE study was the first randomized study to use the 12F method. It started recruiting at the end of 2023 and hopes to enroll 100 patients with intermediate to high risk by the end of 2026. The study will compare thrombectomy with anticoagulation alone [64]. The RV/LV ratio after 48 hours is the main goal. The CATH-PE case-control research will also look at 100 individuals who are at high or intermediate-high risk [65].

CONCLUSION

The pathophysiology of life-threatening pulmonary embolism (PE) involves a critical cycle characterized by an acute increase in right ventricular afterload. This rise leads to right ventricular ballooning and heightened wall tension, resulting in diminished perfusion, septal shift, and impaired left ventricular function. Consequently, these changes culminate in systemic malperfusion and obstructive shock, often accompanied by right heart failure For high-risk patients, full-dose thrombolysis is recommended unless contraindicated. In cases where intermediate-risk patients show no improvement or deterioration with anticoagulation alone, or when high-risk patients have relative contraindications to thrombolysis, thrombectomy should be considered. Current evidence does not strongly endorse catheter-directed thrombolysis (CDT) as the optimal treatment, as its bleeding risk remains higher than that associated with anticoagulation alone. Moreover, the advantages of CDT over reduced-dose thrombolysis via a peripheral vein—administered safely in an ICU—are not clearly established.Emerging thrombectomy techniques have demonstrated the potential to reduce right ventricular afterload and enhance hemodynamic stability. The primary aim of these interventional treatments is not necessarily to completely remove thrombi from the pulmonary arteries but rather to alleviate right ventricular strain and stabilize hemodynamics. However, existing data primarily stem from non-interventional observational studies, and there is a lack of randomized controlled trials (RCTs) advocating for routine thrombectomy in high-risk patients as an alternative to thrombolysis. Ongoing trials involving the Inari FlowTriever and Penumbra Indigo Aspiration System are exploring these possibilities.Investigating high-risk patients poses ethical challenges for RCTs, as it is difficult to justify randomized treatment in life-threatening situations. Additionally, acute PE is associated with significant morbidity due to post-PE symptoms and chronic thromboembolic pulmonary hypertension (CTEPH). Researchers are actively examining whether contemporary catheter techniques can mitigate these long-term complications by reducing thrombus burden and optimizing patient selection for intervention.

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