Catheter-directed therapy for acute pulmonary embolism: navigating gaps in the evidence

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Systemic thrombolysis for acute pulmonary embolism (PE) reduces the risk of death and cardiovascular collapse but is associated with an increased rate of bleeding. The desire to minimize the risk of bleeding events has driven the development of catheter-based strategies for pulmonary reperfusion in PE. These catheter-based strategies utilize lower-dose fibrinolytic regimens or purely mechanical techniques to expedite removal of the embolus. Several devices providing mechanical or suction embolectomy and catheter-directed thrombolysis, with or without facilitation by ultrasound, have been tested. Data are inconsistent regarding the efficacy and safety of mechanical and suction embolectomy. The most comprehensive data on catheter-based techniques stem from trials of ultrasound-facilitated catheter fibrinolysis. Ultrasound-facilitated catheter fibrinolysis relieves right ventricular pressure overload with a lower risk of major bleeding and intracranial haemorrhage than historical rates with systemic fibrinolysis. However, further research is required to determine the optimal application of ultrasound-facilitated catheter fibrinolysis and other catheter-based therapies in patients with acute PE.

Introduction

Pulmonary embolism (PE) is an increasingly common cause of cardiovascular death.1 Rapid implementation of advanced therapies, mainly the administration of systemic thrombolysis, is recommended in acute high-risk PE with shock or sustained hypotension to achieve prompt reversal of pulmonary arterial obstruction and right ventricular (RV) failure.2,3 Evidence-based clinical guidelines also recommend systemic thrombolysis for initially haemodynamically stable patients with both RV dysfunction and elevated cardiac biomarkers if shock or hypotension develops.2,3

Systemic thrombolysis reduces the risk of haemodynamic collapse and mortality in these clinical situations,4,5 and lowers overall in-hospital mortality.6 However, the benefits of systemic thrombolysis are offset by a nearly five-fold increase in the risk of major bleeding and a 10-fold increase in the risk of intracranial haemorrhage, as observed in the randomized, controlled PEITHO study (Pulmonary Embolism ThrombOlysis trial).4 Analyses of non-selected patient data report a rate of thrombolysis-associated intracranial haemorrhage ranging from 3% to 5%.7,8 Furthermore, data from a nationwide database showed that, among unstable patients with acute PE, only 30% actually received recommended thrombolytic therapy.9

The desire to minimize the risk of adverse events such as intracranial bleeding, or to offer alternatives to thrombolysis in patients with high bleeding risk, has driven the development of catheter-based strategies for pulmonary reperfusion. In the present review, we critically appraise the evidence for catheter-directed therapy for the treatment of acute PE including mechanical and suction embolectomy, and catheter-directed thrombolysis, with or without facilitation by ultrasound.

Embolectomy devices

Various catheter-based embolectomy devices have been evaluated for restoration of pulmonary perfusion in acute
Table 1 summarizes the main results of mechanical and suction embolectomy device studies.

**Mechanical embolectomy**

A feasibility study of 20 patients showed that simple fragmentation of thrombus by rotation of a pigtail catheter provided an improvement in haemodynamics, as measured by a decrease from pre- to post-fragmentation of the shock index, from 1.28 ± 0.53 to 0.95 ± 0.38 (P = 0.011), mean pulmonary artery pressure (PAP) from 31 ± 5.7 mmHg to 28 ± 7.5 mmHg (P = 0.02), and mean angiographic score from 7.4 to 5.0. However, it was not clear that fragmentation

| Method                        | Device          | Number of patients | Outcomes                                                                                     |
|-------------------------------|-----------------|--------------------|----------------------------------------------------------------------------------------------|
| Mechanical thrombectomy       | Pigtail¹⁰       | n = 20             | – Δ pre- and post-procedure:                                                                  |
|                               |                 |                    | Shock index: from 1.28 ± 0.53 to 0.95 ± 0.38 (P = 0.011)                                       |
|                               |                 |                    | sPAP: from 31 ± 5.7 mmHg to 28 ± 7.5 mmHg (P = 0.02)                                          |
|                               |                 |                    | Angiographic score: from 7.4 to 5.0                                                          |
|                               | Amplatz System¹¹| n = 9              | – Δ pre- and post-procedure:                                                                  |
|                               |                 |                    | 5 received additional thrombolysis                                                            |
|                               |                 |                    | Miller score: from 18 to 11                                                                   |
|                               |                 |                    | sPAP: from 57 to 55 mmHg (to 39 mmHg after tPA infusion)                                      |
|                               | AngioJet System¹²| n = 51             | – Significant improvement after procedures in:                                               |
|                               |                 |                    | Pulmonary obstruction                                                                        |
|                               |                 |                    | Shock: 27.5%                                                                                 |
|                               |                 |                    | Hypotension: 15.7%                                                                           |
|                               |                 |                    | RV dysfunction: 56.8%                                                                         |
|                               | AngioJet System¹³| n = 15             | – Resolution of symptoms and improvement in heart strain were achieved in all patients       |
|                               |                 |                    | No in-hospital death                                                                         |
|                               |                 |                    | Acute kidney injury: 20%                                                                      |
|                               |                 |                    | Per-procedure cardiac arrest: 1                                                               |
| Suction thrombectomy          | Greenfield      | n = 46             | – Clinical success: 76%                                                                       |
|                               | catheter¹⁴      |                    | – Δ pre- and post-procedure:                                                                  |
|                               |                 |                    | sPAP: from 32 to 24 mmHg                                                                      |
|                               |                 |                    | CO: from 2.59 L/min to 4.47 L/min (P = 0.003)                                                 |
|                               |                 |                    | 30-day survival rate: 70% in the 36 patients with additional IVC filter implantations          |
|                               | AngioVac System¹⁵| n = 3              | – Removal thrombus: 33%                                                                       |
|                               | AngioVac System¹⁶| n = 5              | – Δ Miller index ≥ 5: 40%                                                                     |
|                               |                 |                    | Massive PE: 80%                                                                               |
|                               | AngioVac System¹⁷| n = 7              | – In-hospital death rate: 80% (one death related to RV free wall perforation)                |
|                               | AngioVac System¹⁸| n = 1              | – Partial or complete clot removal: 100%                                                       |
|                               |                 |                    | – No procedure-related death                                                                  |
|                               | Penumbra system¹⁹| n = 6 with submassive PE | – Improvement on RV function on TOE                                                         |
|                               |                 |                    | – Patient discharge at Day 4                                                                   |
|                               | Penumbra system| The EXTRACT trial—ongoing | – Δ pre- and post-procedure:                                                                 |
|                               | Flowtricier System²⁰| n = 106           | sPAP: from 58.2 to 43.0 mmHg                                                                  |
|                               |                 |                    | RV/LV ratio: from 1.7 to 1.1                                                                   |
|                               |                 |                    | CT obstructive index: From 60.4% to 47.0%                                                    |
|                               |                 |                    | No periprocedural complication                                                                |
|                               |                 |                    | – 30-day major adverse events: 3.8%                                                            |

Δ, variation; ECMO, extracorporeal membrane oxygenation; IVC, inferior vena cava; LV, left ventricle; N, number of patients; PE, pulmonary embolism; RV, right ventricle; sPAP, systolic pulmonary arterial pressure; TOE: transoesophageal echocardiography.
itself was helpful in this study, because 75% of the reported cases were performed in conjunction with thrombolytic infusion.\textsuperscript{10}

The Amplatz thrombectomy device (Microvena, White Bear Lake, MN, USA) is a 6-Fr catheter that incorporates a high-pressure, air-driven, high-speed impeller, creating a vacuum vertex that pulls thrombus into the distal tip of the catheter, fragmenting it into small particles. This system was used in nine patients with acute PE, of whom five were treated with additional thrombolysis. The Miller score, which was used to objectively quantify the pulmonary obstruction on angiography, decreased from 18 to 11. The mean PAP was reduced from 57 to 55 mmHg after mechanical embolectomy. The addition of thrombolytic therapy achieved further reduction of mean PAP to 39 mmHg, raising the question of the value of the mechanical component of the procedure.\textsuperscript{11}

The Angiojet catheter (Boston Scientific, Marlborough, MA, USA) provides both clot fragmentation and aspiration of thrombus fragments. Saline jets directed into the thrombus at the distal end of the catheter result in fragmentation. At the same time, aspiration of thrombi is achieved at catheter side ports from high velocity saline looping back into a second lumen creating a Venturi effect. The Angiojet device achieved a significant reduction in pulmonary obstruction in two studies that recruited 66 patients in total.\textsuperscript{12,13} However, the study by Nassiri et al.\textsuperscript{13} which included 15 patients, was complicated by two cases of post-procedural renal failure and one cardiopulmonary arrest. Chechi et al.\textsuperscript{12} reported in 51 patients, 24% of renal failure and bradycardia requiring transvenous pacing in 8%. A meta-analysis of published series on invasive treatment of massive PE found that rheolytic embolectomy with the Angiojet catheter was associated with a higher incidence of bradycardia, haemolysis, and procedure-related deaths compared with other invasive modalities.\textsuperscript{21} As a result, the U.S. FDA issued a black-box warning on the device label regarding its use in PE treatment.\textsuperscript{22}

**Suction embolectomy**

Suction embolectomy was one of the earliest techniques for transcatheter treatment of PE, and was introduced by Greenfield et al.\textsuperscript{14} using a 12-Fr catheter with a cup on its distal end. Suction was applied manually to the catheter hub with a large syringe. The authors reported 46 patients including 33 massive PE, 4 submassive, and 4 chronic. Thrombus was extracted in 35 of 46 patients (76%). Haemodynamic data showed an average reduction in mean PAP of 8 mm Hg and a significant increase in mean cardiac output from 2.59 L/min to 4.47 L/min (P \textless 0.003) after embolectomy. After the adoption of prophylactic inferior vena cava filter insertion following the procedure, the 30-day survival increased from 50% in the first 10 patients to 70% in the next 36 patients.\textsuperscript{14} Because of the size and difficulty of placement of the Greenfield suction embolectomy catheter, the device fell out of favour.

Three available large-bore aspiration catheters have been tested for the treatment of acute PE. The Angiovac system (Angiodynamics Inc., Latham, NY, USA), approved by the U.S. FDA for the percutaneous retrieval of unwanted intravascular material, has been used in the pulmonary arteries. This system is a large 22-Fr catheter that can remove thrombus through a centrifugal pump and venous reinfusion cannula used in cardiopulmonary bypass. There have been case reports and small observational series reporting the use of this device for thrombus removal in the pulmonary arteries with mixed results.\textsuperscript{15–18} A retrospective review of five consecutive cases in whom the Angiovac aspiration cannula was used included four patients with massive PE and one with submassive PE. Technical success, defined as successful removal of some thrombus combined with the reduction of the Miller score \textgeq 5, was achieved in two of the four patients with massive PE. Four patients died at a mean of 7.3 days, all having presented with massive PE. One death was related to catheter perforation of the RV free wall.\textsuperscript{16} In a small series of three patients in whom embolectomy of the pulmonary arteries was attempted with the Angiovac device, the procedure was unsuccessful in two of the three patients. Limited success has been attributed to size, stiffness, and lack of manoeuvrability of the device.\textsuperscript{15}

The Penumbra Indigo aspiration system (Penumbra Inc., Alameda, CA, USA) is an 8-Fr device with the flexibility for placement in segmental branches of the pulmonary arteries. A single-centre study, including six patients with submassive PE (mean age 62.7 ± 19 years), reported that systolic PAP (58.2 mmHg vs. 43.0 mmHg, P < 0.05), RV/ left ventricular (LV) ratio (1.7 vs. 1.1, P < 0.05), Miller index (15.0 vs. 9.8, P < 0.01), and computed tomography-derived obstructive index (60.4% vs. 47.0%, P < 0.01) were significantly reduced after mechanical embolectomy.\textsuperscript{19} The ongoing EXTRACT-PE (Evaluating the Safety and Efficacy of the Indigo Aspiration System in Acute Submassive Pulmonary Embolism) trial is a single-arm, prospective, multicentre trial evaluating the safety and efficacy of the Penumbra Indigo aspiration system in submassive PE (ClinicalTrials.gov: NCT03218566).

An alternative large lumen extraction device, the Flowtriever (Inari Medical, Irvine, CA, USA) includes a 20-Fr sheath, a flow-restoration catheter with three self-expanding nitinol discs, and a retraction aspirator, providing a vacuum for clot aspiration. The FLARE study was a prospective, multicentre, single-arm study evaluating the FlowTriever system in 106 patients with acute PE. Patients with proximal PE and right heart strain ([RV/LV] ratio \textgeq 0.9] were eligible to participate.\textsuperscript{20} The mean RV/LV ratio decreased from a baseline value of 1.53 to 1.15 at 48 h post-procedure (P < 0.0001). Median intensive care unit stay was 1 day, and overall median length of hospital stay was 3 days. The rate of the safety endpoint, major adverse events at 30 days, was 3.8%. Based on these results, the U.S. FDA approved the FlowTriever System for the treatment of acute PE in May 2018.\textsuperscript{22}

**Catheter-directed thrombolysis**

Catheter-directed thrombolysis allows delivery of the thrombolytic agent directly to the area of highest embolic burden via a catheter. The potential advantage of local
complications. The overall success rate, defined by stabilization of haemodynamics, regression of hypoxia and hospital survival, was 86.5% (95% confidence interval (CI) 82.1–90.2). The success rate was higher in patients treated by a combination of embolectomy plus catheter-directed thrombolysis in situ compared to systemic thrombolysis group. In a meta-analysis of 35 non-controlled studies including a total of 544 patients with high-risk PE, 33% of patients were treated by embolectomy alone and 66% by embolectomy plus catheter-directed thrombolysis. The overall success rate, defined by stabilization of haemodynamics, regression of hypoxia and hospital survival, was 86.5% (95% confidence interval (CI) 82.1–90.2). The success rate was higher in patients treated by a combination of embolectomy plus catheter-directed thrombolysis in situ compared to systemic thrombolysis group. In a meta-analysis of 35 non-controlled studies including a total of 544 patients with high-risk PE, 33% of patients were treated by embolectomy alone and 66% by embolectomy plus catheter-directed thrombolysis.

Ultrasound-assisted catheter-directed thrombolysis

The addition of high-frequency, low-power ultrasound to catheter-directed thrombolysis is hypothesized to disaggregate fibrin fibres, potentially exposing a greater number of binding sites for the low-dose thrombolytic agent. The EKOS system (Ekos Corp., Bothell, WA, USA) is an ultrasound-facilitated catheter-directed fibrinolytic device approved for treatment of PE in May 2014 by the U.S. FDA on the basis of two clinical trials and other published observational data. The EKOS system consists of a 5.4-Fr infusion catheter with microscopic side holes and markers delineating the active area, an ultrasound core catheter that has low-intensity ultrasound transducers, and a control unit. The infusion catheter has both a drug delivery lumen and a central coolant channel. Table 2 displays the main characteristics and outcomes of studies focusing on ultrasound-assisted catheter-directed thrombolysis. The European-based Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial randomized 59 patients with PE and RV dysfunction to receive either heparin alone (n = 29), or heparin plus ultrasound-facilitated catheter-directed thrombolysis [10-20 mg of tissue plasminogen activator (t-PA) (n = 30)]. The primary outcome, namely the difference in the RV/LV ratio from baseline to 24h, was reduced in the ultrasound-assisted catheter-directed thrombolysis group compared to heparin alone (0.30 ± 0.20 vs. 0.03 ± 0.16; P < 0.001).

The SEATTLE II trial was a 150-patient prospective, single-arm, multicentre U.S. trial evaluating the EKOS catheter with infusion of 24 mg of t-PA over 24 h. SEATTLE II included both massive (n = 31; 20.7%) and submassive PE patients (n = 119; 79.3%). Mean RV/LV diameter ratio (1.55 vs. 1.33; mean difference, 0.22; P < 0.0001), mean systolic PAP (51.4 mmHg vs. 36.9 mmHg; P < 0.0001), as well as the modified Miller Index score (22.5 vs. 15.8; P < 0.0001) decreased from baseline to 48 h post-procedure.

Table 2 Trials focusing on ultrasound-facilitated catheter-directed thrombolysis and their main outcomes

| Study          | N   | High-risk PE | Mortality with shock or hypotension | Mortality with RV dysfunction | ICH | Major bleeding |
|----------------|-----|--------------|------------------------------------|------------------------------|-----|----------------|
| SEATTLE II      | 150 | 31 (20.7)    | 1 (0.6)                            | 2 (1.3)                      | 0 (0) | 13 (8.6)       |
| Bloomer et al. | 137 | 16 (12)      | 5 (3.6)                            | 0 (0)                        | 2 (1.4)| 13 (9.4)       |
| PERFECT         | 100 | 28 (28)      | 4 (4.0)                            | 2 (2.0)                      | 0 (0) | 0 (0)          |
| Liang et al.    | 69  | 10 (14.5)    | 1 (1.4)                            | 1 (1.4)                      | 0 (0) | 2 (2.9)        |
| Kennedy et al.  | 60  | 12 (20)      | 3 (5)                              | 0 (0)                        | 0 (0) | 0 (0)          |
| McCabe et al.   | 53  | 0 (0)        | 0 (0)                              | 0 (0)                        | 1 (1.8) | 2 (3.7)   |
| Engelberger et al. | 52  | 14 (26.9)    | 2 (3.8)                            | 0 (0)                        | 0 (0) | 1 (1.9)        |
| Nykamp et al.   | 45  | 13 (28.9)    | 0 (0)                              | 0 (0)                        | 0 (0) | 0 (0)          |
| Bagla et al.    | 45  | 0 (0)        | 0 (0)                              | 0 (0)                        | 0 (0) | 0 (0)          |
| ULTIMA          | 30  | 0 (0)        | 0 (0)                              | 0 (0)                        | 0 (0) | 0 (0)          |
| Yoo et al.      | 28  | 12 (42.9)    | 4 (14.2)                           | 0 (0)                        | 0 (0) | 1 (3.6)        |
| Engelberger et al. | 24  | 5 (20.8)     | 0 (0)                              | 0 (0)                        | 0 (0) | 4 (16.6)       |
| Dumantepe et al. | 22  | 8 (36.4)     | 1 (4.5)                            | 0 (0)                        | 0 (0) | 0 (0)          |
| Lin et al.      | 11  | 11 (100)     | 0 (0)                              | 0 (0)                        | 0 (0) | 0 (0)          |
| Quintana et al. | 10  | 2 (20)       | 0 (0)                              | 0 (0)                        | 0 (0) | 0 (0)          |
| Total          | 844 | 172 (20.3)   | 5 (0.6)                            | 22 (2.6)                     | 3 (0.3)| 37 (4.4)       |

ICH: intracranial haemorrhage; PE, pulmonary embolism; RV, right ventricle.

aPulmonary embolism without haemodynamic instability but with right ventricular dysfunction on imaging.

b36% of patients treated with ultrasound-facilitated catheter-directed thrombolysis.
No intracranial haemorrhage was observed, and major bleeding occurred in 15 patients (10%). Major bleeding was primarily related to access site bleeding due to multiple venous access attempts (odds ratio 10.1, 95% CI 1.98–51.5; \( P = 0.005 \)).

Numerous other non-randomized, non-comparative studies including both haemodynamically stable and unstable PE patients, albeit all with RV dysfunction, have reported comparable results in terms of improvement in RV function. Figures 1 and 2 illustrate changes in systolic PAP and RV/LV ratio endpoints in studies evaluating ultrasound-assisted catheter-directed thrombolysis for the treatment of acute PE. A meta-analysis showed an average reduction in systolic PAP of 15.8 mmHg (95% CI 12.2–19.5), and in the RV/LV ratio of 34% (95% CI 25–42) with the use of ultrasound-facilitated catheter-directed thrombolysis. The in-hospital mortality rate was 12.9% among patients with high-risk PE with hypotension, and 0.74% in patients with normotensive PE and associated RV dysfunction. Data from the Italian Pulmonary Embolism Registry (IPER), which reported in-hospital management and outcomes of patients diagnosed with PE in everyday clinical practice, showed mortality rates of 31.8% in massive PE and 4.3% in haemodynamically stable patients. Tafur et al. performed a meta-analysis including a total of 653 patients that showed a mortality rate of 9% among patients treated by catheter-directed thrombolysis without ultrasound-assistance, and of 4% in those treated with ultrasound-assisted thrombolysis.

The OPTALYSE PE study demonstrated that shorter delivery duration and a lower dose of tPA was an effective strategy. In this study, 101 intermediate-risk PE patients (mean age 58 years; 48% women) were randomly assigned to four different tPA infusion regimens: 8 mg/2 h, 8 mg/4 h, 12 mg/6 h, and 24 mg/6 h. The primary endpoint (RV/LV ratio change from baseline to 48 h) decreased significantly by between 23% and 26% in all four treatment groups. The overall major bleeding rate was 3%. Two patients suffered intracranial haemorrhage; however, one of these patients received an additional 50 mg of systemic tPA after the procedure. No major bleeding was observed in the arms receiving 8 mg tPA/2 h and 12 mg tPA/6 h.

**Discussion and perspectives**

When viewed in aggregate, data are inconsistent regarding the efficacy and safety of mechanical and suction embolectomy, except with the use of the FlowTriever system, which showed promising results. Evidence is mounting for ultrasound-facilitated catheter-directed thrombolysis for the improvement of RV function in patients with shock or RV dysfunction, with a low rate of procedural adverse events, including intracranial haemorrhage. Recently published data from the OPTALYSE-PE study with the use of even lower doses of thrombolytic agent show greater safety for ultrasound-facilitated catheter-directed thrombolysis.

However, clinical outcome-based trials with appropriate comparator groups are still lacking to define the optimal utilization of ultrasound-facilitated catheter-directed thrombolysis. Only 59 patients were included in one randomized trial evaluating ultrasound-facilitated catheter-based thrombolysis, compared with over 1700 patients included in randomized studies of systemic thrombolysis. Increased RV/LV ratio and PAP are reproducible and well-validated tools for identifying PE patients at risk of adverse outcomes. Although an improvement in RV function is an important surrogate endpoint, further studies with clinical outcomes are needed to confirm the positive results of catheter-based therapy in PE. Moreover, the role of catheter-directed therapy should be defined for intermediate-high risk PE with both right heart strain and myocardial injury, a clinical situation in which management is still a subject of debate. The randomized PEITHO trial showed a lower rate of early haemodynamic
decompensation for systemic thrombolysis compared to standard anticoagulation but failed to demonstrate efficacy of t-PA on residual pulmonary hypertension or RV dysfunction at follow-up, as well as on early and late death.\textsuperscript{4,47} The low level of evidence of current clinical PE guidelines, which recommend catheter-directed therapy as an alternative to surgical embolectomy if systemic thrombolysis is contraindicated or has failed, reflects all of these unresolved questions.\textsuperscript{2}

Several prospective cohort and randomized studies are ongoing to better define the position of catheter-directed therapy in the PE treatment algorithms. The KNOCOUT PE registry is a U.S.-based registry designed to further evaluate the efficacy and safety of the ultrasound-facilitated catheter thrombolysis in PE with RV dysfunction and will include important outcomes such as change in RV function as well as death, recurrent of venous thromboembolism (VTE), bleeding, and quality of life with a follow-up of 1 year. The estimated enrolment is 1500 participants and the expected completion date is 2020. Two randomized studies using robust primary outcome criteria (i.e. mortality, recurrent VTE) are under way to compare catheter-directed thrombolysis, with or without ultrasound-assistance [SUNSET sPE trial (ClinicalTrials.gov NCT02758574) and USAT-CDT Trial (ClinicalTrials.gov NCT03086317)].

**Conclusion**

In conclusion, encouraging results with a suction embolectomy device have recently been reported. The ultrasound-facilitated catheter-directed thrombolysis system has demonstrated an improvement in RV function after procedures with a low rate of adverse events. It is possible with further research that an approach involving catheter-directed therapy may become the preferred method for PE reperfusion for the treatment of both high and intermediate-high risk PE.

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**Figure 2** Changes in right ventricular/left ventricular ratio in studies focusing on ultrasound-assisted catheter-directed therapy. CI, confidence interval; RV/LV, right ventricle/left ventricle; SD, standard deviation.

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