Current Trends in Catheter-Directed Therapy for Acute Pulmonary Embolism

Tendências Atuais na Terapêutica Percutânea do Tromboembolismo Pulmonar Agudo

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https://doi.org/ 10.48687/lsj.228

Abstract

Acute pulmonary embolism is a leading cause of in-hospital and cardiovascular mortality, and it keeps posing important diagnostic and therapeutic challenges. Traditional treatment options such as anticoagulation, thrombolysis, and surgery are increasingly being challenged by new catheter-based procedures, including catheter-directed thrombolysis, mechanical thrombectomy, and pharmacomechanical hybrid techniques.

Emerging evidence supports the effectiveness and safety of these percutaneous methods, which may facilitate faster recovery of right ventricular function and hemodynamics in selected patients, with a lower risk of bleeding compared to standard medical therapy. These interventions may be particularly beneficial for high-risk patients for whom thrombolysis is contraindicated or has proven ineffective, as well as for initially stable intermediate-risk patients who experience hemodynamic decline despite appropriate anticoagulation.

Nevertheless, significant knowledge gaps continue to impede the optimization of these techniques and limit the shifting of treatment recommendations for acute pulmonary embolism. This paper provides a summary of the various catheter-directed interventions currently available, highlighting their indications, technical considerations, clinical effectiveness, and potential complications, offering a comprehensive overview of their current future trends in the management of acute pulmonary embolism.

Keywords: Catheters; Pulmonary Embolism/therapy; Thrombectomy/methods; Thrombolytic Therapy/adverse effects; Thrombolytic Therapy/methods

Resumo

O tromboembolismo pulmonar agudo é uma das principais causas de mortalidade hospitalar e cardiovascular, apresentando importantes desafios diagnósticos e terapêuticos. As opções terapêuticas tradicionais, como a anticoagulação, a trombólise e a cirurgia, estão cada vez mais a ser confrontadas por novos procedimentos percutâneos, incluindo a trombólise dirigida por cateter, a trombectomia mecânica e as técnicas híbridas farmacomecânicas.

Evidências emergentes apoiam a eficácia e segurança destas técnicas endovasculares, que permitem uma recuperação mais rápida da da função ventricular direita e dos parâmetros hemodinâmicos em pacientes selecionados, com menor risco hemorrágico em

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Recebido/Received: 06/09/2024 **– Aceite/Accepted:** 15/09/2024 **– Publicado online/Published online:** 30/09/2024 **– Publicado / Published:** 30/09/2024

comparação com a terapia médica padrão. Estas intervenções podem ser particularmente benéficas para pacientes de alto risco em que a trombólise seja contraindicada ou se mostre ineficaz, assim como para pacientes inicialmente estáveis de risco intermédio que experienciem um declínio hemodinâmico apesar de anticoagulação adequada.
Contudo, lacunas significativas no conhecimento continuam a limitar a otimização destas técnicas e a atualização das recomendações terapêuticas para o tromboembolismo pulmonar agudo. Este artigo resume as diferentes intervenções percutâneas atualmente disponíveis, destacando as suas indicações, considerações técnicas, eficácia clínica e potenciais complicações, oferecendo uma visão abrangente das tendências atuais e futuras na abordagem desta patologia.

Palavras-chave: Cateteres; Embolia Pulmonar/tratamento; Trombectomia/métodos; Terapia Trombolítica/efeitos adversos; Terapia Trombolítica/métodos

Introduction

Acute pulmonary embolism (PE) is a prevalent and potentially life-threatening condition that requires prompt diagnosis and treatment. Its incidence is estimated at 0.5 to 1 per 1000 individuals, and has risen over the last twenty years due to advancements in diagnostic techniques, an ageing population, and an increase in invasive medical procedures.[1,2] Acute PE ranks as the third leading cause of cardiovascular mortality, following myocardial infarction and stroke, and is the most common cause of preventable in-hospital death, accounting for 5%-10% of such cases.[3] In the last decade, the management of acute PE has significantly advanced and now encompasses a diverse range of strategies. Early risk assessment is essential for determining the appropriate treatment and reducing morbidity and mortality. Patients with low-risk PE typically have favorable outcomes with anticoagulation alone, showing a mortality rate of less than 1% at one month.[4] Conversely, those with intermediate-risk and high-risk PE exhibit short-term mortality rates of 3% to 15% and over 30%, respectively.[5] While the advantages of systemic thrombolysis for these higher-risk groups are well-documented, they come with the risk of severe bleeding. [6]

These challenges have led to increased interest in catheter-directed therapies (CDT) for managing these patients, including catheter-directed thrombolysis (CDL) and mechanical thrombectomy (MT). These approaches aim to rapidly reduce the clot burden, alleviate right ventricular (RV) dysfunction, and enhance cardiac output.[7,8] This article seeks to summarize the current role of endovascular interventional therapy in acute PE, detailing the available technologies, their specific indications, risk profiles, and outcomes.

Risk Stratification and Therapeutic Options

The management of acute PE is heavily influenced by the associated risk of acute mortality. Various clinical, imaging, and laboratory parameters have been shown to affect early (in-hospital or 30-day) mortality, forming the basis for the European Society of Cardiology (ESC) classification into high-, intermediate-, and low-risk PE categories.[9] Hemodynamically stable patients without clinical indicators of severity —assessed using the original or simplified Pulmonary Embolism Severity Index (PESI)—or without signs of RV dysfunction on echocardiography or elevated cardiac biomarkers like troponin and BNP are classified as low-risk, with a mortality rate of about 1%-2%.[10,11] In contrast, hemodynamically stable patients exhibiting clinical signs of severity fall into the intermediate-risk category, with mortality rates ranging from 3% to 15%.[12,13] These patients can be further divided into intermediate-low and intermediate-high risk based on the presence of RV dysfunction and/or elevated cardiac biomarkers.[6] Hemodynamically unstable patients, characterized by sustained hypotension (systolic BP <90 mmHg or a drop in systolic BP exceeding 40 mmHg for at least 15 minutes), obstructive shock with signs of end-organ hypoperfusion, or experiencing a cardiac arrest, have an in-hospital mortality rate of up to 30% and are classified as high-risk PE.[14] The use of angiographic clot burden (Miller index) or computed tomography pulmonary angiography (CTPA) obstruction index (Quanadli score) for risk stratification has been abandoned due to its poor correlation with mortality risk.[15,16]

While the ESC classification provide a framework for risk stratification in acute PE, treatment decisions can be complex. Anticoagulation remains the cornerstone of management for most PE patients and is the sole therapy required for low-risk patients. Although anticoagulation does not directly dissolve thrombus, it facilitates endogenous thrombolysis, prevents further clot formation, and reduces thromboembolic burden. Historically, initial treatment was limited to unfractionated heparin (UFH) and primary treatment to vitamin K antagonists (VKAs). In the 1980s, low-molecular weight heparins (LMWH) and fondaparinux emerged as first-line treatments for the acute phase. LMWH is associated with a lower risk of venous thromboembolism recurrence, major bleeding, and heparin-induced thrombocytopenia compared to UFH.[16,17] In recent years, direct oral anticoagulants (DOACs) have challenged both VKAs for primary and, in some cases, LMWH for initial treatment. DOACs demonstrate similar efficacy to LMWH and

VKAs while significantly reducing the risk of major non-fatal and fatal extra and intracranial hemorrhage (ICH), making them the preferred choice for most PE patients.[18,19]

For patients with high-risk PE, more aggressive interventions are typically necessary due to their higher likelihood of mortality. Systemic fibrinolysis aims to rapidly decrease clot burden and improve hemodynamic instability, and is a Class I recommendation for these patients.[9] The most studied thrombolytic agents include recombinant tissue plasminogen activators like alteplase and tenecteplase. A pooled analysis of 17 trials indicated that patients receiving thrombolytic therapy had a lower risk of death (OR: 0.57; 95%CI: 0.37-0.87) and PE recurrence (OR: 0.51; 95%CI: 0.29-0.89) (OR: 2.9; 95%CI: 1.95-4.31) but a higher risk of major bleeding compared to those treated with heparin, leading to a great underutilization of this therapy.[20]

In the case of intermediate-risk PE, there is no straightforward algorithm to determine the need for advanced therapy. Treatment decisions are influenced by various factors, including institutional expertise, bleeding risks, clot extent and location, and individual patient characteristics. The use of thrombolytic therapy in intermediate-risk patients seeks to prevent hemodynamic collapse in those with RV dysfunction and to hasten symptom resolution. A meta-analysis of 16 randomized trials showed that thrombolytic therapy was linked to reduced all-cause mortality among intermediate-risk patients (OR: 0.48; 95%CI: 0.25–0.92), although this benefit came with an increased risk of ICH (OR: 4.78; 95%CI: 1.78–12.04) and major bleeding (OR: 2.73; 95%CI: 1.91–3.91).[6] This analysis was largely driven by the double-blind randomized PEITHO study, which evaluated systemic thrombolysis in 1005 intermediate-risk PE patients. Although tenecteplase showed a significant benefit in the composite endpoint death and hemodynamic decompensation (2.6% *vs* 5.6%; OR: 0.44; 95%CI: 0.23-0.87), the overall mortality rates were similar between treatment groups (OR: 0.73; 95%CI: 0.34-1.57), and there were increased instances of major extracranial bleeding (6.3% *vs* 1.2%; OR: 5.55; 95%CI: 2.3-13.39) and stroke (2.4% *vs* 0.2%; OR: 12.10; 95%CI: 1.57-93.39) associated with tenecteplase, particularly in patients over 75 years.[21] Consequently, current evidence does not support the routine use of thrombolytic therapy in unselected intermediate-risk PE patients.

Surgical embolectomy may be a viable treatment option for high-risk PE patients who have contraindications to systemic thrombolysis or who do not show clear clinical improvement after such treatment.[9] Additional indications for this procedure include cases with thrombus in transit or a patent foramen ovale leading to paradoxical embolism. Most data regarding surgical outcomes come from small observational studies conducted in specialized centers, showing that 30-day mortality and 5-year survival rates are comparable to those associated with systemic thrombolysis.[22] However, access to this treatment is limited to selected facilities, and surgical embolectomy carries a significant risk of morbidity and mortality, particularly in patients who have not responded to thrombolytic therapy. Thus, it should only be considered when other treatment options are not viable and when the potential benefits outweigh the associated risks.

Role of Catheter-Directed Therapy

Catheter-directed therapies (CDT) have gained attention for use in both intermediate and high-risk PE patients, primarily due to the limitations of anticoagulation therapy and the associated risks of systemic thrombolysis and surgical embolectomy. Two main CDT strategies have emerged: mechanical retrieval of thrombi through aspiration or thrombectomy, and in situ fibrinolysis using various catheter systems. Most of these devices have shown effectiveness in reducing pulmonary artery obstruction and improving hemodynamic parameters, achieving procedural success rates—defined as hemodynamic stabilization and in-hospital survival—close to 90%. Additionally, the incidence of major bleeding complications is relatively low, with reports indicating under 1% for ICH and about 5% for major bleeding or vascular injury.[23, 24] However, high-quality evidence from randomized controlled trials to support the efficacy and safety of these approaches is lacking. Due to challenges in powering trials for clinically significant outcomes, most studies on CDT for acute PE have concentrated on short-term surrogate outcomes. Previous observational studies have found that a right ventricular to left ventricular (RV/LV) diameter ratio greater than 0.9 correlates with 30-day mortality, becoming a reliable tool for assessing patients at risk for adverse outcomes.[25, 26]

According to the 2019 ESC guidelines, current indications for CDT in high-risk PE include the urgent treatment of patients with contraindications to systemic thrombolysis, which may account for one-third to over half of this population, and of patients who receive systemic thrombolysis but remain in refractory shock, representing another 10%. For intermediate-high risk PE patients, CDT are recommended when there is hemodynamic deterioration despite anticoagulation, serving as an alternative to rescue thrombolytic therapy.[9] The 2022 ESC/EAPCI clinical consensus on percutaneous treatment options for acute PE has expanded this indication to include cases of treatment failure defined as a lack of improvement in vital signs after 24-48 hours of therapeutic-dose anticoagulation.[27] For optimal outcomes, it is essential that CDT is conducted exclusively at centers with teams skilled in endovascular procedures, including interventional cardiologists or radiologists. Additionally, a multidisciplinary pulmonary embolism response team (PERT) should be present to assess, select, and implement the treatment.

Catheter-Directed Thrombolysis

The rationale for using catheter-directed lysis (CDL) is to achieve similar effectiveness in clot reduction and hemodynamic improvement while minimizing bleeding risks compared to systemic thrombolysis. By administering thrombolytic therapy directly into the thrombus, CDL exposes a larger surface area of the clot to the drug and prevents the agent from being shunted to unobstructed pulmonary segments.[28] This targeted approach allows for a higher local concentration of the thrombolytic agent, often using lower doses, which results in fewer bleeding complications while maintaining similar efficacy in surrogate outcomes.

CDL typically employs one or two catheters, either a pigtail or, more commonly, a dedicated side-hole catheter to deliver the thrombolytic agent directly into the pulmonary arteries. Examples of dedicated catheters include the Uni-Fuse (AngioDynamics; 4 or 5 Fr), Cragg-McNamara (Medtronic; 4 or 5 Fr), and the Pulse-Spray infusion system (AngioDynamics; 3,4 or 5 Fr).[29] Another device, the Bashir endovascular catheter (Thrombolex; 7 Fr), features an expandable nitinol basket with multiple side holes that facilitate both thrombolytic infusion and mechanical thrombus disruption.[30] While dosing regimens may vary, they generally consist of an initial bolus followed by an infusion of 0.5-1 mg/h of alteplase per catheter for 12-24 hours, with a total dose not exceeding 30 mg. The infusion can be halted earlier if major bleeding occurs, and catheters can often be removed bedside without requiring repeat imaging.[31]

Ultrasound-assisted thrombolysis (USAT) is another technique that combines ultrasound energy with local thrombolysis to enhance pulmonary reperfusion. The EKOS Endovascular System (Boston Scientific; 5.4 or 7.8 Fr) is the most common ultrasound-assisted catheter, featuring a double lumen: one for thrombolytic infusion and the other containing a filament with multiple ultrasound transducers that emit pulsed high-frequency, low-energy waves. The ultrasound energy is thought to enhance the lysis process by aiding in the propagation of lytic agents and directly altering the structure of the fibrin clot by dissociating the fibrin strands, potentially increasing the efficacy of CDL and allowing for shorter infusion times.[32]

Evidence supporting CDL is limited, comprising a small randomized trial and several single-arm prospective studies. The ULTIMA trial was a landmark randomized controlled study that evaluated the efficacy and safety of USAT in 59 patients with acute intermediate-risk PE, demonstrating significant reductions in RV/LV ratio and RV dysfunction at 24 hours, with no increase in bleeding risk compared to systemic anticoagulation alone.[33] The PERFECT and SEATTLE II trials were single-arm studies involving respectively 101 and 150 intermediate and high-risk PE patients, both showing significant reductions in RV/LV ratio and pulmonary artery systolic pressures with CDL.[29,34] In the SEATTLE II trial, an 11% major bleeding rate was reported among patients treated with USAT, primarily related to access site complications. Concerns about safety prompted the OPTALYSE PE trial to evaluate lower doses of thrombolytic agents. This trial included 101 patients divided into four groups with varying doses and infusion durations of alteplase, yielding similar reductions in RV/LV ratio at 48 hours, although lower doses (4-12 mg) and shorter duration (2-6 hours) resulted in diminished thrombus clearance.[35] Subsequent safety analyses, including the CANARY trial in intermediate-high risk patients (N=94) submitted to standard CDL and the KNOCOUT PE registry in intermediate-high to high-risk PE patients (N=489) submitted to USAT, confirmed the efficacy of CDL techniques with lower rates of major bleeding.[36,37] The RESCUE trial further demonstrated the efficacy of the Bashir catheter in 109 intermediate-risk PE patients, showing a significant decrease in RV/LV diameter and pulmonary artery obstruction at 48 hours, with only one reported major bleed.[30]

A recent meta-analysis of 45 studies involving 81 705 patients compared the efficacy and safety of CDT, systemic thrombolysis, and anticoagulation alone for acute PE. CDT showed lower mortality rates (OR 0.55, 95% CI: 0.39-0.80) but higher risks of major bleeding (OR 1.84, 95% CI: 1.10-3.08) and ICH (OR 1.51, 95% CI: 0.75-3.04) compared to anticoagulation. However, when compared to systemic thrombolysis, CDT demonstrated both lower mortality (OR 0.48, 95% CI: 0.34-0.68) and reduced risk of ICH (OR 0.66, 95% CI: 0.50-0.88).[38] USAT has been compared to standard CDL in the PERFECT trial, which found no differences in outcomes.[29] Additionally, in the randomized SUNSET-sPE trial involving 81 patients with intermediate-risk PE, no significant differences were observed in thrombus clearance, the primary endpoint, and the USAT group demonstrated a smaller RV/LV ratio reduction and a higher rate of major bleeding.[39] A recent meta-analysis of nine studies with 2610 patients indicated a significantly greater improvement in the RV/LV ratio for the standard CDL group compared to the USAT group, without notable differences in other outcomes, including in-hospital mortality or major bleeding.[40]

The key studies of catheter-directed thrombolysis are summarized in Table 1.

Table 1. Main studies of catheter-directed thrombolysis.

Study	Design	N	Population	Devices	Intervention	Control	Efficacy outcome	Safety outcomes
ULTIMA [33] (NCT01166997), 2013	Randomized, open-label	59	Intermediate--risk PE	EKOS	Anticoagulation plus USAT	Anticoagulation	ΔRV/LV ratio: 0.30±0.20 *vs* 0.03±0.16 (p<0.001) at 24h	All-cause death: 0 *vs* 3.4% major bleeding: 0 *vs* 0 at 90 days
SEATTLE II [34] (NCT01513759), 2015	Single-arm	150	Intermediate--high-risk PE	EKOS	Anticoagulation plus USAT	-	ΔRV/LV ratio at 48 h: 0.42±0.36 (p<0.0001)	All-cause death: 2.0% in-hospital, major bleeding: 10.0% at 30 days
PERFECT [29] (NCT01097928), 2015	Prospective, non- randomized	101	Intermediate--high and high-risk PE	EKOS vs Uni-Fuse / Pigtail vs Low-profile catheter	Anticoagulation plus CDT	4 CDT strategies*	ΔsPAP: 51.1±14.1 to 37.2±15,8 (p<0.0001) post-CDT	All-cause death: 5.9% in-hospital, 0 major bleeding at 30 days
OPTALYSE PE [35] (NCT02396758), 2018	Randomized, open-label	101	Intermediate--risk PE	EKOS	Anticoagulation plus USAT	4 tPA strategies **	RV/LV ratio reduced in all arms at 48±6h (p<0.01)	All-cause death:1.0% at 30 days, major bleeding: 4.0% at 72h
SUNSET sPE [39] (NCT02758574), 2021	Randomized, single-blind	81	Intermediate--risk PE	EKOS vs Cragg--McNamara or Uni-Fuse	Anticoagulation plus USAT	Anticoagulation plus CDL	ΔRV/LV ratio: 0.37±0.34 *vs* 0.59±0.42 (p=0.01) at 48h	All-cause death: 2.5% *vs* 0, major bleeding: 5.0% *vs* 0 at 3 months
CANARY [36] (NCT05172115), 2022	Randomized, open-label	94	Intermediate--high-risk PE	Cragg--McNamara	Anticoagulation plus CDT	Anticoagulation	RV/LV ratio >0.9: 4.3% *vs* 12.8% (p=0.24) at 90 days	All-cause death: 0 *vs* 6.5%, major bleeding: 2.2% *vs* 0 at 90 days
RESCUE [30] (NCT04248868), 2022	Single-arm	109	Intermediate--risk PE	Bashir	Anticoagulation plus CDT	-	ΔRV/LV ratio: 0.56±0.41 (p<0.0001) at 48h	All-cause death: 0, MAE: 0.9% at 72h
KNOCOUT PE [37] (NCT03426124), 2024	Prospective, non- randomized	489	Intermediate--high and high-risk PE	EKOS	Anticoagulation plus USAT	-	ΔRV/LV ratio: 0.37±0.38 (p<0.0001) at 48h	All-cause death: 0, MAE: 1.6% at 72h

* Standard CDL, USAT, MT, hybrid procedure. **Arm 1 (4 mg/lung/2 h), arm 2 (4 mg/lung/4 h), arm 3 (6 mg/lung/6 h), and arm 4 (12 mg/lung/6 h). CDL: catheter-directed thrombolysis; CDT: catheter-directed therapy; h: hours; LV: left ventricular; MAE: major adverse events; PE: pulmonary embolism; RV: right ventricular; tPA: tissue plasminogen activator; USAT: ultrasound-assisted thrombolysis.

Mechanical Thrombectomy

Mechanical thrombectomy (MT) refers to non-lytic, catheter--based therapies aimed at removing thrombus and alleviating obstruction in the pulmonary arteries. This approach employs various devices and techniques, including catheter-directed thrombus fragmentation, and rotational, rheolytic and aspiration thrombectomy. It can also be performed in combination with thrombolytic drug administration in a pharmacomechanical hybrid procedure, which enhances and accelerates the removal of thromboembolic obstruction and restores pulmonary perfusion.

Mechanical thrombectomy may be the preferred option for high-risk acute PE patients who have contraindications to systemic thrombolytics, as well as for up to 10% of patients who remain in shock after receiving thrombolytic therapy.[41] In unstable patients, the goal of MT is not complete thrombus removal but rather downstaging from high-risk to intermediate--risk PE. Among intermediate-risk acute PE patients, it is crucial to identify those with clinical signs indicative of a higher risk of hemodynamic instability despite adequate anticoagulation.[9] Additionally, patients must meet specific anatomical criteria; only thrombus located in the main, lobar, or interlobar pulmonary arteries should be targeted, as more distal emboli are more challenging to remove due to anatomical constraints and pose a higher risk.[42]

Catheter-Based Thrombus Fragmentation

Thrombus fragmentation can be achieved by manually rotating a pigtail catheter or inflating a peripheral balloon to break down proximal occlusive thrombus in hemodynamically unstable patients. This technique promotes distal embolization of smaller fragments, allowing for recovery of forward blood flow and partial decompression of the right ventricle until further treatment can be administered.[43] However, in the current era with dedicated embolectomy devices available, this method has largely become obsolete and is not without risks, particularly the potential for macroembolization and hemodynamic instability in previously non-occluded pulmonary artery branches.

Rheolytic Thrombectomy

The Angiojet device (Boston Scientific; 6Fr) employs high-speed saline jets that disrupt blood clots and create a vacuum to actively remove debris from the catheter tip. It can also deliver thrombolytic agents into the thrombus through its Power Pulse feature. While this technology is effective for treating acute PE, offering short treatment times and rapid restoration of blood flow, it has been associated with a higher incidence of severe bradyarrhythmias, including asystole and atrioventricular blocks secondary to the release of adenosine, bradykinin, or potassium due to hemolysis, as well as other procedure-related complications like hemoptysis and major haemorrhage at both access and non-access sites.[44] Consequently, the US Food and Drug Administration has issued a Black Box warning regarding its use in treating acute PE.

Rotational Thrombectomy

The Aspirex thrombectomy system (Becton Dickinson; 8Fr) is an over-the-wire rotational thrombectomy device equipped with a motor-driven, high-speed rotating spiral inside a catheter. This mechanism generates negative pressure through an aspiration system, which macerates and removes the thrombus via suction.[45] Research on rotational thrombectomy is limited, and its effectiveness and safety are not well established.[46] However, the procedure carries a considerable risk of vascular wall injury, and its use is currently not recommended for treating acute PE.

Aspiration Thrombectomy

Aspiration thrombectomy aims to remove thromboembolic material and prevent distal embolization by advancing a catheter directly into the thrombus and creating a vacuum (Fig. 1). Currently, it is the leading thrombectomy technique and includes three main devices.

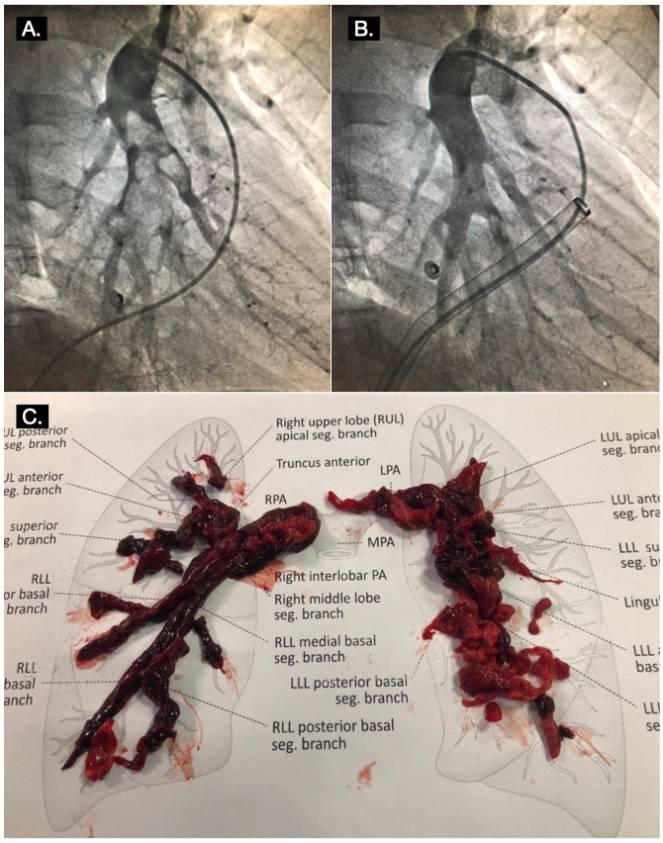

Figure 1. Bilateral central acute pulmonary embolism. A. Baseline angiography of the left pulmonary artery; B. Angiography of the left pulmonary artery following mechanical thrombectomy using the FlowTriever 24 Fr device; C. Reconstruction of the aspirated thrombus.

The FlowTriever system (Inari Medical) consists of three large-bore Triever aspiration catheters (16, 20 and 24 Fr) and a 60 mL aspiration syringe for manual thrombus aspiration. If aspiration is unsuccessful or incomplete, a self-expanding nitinol disc can be deployed inside the thrombus to mechanically engage and disrupt the clot. An important feature is the FlowSaver blood return system, which includes a microfilter that allows for the filtration and reinfusion of aspirated blood back to the patient, minimizing the blood loss associated with earlier device versions. The system can be accessed via the femoral or internal jugular vein using ultrasound guidance and can be positioned in the pulmonary vasculature through a stiff wire with short flexible tip. Although the device offers good flexibility and trackability, its size may limit its ability to safely navigate into more distal vessels. The use of the FlowTriever is supported by several key studies. The FLARE Study was a single-arm clinical trial involving 104 intermediate-risk PE patients, demonstrating significant improvements in RV/LV ratio and mean pulmonary artery pressure at 48 hours, with a 3.8% rate of major adverse cardiovascular events (MACE).[47] These findings were confirmed in the ongoing FLASH registry, which reported significant reductions in RV/LV ratio, mean pulmonary artery pressure, and severe dyspnea at 48 hours in the first 800 patients (92% intermediate-risk), with a MACE rate of 1.8% and

no device-related deaths.[48] The more recent non-randomized FLAME trial compared high-risk PE patients treated with the FlowTriever to those receiving other strategies, primarily systemic thrombolysis or anticoagulation alone. The composite primary endpoint—comprising in-hospital all-cause mortality, clinical deterioration, major bleeding, and bailout therapy—occurred in 17.0% of the FlowTriever group compared to 63.9% in the control group, with in-hospital mortality rates of 1.9% and 29.5%, respectively.[49]

The Indigo aspiration system (Penumbra) features an aspiration catheter connected to a continuous suction vacuum system. The first-generation 8 Fr catheter was replaced by a 12 Fr and 16 Fr caliber catheter in the latest models, respectively the Indigo Lightning and Indigo Lightning Flash systems. A continuous vacuum of -742 mmHg is generated by the Engine pump, allowing for the aspiration of blood and thrombus. The operator controls the application and removal of the vacuum via a flow switch, and an optional separator wire can be used to clear thrombus from the catheter tip. Current models incorporate computer-assisted vacuum thrombectomy (CAVT) technology, consisting on a microprocessor, flow sensors, and high-frequency electromechanical valves which automatically regulate aspiration to enhance thrombus removal while minimizing blood loss. Aspiration can be repeated across multiple pulmonary vessels until satisfactory results are achieved. Evidence supporting the Indigo device primarily comes from the EXTRACT-PE trial, which assessed the safety and efficacy of the first-generation Indigo system in 119 patients with intermediate-risk acute PE, showing a significant 27% reduction in RV/LV ratio at 48 hours with low rates of major bleeding (1.7%) and device-related deaths (0.8%).[50] The ongoing STRIKE-PE trial recently published interim results from its first 150 patients (94.7% intermediate-risk) using the Lightning 12 Fr device, which demonstrated a 25.7% reduction in RV/LV ratio, a 2.7% MACE rate, and no deaths at 48 hours. Follow-up at 90 days also indicated significant improvements in functional and quality of life measures.[51] This study has been recently expanded to include a total of 1500 patients, incorporating the Lightning Flash 16 Fr model.

The AngioVac system (AngioDynamics) consists of a 22 Fr catheter with a funnel-shaped balloon-expandable tip, a centrifugal pump, and an extracorporeal veno-venous bypass system that reinfuses filtered blood back into the patient. While it allows for the aspiration of large volumes of blood and thrombus, its size and rigidity can make navigation through complex anatomies challenging, and requires support from a perfusion team.[52] Data on its use for pulmonary emboli are limited to case reports and small series, indicating a significant rate of bleeding events. Currently, the AngioVac device is not considered optimal for PE extraction and is approved only for removing thrombi from the superior and inferior vena cava and the right atrium.[53] Recently, the same company introduced the AlphaVac, an 18 Fr or 22 Fr angulated cannula with a funnel-shaped tip, designed for manual aspiration without the need for circulatory support. Preliminary unpublished results from the single-arm APEX-AV study suggest significant reductions in LV/RV ratio and a 4.1% MACE rate at 48 hours in 122 intermediate-risk patients.

At present, there are no direct comparisons published between different MT devices. Additionally, clear comparative data between CDL and MT techniques for acute PE are lacking. Clinical trials evaluating each strategy against anticoagulation alone employed similar inclusion and exclusion criteria and endpoints, and reached comparable results in terms of right heart recovery, pulmonary arterial pressure reduction, and major adverse events, with slight excess bleeding noted in the CDL group and periprocedural complications in MT patients. Direct comparisons, such as those in the PERFECT registry between CDL and small-bore MT, or studies by Avgerinos *et al* and Graif A *et al* comparing CDL with various MT devices, have been underpowered and unable to demonstrate significant differences in effectiveness or safety.[29,54,55] The safety of both strategies was recently evaluated in the REAL-PE analysis, which examined electronic health records from over 83 million patients in the U.S. Among 2259 patients treated with CDL (Ekos) or MT (FlowTriever), the FlowTriever group exhibited a higher incidence of major bleeding according to ISTH and BARC definitions, as shown by direct laboratory analyses and transfusion records (ISTH MT 17.3% *vs* USCDT 12.4% p=0.002; BARC 3b MT 15.4% *vs* USCDT 11.8% p =0.019), and of ICH.[56]

The key studies of mechanical thrombectomy are summarized in Table 2.

Table 2. Main studies of mechanical thrombectomy.

Study	Design	N	Population	Devices	Intervention	Control	Efficacy outcome	Safety outcomes
FLARE [47] (NCT02692586), 2019	Single-arm	106	**Intermediate--risk PE**	FlowTriever	Anticoagulation plus MT	-	ΔRV/LV ratio: 0.38 (p<0.0001) at 48h	All-cause death: 0, MAE: 3.8% at 48h
EXTRACT-PE [50] (NCT03218566), 2021	Single-arm	119	Intermediate--risk PE	Indigo	Anticoagulation plus MT	-	ΔRV/LV ratio 0.43±0.26 (p<0.0001) at 48h	All-cause death: 0.8%; MAE: 1.7% at 48h
FLASH [48] (NCT03761173), 2023	Single-arm	800*	Intermediate and high-risk PE	FlowTriever	Anticoagulation plus MT	-	ΔRV/LV ratio: 1.23±0.36 to 0.98± 1.31 (p<0.0001) at 48h	All-cause death: 0.3%; MAE: 1.8% at 48h
FLAME [49] (NCT04795167), 2023	Prospective, non-randomized	104	High-risk PE	FlowTriever	Anticoagulation plus MT	Medical therapies	Composite of all-cause mortality, clinical deterioration, bailout, and major bleeding: 17% *vs* 63.9% in-hospital	All-cause death: 1.9% *vs* 29.5%; major bleeding: 11.3% *vs* 24.6% in-hospital
STRIKE-PE [51] (NCT04798261), 2024	Single-arm	150*	Intermediate--risk PE	Indigo Lighting	Anticoagulation plus CAVT	-	ΔRV/LV ratio: 0.38±0.27 (p<0.001) at 48h	All-cause death: 0, MAE: 2.7% at 48h
APEX-AV (NCT05318092), waiting to be published	Single-arm	122	Intermediate--risk PE	AlphaVac F18	Anticoagulation plus MT	-	ΔRV/LV ratio: 0.45±0.27 (p<0.001) at 48h	All-cause death 0, MAE: 4.1% at 48h

* Studies ongoing. CAVT; computer-assisted vacuum thrombectomy; h: hours; LV: left ventricular; MAE: major adverse events; MT: mechanical thrombectomy; PE: pulmonary embolism; RV: right ventricular.

Pharmacomechanical Strategies

Hybrid pharmacomechanical procedures, which involve the simultaneous or sequential use of MT and CDL, represent an appealing strategy due to their complementary and synergistic mechanisms of action. Thrombectomy typically provides a rapid hemodynamic improvement primarily through its debulking effect in proximal branches, while intrapulmonary thrombolysis can target more distal thrombus located in smaller vessels. Additionally, mechanical thrombus fragmentation enhances disaggregation by increasing the surface area exposed to locally infused fibrinolytics. Despite its implementation in some highly experienced centers, current evidence—mostly derived from small single--center registries—supports its feasibility and efficacy but raises concerns about a potentially higher bleeding risk.[57] As such, there is insufficient justification for its routine use at this time.

Ongoing Trials and Future Directions

Many current limitations in the evidence regarding the effectiveness and safety of CDT for managing acute PE may soon be addressed. Several ongoing clinical trials are investigating and comparing various percutaneous techniques, particularly in intermediate-high risk populations.

The PE-TRACT trial (ClinicalTrials.gov: NCT05591118) is an open--label, assessor-blinded, randomized study designed to compare CDL or MT combined with anticoagulation against anticoagulation alone in 500 patients with intermediate-high risk PE, proximal pulmonary artery thrombus, and right ventricular dilation.

CDL is also being compared to standard anticoagulation protocols in the HI-PEITHO (ClinicalTrials.gov: NCT04790370) and PRAGUE-26 (ClinicalTrials.gov: NCT05493163) trials. These studies aim to enroll approximately 406 and 558 intermediate-high risk patients, respectively, to evaluate the impact of USAT and heparin compared to standard anticoagulation on the 7-day incidence of all-cause mortality, hemodynamic decompensation, and PE recurrence. The STRATIFY study (ClinicalTrials.gov: NCT04088292) is a randomized single-blind, phase 3 trial that will compare USAT, low-dose systemic thrombolysis, and standard anticoagulation in a three-arm design, enrolling 210 intermediate-high risk patients. This trial aims to demonstrate a reduction in Miller score as assessed by CTPA at 96 hours.

Several studies evaluating MT devices are also in progress. The STORM-PE trial (ClinicalTrials.gov: NCT05684796) is a randomized clinical trial assessing the safety and efficacy of the Indigo Lightning system, comparing anticoagulation alone to anticoagulation

plus computer-assisted vacuum thrombectomy in 100 acute intermediate-high risk PE patients. Primary endpoints include changes in RV/LV ratio assessed by CTPA at 48 hours, major adverse events within 7 days, and functional outcomes and quality of life assessments at 90 days. The PEERLESS II trial (ClinicalTrials.gov: NCT06055920) is evaluating the FlowTriever system in 1200 intermediate-risk patients, randomizing them to receive either MT treatment or standard anticoagulation alone. The trial aims to assess 30-day hemodynamic decompensation, bailout therapy and all-cause hospital readmission, and 3-month all-cause mortality, PE-related mortality, and major bleeding. Additionally, the open-label, randomized PEERLESS Study (ClinicalTrials.gov: NCT05111613) will compare the outcomes of MT using the FlowTriever system with CDL using the Ekos device in 550 intermediate-high risk patients. The primary endpoint will be a composite measure including all-cause mortality, ICH, major bleeding, clinical deterioration, and ICU admission by discharge or 7 days. Finally, the PERSEVERE trial was just announced, and will randomize 200 high-risk PE patients to MT with FlowTriever device or to standard of care therapy. The primary composite endpoint will be all-cause mortality, cardiac arrest with loss of consciousness requiring CPR, bailout to an alternative therapeutic strategy, major bleeding and persistent need for ECMO at 7 days.

The conclusions drawn from these trials will be crucial in clarifying the role of CDT in the treatment of acute PE.

Conclusion

In the past decade, catheter-directed therapies for acute PE have seen significant advancements in both the devices available and the supporting scientific evidence. While these techniques have emerged as effective and safe options, demonstrating marked improvements in right ventricular strain and hemodynamics with a low incidence of bleeding complications, there remains a lack of high-quality evidence to support their use as a first-line treatment for any risk category of PE. Nevertheless, a shift towards a personalized treatment approach in specialized centers is anticipated, with the outcomes of ongoing clinical trials playing a crucial role in defining the place of percutaneous therapies in PE management.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.

Suporte Financeiro: Não existiram fontes externas de financiamento para a realização deste artigo.

Proveniência e Revisão por Pares: Comissionado; sem revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Commissioned; without external peer review.

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