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Catheter-directed therapy to treat intermediate- and high-risk pulmonary embolism: Personal experience and review of the literature

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Abstract

Pulmonary embolism (PE) is the third leading cause of cardiovascular death in the western world. Prompt recognition, risk stratification, and individualized treatment are crucial to improve outcomes in patients with PE. Anticoagulation alone is a sufficient therapeutic option in low-risk patients, whereas primary reperfusion with systemic thrombolysis (ST) is usually chosen in high-risk patients. The choice of treatment in intermediate-risk patients is complex and depends on the clinical presentation. Catheter-directed therapy (CDTh) includes all therapies delivered via a catheter placed in the branches of the pulmonary arteries directly into the thrombus. Because ST bears a high risk of major bleeding and numerous patients have contraindications to ST, CDTh is an alternative to ST in intermediate- and high-risk PE patients. CDTh includes local thrombolysis using low-dose alteplase, ultrasound-assisted thrombolysis, and mechanical fragmentation and aspiration of the thrombi, as well as their combinations. In this review article, we have summarized devices and technical details for CDTh, discussed the efficacy and safety of CDTh in comparison to ST in previous clinical trials, and outlined future research directions regarding CDTh, both based on the literature and our personal experience from the local PE Response Team of the Center for the Management of Pulmonary Embolism (CELZAT) in Warsaw.
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Key words: pulmonary embolism, catheter-based therapy, interventional cardiology, review

Introduction

Pulmonary embolism (PE) is the third leading cause of cardiovascular death in the western world, associated with 5–10% in-hospital mortality [1]. PE is frequently a complication of deep vein thrombosis (DVT), referred to as venous thromboembolism (VTE) [2]. The symptoms of PE range from shortness of breath, through severe dyspnea, chest pain, and hemoptysis, to the clinical picture of cardiogenic shock. Because these symptoms are unspecific, clinical scores have been proposed to evaluate the risk of PE, such as the Wells score and the Geneva score. These scores include the main risk factors for VTE, including previous DVT or PE, immobilization, surgery, especially after pelvis

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and femoral neck fracture, or active malignancy. Other risk factors for VTE are states of overall hypercoagulability such as pregnancy, antiphospholipid state, or genetic mutations of proteins C and S [3, 4]. All these factors contribute to blood flow stasis, vessel wall damage, and/or hypercoagulability, which are known as the Virchow triad [5].

Besides unspecific symptoms, stratification of the risk of early mortality also poses a clinical challenge in PE patients. The Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI), which are scores based on clinical presentation and the patient's history, are useful to determine the risk of PE-associated mortality. PESI class III–V or sPESI ≥ 1 denotes intermediate- or high-risk patients. In addition, right ventricle (RV) dysfunction on transthoracic echocardiography (TTE) or computed tomography pulmonary angiography (CTPA), and elevated biomarkers of cardiac injury are indicative of intermediate- or high-risk PE. Signs of hemodynamic instability with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE are sufficient to classify a patient into the high-risk PE category [6–8]. Currently, hemodynamic instability, which delineates acute high-risk PE, is defined as one of the following clinical manifestations at presentation: (i) cardiac arrest; (ii) obstructive shock (systolic blood pressure [SBP] < 90 mmHg or the need for vasopressor therapy, and end-organ hypoperfusion); or (iii) persistent hypotension (SBP < 90 mmHg or a drop ≥ 40 mmHg for more than 15 min). Altogether, patients with high-risk PE present with clear signs of hemodynamic instability, whereas intermediate-/high-risk patients are hemodynamically stable but have signs of RV dysfunction or myocardial necrosis.

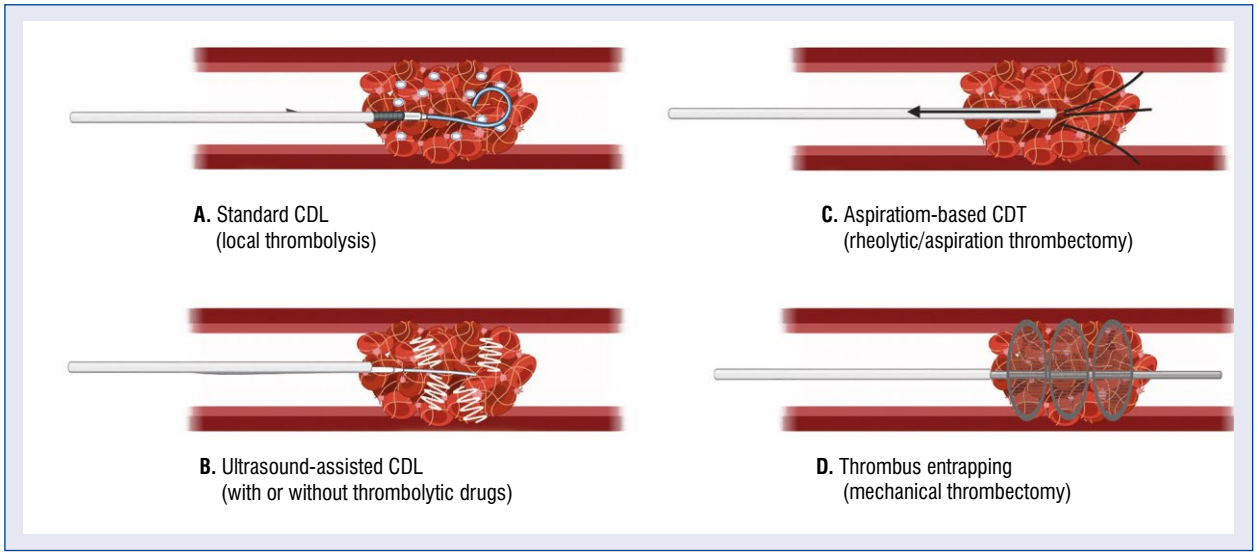
Prompt recognition, risk stratification, and individualized treatment are crucial to improve outcomes in patients with PE. Anticoagulation alone is a sufficient therapeutic option in low-risk patients, whereas systemic thrombolysis (ST) is usually chosen in high-risk patients. The choice of treatment in intermediate-risk patients is complex and depends on the clinical presentation. Moreover, in numerous patients, the hemodynamic status changes over time, requiring adjustment of therapy [9, 10].

Whereas ST decreases RV overload, thus improving the hemodynamic state in patients with PE, the high doses of thrombolytic agents administered during ST, delivered in a short time frame (50–100 mg tissue plasminogen activator [TPA] over 15 min – 2 h), bear a high risk of major bleeding (9.9%), including intracranial hemorrhage (1.7%) [11, 12]. Hence, the net clinical benefit of ST is hampered by the associated complications. Numerous patients have contraindications to ST, such as active internal bleeding, recent ischemic stroke, intracranial surgery or arterial puncture, history of previous intracranial hemorrhage, low platelet count, or coagulation disturbances at presentation [13, 14].

Catheter-directed therapy (CDTh) and surgical embolectomy are alternatives to ST in intermediate- and high-risk PE patients with hemodynamic deterioration despite anticoagulation and in patients in whom thrombolysis is contraindicated or has failed. Whereas surgical embolectomy is an invasive procedure carried out with cardiopulmonary bypass and requiring the incision of the pulmonary arteries to remove the thrombi, CDTh is a less invasive approach to interventional PE treatment. CDTh includes all therapies that are delivered via a catheter placed in the branches of the pulmonary artery (PA) directly into the thrombus. CDTh ranges from local catheter-directed thrombolysis (CDL) using low-dose alteplase, through ultrasound-assisted thrombolysis, to mechanical fragmentation and aspiration of the thrombi, known as catheter-directed thrombectomy (CDT), as well as combinations of these methods [15, 16]. Preliminary data suggest that CDTh has a procedural success rate of above 80%, defined as hemodynamic stabilization, correction of hypoxemia, and survival to hospital discharge. In addition, the rate of major bleeding complications might be reduced in CDTh, compared with ST. However, a clear mortality benefit of CDTh remains to be demonstrated [16–19]. In this review article, we have summarized devices and technical details for CDTh, discussed the efficacy and safety of CDTh in comparison to ST in the main clinical trials, and outlined future research directions to investigate whether CDTh is a viable alternative to ST in intermediate- and high-risk PE patients, or in those with contraindications to ST. The presented information is based both on the literature and our personal experience, gathered during the interdisciplinary consultation of the PE patients within the local PE Response Team of the Center for the Management of Pulmonary Embolism (PERT CELZAT) in Warsaw.

Devices and technical details for CDTh

Although CDTh emerged about two decades ago, evidence-based data on its efficacy and safety are scarce. Numerous devices have been approved for CDTh of PE and are mentioned in the guidelines, but no device is specifically recommended, so the choice of the device for CDTh is at the operator's discretion [20].



Central illustration. Devices approved for catheter-directed therapy (CDTh) in pulmonary embolism; **A.** Standard catheter-directed thrombolysis (CDL); **B.** Ultrasound-assisted CDL (EKOS™ Endovascular System); **C.** Aspiration--based catheter directed thrombectomy (CDT) (AngioJet™, Penumbra Indigo® System, AngioVac System); **D.** Thrombus entrapping using mesh discs (FlowTriever Infusion Aspiration System).

Catheter-directed therapy can be used with or without thrombolysis (catheter-directed thrombolysis; CDL or CDT). CDL includes standard local thrombolysis and ultrasound-assisted thrombolysis. CDT comprises rheolytic thrombectomy, aspiration thrombectomy, and mechanical thrombectomy. There are also combinations of thrombolysis- and thrombectomy-based techniques [7]. Devices approved for CDTh in PE are shown in the Central illustration. The pros and cons of currently available CDTh are shown in Table 1.

Devices

Standard CDL

Standard CDL (Central illustration A) is based on local administration of the low-dose alteplase, compared to the high dose administered during ST (1 mg/h up to a total of 24 mg of TPA vs. 50–100 mg of TPA, respectively). Standard CDL is performed using a multi-hole infusion catheter such as the Uni-Fuse™ (AngioDynamics, Lanthan, US), advanced through a venous access site (jugular or common femoral vein) towards the right atrium, RV, and placed in the PA, in the vicinity of the thrombus [13, 21, 22].

Ultrasound-assisted thrombolysis

Ultrasound-assisted thrombolysis (USAT; Central illustration B) is another method of CDL. During USAT, ultrasound waves are used for thrombus fragmentation, thus accelerating local TPA dispersion and facilitating thrombolysis [23]. USAT requires a specialized type of catheter with small ultrasound transducers such as the EKOS™ Endovascular System (Boston Scientific, Bothell, WA, USA) [24]. Although initially considered more efficient than standard thrombolysis, in the SUNSET sPE trial, patients with sub-massive PE treated with USAT had similar 48-h clearance of pulmonary thrombus compared with those undergoing standard CDL, using comparable mean lytic doses and durations of lysis [25].

Rheolytic CDT

Rheolytic thrombectomy (Central illustration C) is based on the Bernoulli principle, in which high velocity retrograde-directed saline jets are used to create a low-pressure area for thrombus aspiration at the distal part of the catheter [26]. The aspiration is facilitated by the local pulse spray of a thrombolytic drug. Rheolytic CDT can be performed using an AngioJet™ (Boston Scientific, Marlborough, MA, USA) [27]. Although initially promising and effective in peripheral arteries and veins [28], when used in the pulmonary arteries, AngioJet™ was associated with bradycardia, pulmonary vasospasm, and worsening hypoxia, as well as increased mortality [28]. These side effects have been attributed to the release of adenosine from disrupted platelets. Therefore, the Food and Drug

Table 1. Pros and cons of current Food and Drug Administration (FDA)-approved catheter-directed therapies (CDTh) in pulmonary embolism.

Name of technique	Pros	Cons	Example of device	Ref.
Catheter-directed thrombolysis (CDL)				
Standard CDL	Can be performed using a multi-hole infusion catheter Enables to decrease the dose of thrombolytic drug, compared to systemic thrombolysis	Risk of hemorrhagic complications inherent to administration of thrombolytic drug	UniFuse® (AngioDynamics) Cragg-McNamara® (ev3 Endovascular)	[7, 20]
Ultrasound-assisted CDL	Ultrasound facilitates penetration of the thrombolytic agent over a shorter duration	Requires a specialized catheter No difference compared to standard CDL	EKOS™ Endovascular System (Boston Scientific)	[23, 26]
Without thrombolysis				
Rheolytic thrombectomy	Easy to apply Enables clot fragmentation and aspiration without the need to administer thrombolysis	High incidence of bradycardia, hemoptysis, renal failure Black box warning by FDA regarding its use in pulmonary embolism	AngioJet™ (Boston Scientific)	[30]
Aspiration thrombectomy	Easy to apply Enables clot fragmentation and aspiration without the need to administer thrombolysis	Provides inconsistent suction and requires experience to operate the syringe	(Penumbra Indigo® System, Penumbra)	[31–33]
Vacuum thrombectomy	Limited blood loss due to a centrifugal pump reinfusing blood into a venous canula	Size and stiffness of the apparatus limit its maneuverability	AngioVac System (Angio Dynamics)	[34–36]
Mechanical thrombectomy	Rotator drive unit attached to a wire which rotates at ~4000 RPM, enabling de-clotting Retractable nitinol disks that mechanically retrieve the clot, additional vacuum provided by an aspirator	Potential fatigue of the sinuous wire may occur with prolonged activation Kinking of the device may limit its maneuverability	Cleaner XT™ (Argon Medical)* FlowTriever Infusion Aspiration System (Inari Medical)	[37]

*The Cleaner XT™ Rotational Thrombectomy System is registered for mechanical de-clotting of dialysis fistulae and peripheral vasculature, but its use in patients with pulmonary embolism remains off-label.

Administration has issued a "black box" warning for AngioJet™ [29].

Aspiration thrombectomy

During aspiration thrombectomy, an end-hole catheter is placed inside the thrombus. Using a syringe, negative pressure (vacuum) is applied, and the thrombus is manually aspirated [30]. While easy to apply, it provides inconsistent suction and requires experience to operate the syringe. To circumvent these disadvantages, another system available on the market (Penumbra Indigo® System, Penumbra, Alameda, CA, USA) implements automatic suction, ensuring consistent and labor-free suction through an 8F catheter [31, 32]. This system also uses a retractable separator that moves back and forth, thus facilitating thrombus fragmentation [33]. The short-term (48 h) safety

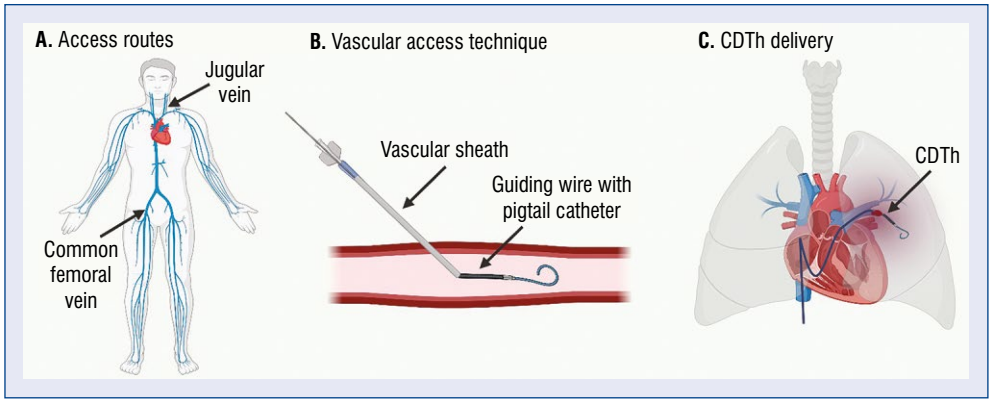


Figure 1. Common steps of catheter-directed therapy (CDTh) in pulmonary embolism; **A.** Access routes; **B.** Vascular access technique; **C.** CDTh delivery.

and efficacy of the Penumbra Indigo® System was confirmed in the EXTRACT-PE study [31]. An ongoing multicenter STRIKE-PE study is evaluating the long-term (90 days) safety and efficacy of this system in patients with PE (NCT04798261).

AngioVac

Aspiration methods are all burdened with blood loss due to suction. A potential solution to this problem is the AngioVac System (Angio Dynamics, Latham, NY, USA). It is an aspiration-based method, in which the blood that has been sucked out is at the same time administered into a venous access port. Although mitigating the blood loss, this device requires a cardiovascular pump and a perfusionist to operate on it [34–36].

FlowTriever

Finally, there is a new device called the FlowTriever Infusion Aspiration System (Inari Medical, Irvine, CA, USA). Instead of a simple, large-bore catheter, the FlowTriever removes the thrombus by ensnaring it between 3 retractable mesh disks that are unfolded out of the catheter. Once the thrombus is trapped, the 3 disks are re-sheathed and removed together with the clotting material [37].

Technical details

Although the devices for CDTh vary, the procedures consist of common steps. These steps have been summarized in Figure 1.

Before the procedure, it is important to check whether no left bundle branch block is present because manipulations of the catheters in the right heart chambers can cause a right bundle branch block, resulting in a complete heart block. In addition, it is crucial to exclude right heart mobile thrombi, which are contraindications performing CDTh.

First, a venous access must be obtained, which is based on the operator's preference. The femoral common vein and the internal jugular vein are both common access sites (Fig. 1A). The disadvantage of the femoral vein is that the thrombus can be present there due to DVT, which might complicate the procedure. Furthermore, if an inferior vena cava filter has previously been inserted, for example in patients with recurrent PE, it may cause problems with advancement of the catheter [38]. Therefore, ultrasound guidance during venipuncture is useful. If the clot is bilateral and a thrombolysis-based technique is used, it is advisable to use two sheaths, one for each catheter, which are subsequently placed in the right and left PA.

Following insertion of the vascular sheath, a guidewire is advanced via the inferior vena cava towards the right atrium and RV, and further into the PA (Fig. 1B, C). Because advancing the catheters via the right heart chambers may damage the chordae of the tricuspid valve, it is common to start the procedure using a pigtail catheter [39].

After advancing the catheter the PA pressure should be measured. Normal mean PA pressure ranges between 8 and 20 mmHg [36]. After the placement of the catheter, the next steps vary depending on the device used. As an example, we will use a standard CDL. The catheter is placed in the vicinity of the pulmonary embolus and low doses of thrombolytic agent are administered (usually TPA at the rate of 0.5–1.0 mg/h over the course of 12–24 h). The continuous infusion of unfrac-

tionated heparin is also used to achieve 2.5-fold prolongation of the activated partial thromboplastin time to prevent peri-sheath thrombus formation. After the procedure, the patient should be admitted to the intensive care unit and monitored for any major bleeding events, especially intracranial hemorrhage. The procedure is deemed a clinical success if the pressure in the PA drops and signs of RV strain decrease. The catheter may then be removed at bedside [19].

To perform a CDT procedure, similar steps are applied. Through a venous access, a thrombectomy catheter is advanced using a guidewire into the PA. After the catheter has been placed in the vicinity of the thrombus, clot is fragmented and aspired manually or with the help of vacuum force, without the need to administer thrombolysis. This process can be facilitated using retractable separators, available in some devices [30, 31].

Efficacy and safety of CDTh in clinical trials

Currently, percutaneous CDTh should be performed with high-risk PE patients who are unsuitable candidates for thrombolysis due to contraindications or failure of previous therapy, as well as in low- or intermediate-risk PE as an alternative to rescue thrombolytic therapy for patients with hemodynamic deterioration on anticoagulation treatment (class IIa recommendations, based on expert opinion) [7]. However, it is still unclear which therapeutic approach to choose for patients suffering from intermediate- or high-risk PE on anticoagulation treatment, whose hemodynamic status is not improving or is worsening [40]. These recommendations are based on 5 main clinical trials, which aimed to evaluate the outcomes in PE patients treated with CDTh. Despite the differences in study designs and methods to evaluate RV strain (RV/LV ratio, PA pressure, RV dilatation) [40], all these trials concluded that CDTh improved the hemodynamic status in patients with PE and may be associated with less bleeding events than ST, although no direct head-to-head comparisons between CDTh and ST are available. Because all these studies were single arm and conducted in relatively small groups of patients (59–150), their results should be interpreted with caution and require confirmation in future randomized trials. Evidence regarding the efficacy and safety of CDTh in patients with PE is summarized in Table 2.

SEATTLE II trial

The SEATTLE II study was a single-arm, multicenter trial to evaluate the efficacy safety of

Table 2. Efficacy and safety of catheter-directed therapy vs. systemic thrombolysis in patients with pulmonary embolism.

	SEATTLE II	PERFECT	ULTIMA	OPTALYSE PE	FLARE	EXTRACT-PE
Patients (number)	150	101	30	101	106	119
Mean age [years]	59	60	63	60	55	59
Mean BMI [kg/m^2]	35.6	31.0	31.0	35.8	35.8	36.7 women 31.7 men
RV/LV index change	1.55 → 1.13	NA	1.28 → 0.99	Arm 1: 1.47 → 1.07 Arm 2: 1.43 → 1.08 Arm 3: 1.49 → 1.02 Arm 4: 1.51 → 1.03	1.56 → 1.15	1.47 → 1.03
Decrease in SPAP [mmHg]	51.4 → 37.5	51.7 → 37.23	52.0 → 39.7	NA	29.8 → 27.8	NA
Bleeding events (number, %)	17 major (11%) 0 minor (0%)	0 major (0%) 13 minor (12%)	0 major (0%) 3 minor (10%)	4 major (3.9%) NA	1 major (0.9%) NA	2 major (1.7%)
Mortality (number, %)	4 (3%)	6 (9%)	0 (0%)	1 (1%)	1 (0.9%)	3 (2.5%)

BMI — body mass index; LV — left ventricle; NA — not available; RV — right ventricle; SPAP — systolic pulmonary artery pressure

ultrasound-assisted, catheter-directed fibrinolysis using the EKOS™ Endovascular System. To classify PE as massive (31 patients), patients had to present signs of syncope, systolic hypotension, or cardiogenic shock. Sub-massive PE (119 patients) was diagnosed in patients with PE, normotension, and RV disfunction. Other inclusion criteria were proximal PE, PE symptoms for less than 14 days, and an RV/LV index greater than 0.9. Patients with stroke or transient ischemic attack, head trauma, massive surgery during the last 7 days, major bleeding, or coagulation disorders were excluded from the study. All 151 patients (mean age 59 years, 51% female) received unfractionated heparin to achieve activated partial thromboplastin time between 40 and 60 s. The doses of thrombolytic drugs were as follows: 1 mg/h for 24 h with a unilateral catheter or 1 mg/h per catheter for 12 h with bilateral catheters. PA pressure was measured at the start of the procedure (after 24 h in patients with unilateral PE and after 12 h in patients with bilateral PE). The primary safety outcome (major bleeding within 72 h of procedure initiation) occurred in 17 (11%) patients, including 1 severe bleeding event and 16 moderate bleeding events, according to GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) scale [41]. The primary efficacy outcome showed a decrease in the RV/LV diameter ratio within 48 h of procedure initiation, measured with computed tomography, from 1.55 at baseline to 1.13 after 48 h from initiation ($p < 0.0001$). The mean PA systolic pressure (51.4 mmHg vs. 36.9 mmHg) and mean Miller angiographic obstruction index score (22.5 vs. 15.8; also decreased at 48 h after CDL initiation; $p < 0.0001$ for both). Three patients died during hospitalization, and one died during 30 days after discharge.

Altogether, SEATTLE II showed that ultrasound-assisted CDL reduced RV dilation, pulmonary hypertension, and anatomic thrombus burden, and was associated with moderate bleeding risk in patients with acute-massive and sub-massive PE.

PERFECT trial

The PERFECT TRIAL evaluated the efficacy and safety of CDTh in 101 patients with acute PE (mean age 60 years, 52% female), either massive ($n = 28$), defined as acute PE with hypotension (SBP < 90 mmHg), or sub-massive ($n = 73$), defined as acute PE with increased RV strain, but without hypotension [42]. Massive PE was treated using pharmacomechanical methods excluding the AngioJet™ device. For treatment of sub-massive PE, standard CDL or USAT were used. The thrombolytic agent was either urokinase (100,000 IU/h) or TPA (0.5–1.0 mg/h). All patients were administered a low dose of heparin (300–500 IU/h) to prevent peri-sheath thrombosis. The primary efficacy endpoints were defined as meeting the following criteria: decrease in PA pressure and/or right heart strain, stabilization of hemodynamic parameters (SBP > 90 mmHg without pressor support), and in-hospital survivability. Safety endpoints were measured in bleeding events and procedure-related complications. Twenty-four of 28 (85.7%) patients with massive PE and 71/73 (97.3%) with sub-massive PE were treated with clinical success. Seventy-eight of 82 (89.1%) patients had a PA pressure decrease (51.2 mmHg before treatment vs. 37.2 mmHg after the procedure). Fifty-seven of 64 (89.1%) patients monitored with follow-up echocardiography showed improvement in RV function. In terms of safety outcomes, there were no major procedure-related complications, no major hemorrhages, and no hemorrhagic strokes. Thirteen of 101 (95%) patients had a minor bleeding event. All of them were self-limited. Six patients died: 4 due to massive PE and 2 due to sub-massive PE.

The PERFECT trial showed that CDTh leads to a decrease in PA pressure and right heart strain and is not associated with major bleeding events. Similar outcomes were observed in patients treated with standard CDL and USAT-assisted CDL, questioning the superiority of USAT over CDT in patients with massive and sub-massive PE.

ULTIMA trial

The ULTIMA trial compared the efficacy and safety of USAT and anticoagulation alone in 59 patients with intermediate-risk acute PE (mean age 63 years). Patients were randomized to receive either USAT, along with local administration of 20 mg of TPA on top of anticoagulation (30 patients), or to receive unfractionated heparin alone (29 patients). All patients suffered from acute PE for less than 14 days and had an RV/LV dilatation ratio > 1.0. The exclusion criteria were age < 18 and > 80 years, major bleeding or high bleeding risk, PE symptoms for > 14 days, low image quality in echocardiographic study, and no possibility to assess the RV/LV dilatation ratio. Patients with signs of cardiogenic shock (SBP < 90 mmHg) were also excluded from the trial. The main outcome measure was the change in RV/LV dilatation ratio between baseline and 24 h after the initiation of USAT or administration of heparin. Mean PA

pressure was measured before the procedure and after 24 h. A 90-day follow-up was scheduled, including echocardiography. Safety outcomes included bleeding, hemodynamic decompensation, and death during 90 days after the procedure. In the USAT group the mean RV/LV dilatation ratio decreased from 1.28 at baseline to 0.99 after 24 h. In contrast, hardly any decrease was observed in the heparin group — from 1.20 at baseline to 1.17 at 24 h. Mean PA systolic pressure decreased from 52.0 mmHg to 39.7 mmHg after 18 h in the USAT group (no invasive PA pressure measurement was performed in the heparin group). There were no deaths in the USAT group and 1 death in the heparin group, unrelated to PE. No patient suffered from hemodynamic decompensation or major bleeding events. Minor bleeding occurred in 3 patients from the USAT group and in one patient from the heparin group [43].

To conclude, USAT resulted in a greater short-term reduction in the RV/LV dilatation ratio than anticoagulation alone. However, the differences between the two groups at 90 days were no longer significant, leaving the question regarding the long-term benefits of USAT unanswered.

OPTALYSE PE trial

The OPTALYSE PE trial aimed to study the lowest optimal TPA dose and delivery using USAT for the treatment of acute PE. A total of 101 patients (18–75 years of age) presenting symptoms of acute, intermediate-risk PE were enrolled. All patients suffered from PE for less than 14 days, had normal SBP (defined as > 90 mmHg), and a RV/LV diameter ratio > 0.9. The exclusion criteria were head injury, active or recent major bleeding, stroke or transient ischemic attack, low platelet count, and hematocrit < 30%. Those who had had major surgery up to 7 days before enrolment were also excluded from the trial. All patients received therapeutic anticoagulation with unfractionated heparin. Patients were randomized into 4 arms: 2 mg/h TPA for 2 h (total 4 mg TPA for unilateral PE and 8 mg TPA for bilateral PE); 1 mg/h TPA for 4 h (total 4 mg TPA for unilateral PE and 8 mg TPA for bilateral PE); 1 mg/h TPA for 6 h (total 6 mg TPA for unilateral PE and 12 mg TPA for bilateral PE); and 2 mg/h TPA for 6 h (total 12 mg TPA total for unilateral PE and 24 mg TPA for bilateral PE). The primary efficacy endpoint was the change in the RV/LV diameter ratio measured at baseline and 48 h after the procedure. The secondary efficacy endpoint was the change in the modified Miller score, measured at baseline and 48 h after the procedure. The safety outcomes were major bleeding events within 72 h after the procedure, symptomatic recurrent PE, and mortality. A decrease in RV/LV diameter ratio was observed in all arms (0.40, 0.35, 0.42, and 0.48 decrease, respectively). The modified Miller score decreased by 5.5% in arm 1, 9.2% in arm 2, 14.0% in arm 3, and 25.7% in arm 4. No major bleeding events occurred in arm 1. In other arms, 5 bleeding events occurred in 4 patients. One patient died within 30 days, and the estimated 12-month mortality was 2% [44].

In conclusion, a decrease of RV/LV diameter ratio was registered in all 4 infusion regimens. There was no evidence of one regimen being superior in efficacy and safety to the other.

FLARE trial

The FLARE trial evaluated the safety and efficacy of percutaneous mechanical thrombectomy using the FlowTriever System (Inari Medical, Irvine, CA, USA) in 106 patients with acute, intermediate-risk PE, aged 18–75 years, with a PE duration < 14 days. Patients had to be hemodynamically stable (SBP > 90 mmHg, heart rate < 130 beats/min) and have a RV/LV ratio > 0.9. Among the exclusion criteria were contraindication to anticoagulant therapy, thrombolytic therapy within 30 days of the trial and active cancer. The decrease in RV/LV ratio during the initial 48 h after treatment was the main efficacy endpoint. Safety endpoints were defined as major bleeding, mortality, and device- or treatment-related adverse effects. Two out of 106 patients received additional thrombolytic drugs due to a large thrombus burden. In total, 101 patients received anticoagulation before the procedure. The mean decrease in RV/LV ratio at 48 h was 0.38. Four patients experienced 6 major adverse effects [37]. It was concluded that the use of the FlowTriever System for percutaneous mechanical thrombectomy seems to be safe and effective in patients with acute intermediate-risk PE.

EXTRACT-PE trial

The Extract-PE trial evaluated the safety and efficacy of the Indigo Aspiration System (Penumbra, Alameda, CA, USA) for the treatment of acute PE without the use of thrombolytic drugs. It enrolled 119 patients > 18 years old (44.5% women), who presented with symptoms of acute, sub-massive PE for less than 14 days. The inclusion criteria comprised also SBP > 90 mmHg and RV/LV ratio > 0.9. Exclusion criteria were as follows: TPA administration within 14 days of

baseline, major trauma within 14 days, active cancer, cardiovascular or pulmonary surgery within 7 days, and pulmonary hypertension. The main efficacy endpoint was the change in RV/LV ratio from baseline to 48 h after the procedure. The main safety endpoints were the rates of major adverse effects such as major bleeding, device-related death, and other device-related adverse effects within 48 h after the procedure. Secondary safety endpoints consisted of all-cause mortality, procedure-related adverse effects, and the recurrence of PE symptoms within 30 days. The mean RV/LV dilatation ratio decreased from 1.47 at baseline to 1.04 at 48 h after the procedure (0.43 reduction). A 4.3-mmHg reduction in PA pressure was observed immediately after thrombus aspiration. An overall 4.7-mmHg decrease in PA pressure was measured after the procedure. During the initial 48 h, 2 patients experienced serious adverse effects. One patient suffered from major bleeding and one from both device-related hemoptysis and major bleeding, which led to the patient's death. During the 30-day observation period, 2 patients died due to progression of pre-existing diseases. Three patients experienced procedure-related adverse effects [31]. The authors concluded that the use of the Indigo Aspiration System led to a reduction in the RV/LV ratio and was associated with a low rate of major adverse events in intermediate-risk PE patients and may be considered for use in this subpopulation.

Conclusions and future directions

Catheter-directed therapies are emerging and promising methods to treat both high-risk PE, if ST is contraindicated or has failed, or low- or intermediate-risk PE in the case of hemodynamic deterioration despite anticoagulation. Previous trials have consistently shown that CDTh leads to a significant decrease in PA pressure and right heart strain, thus improving hemodynamic status. They seem to be associated with fewer bleeding events compared to ST, which clearly indicates that CDTh might be a similarly efficient and safer option compared to ST and may therefore lead to a breakthrough in the treatment of acute PE. The low doses of thrombolytic drugs seem safer than systemic therapy, even in patients with contraindications to thrombolysis, which might improve outcomes. Furthermore, CDT may be used without administration of thrombolytic drugs, as a mechanical way of clot debulking, which further decreases the bleeding risk. Based on our experience in the last 5 years, there were 235 PERT activations, including 80 (34.0%) activations in intermediate-/high-risk patients and 21 (8.9%) activations in high-risk patients. CDTh was used in 11 (4.7%) patients and included aspiration thrombectomy in 5 patients (Penumbra Indigo® System, Penumbra), mechanical thrombectomy in 2 patients (Cleaner XT™, Argon Medical), and the combined use of different techniques in 4 patients (aspiration or mechanical thrombectomy along with catheter-directed thrombolysis).

The trials that addressed the efficacy and safety of CDTh evaluated imaging surrogates as endpoints but did not provide firm evidence regarding improved outcomes, including mortality. In addition, the single-arm design of most trials, without a control group receiving ST or treated with surgical pulmonary embolectomy, as well as the use of different CDTh methods evaluated in previous studies, complicate the interpretation of the results. Finally, different inclusion criteria and endpoints make it difficult to compare the studies and objectively determine the results of treatment with CDTh. Altogether, more randomized trials are urgently needed to draw firm conclusions considering the potential superiority of CDTh over ST, as well as to form new recommendations regarding the most efficient and safe method of CDTh and to identify the target groups of patients who might especially benefit from catheter-directed treatment [39].

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