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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Repeat angiography in patients undergoing conventional catheter-directed thrombolysis for submassive pulmonary embolism: a large single-center experience

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PURPOSE
Few studies have examined conventional catheter-directed thrombolysis (CDT) for the treatment of submassive pulmonary embolism (PE). Moreover, angiographic resolution of thrombus burden following CDT has infrequently been characterized. This study describes a single-center experience treating submassive PE with CDT while utilizing repeat angiography to determine treatment effectiveness.

METHODS
A retrospective analysis of 140 consecutive patients who underwent CDT for submassive PE from December 2012 to June 2019 was performed. Angiographic resolution of thrombus burden after CDT was reported as high (>75%), moderate (51%–75%), low (26%–50%), or insignificant (≤25%). All angiograms were reviewed by two interventional radiologists. Secondary endpoints included reduction in pulmonary artery pressure (PAP) and clinical outcomes. Bleeding events were classified according to the Society of Interventional Radiology (SIR) adverse event criteria.

RESULTS
CDT was performed in 140 patients with a mean recombinant tissue plasminogen activator (rtPA) dose of 25.3 mg and a mean treatment time of 26.0 hours. Angiographic resolution of thrombus burden was high in 70.0%, moderate in 19.3%, low in 5.7%, and insignificant in 3.6%; in 2 patients (1.4%) repeat angiography was not performed. Systolic PAP was reduced (47 vs. 35 mmHg, $p < 0.001$), mean PAP was reduced (25 vs. 21 mmHg, $p < 0.001$), and 129 patients (92.1%) improved clinically. Patients with high or moderate resolution of thrombus burden had a clinical improvement rate of 95.2%, while patients with low or insignificant thrombus burden resolution had a clinical improvement rate of 76.9% ($p = 0.011$). Ten patients (7.1%) had hemodynamic or respiratory decompensation requiring mechanical ventilation, systemic thrombolysis, cardiopulmonary resuscitation, or surgical intervention. Seven patients (5.0%) experienced moderate bleeding events and one patient (0.7%) with metastatic disease developed severe gastrointestinal bleeding that resulted in death. Thirty-day mortality was 1.4%.

CONCLUSION
In patients with submassive PE undergoing CDT, angiographic resolution of thrombus burden is a safe and directly observable metric that can be used to determine procedural success. In this study, CDT with repeat angiography was associated with a 5.7% bleeding event rate and 30-day mortality of 1.4%.

Pulmonary embolism (PE) is a major cause of morbidity and mortality in the United States, with an estimated 300 000–600 000 cases per year resulting in 100 000–180 000 deaths (1). Among patients with acute PE, there is significant heterogeneity in clinical presentation. Submassive or intermediate-risk PE comprises at least 25% of PE cases and has a 30-day mortality rate of approximately 2%–3% (2–5). Patients with submassive PE have signs of right ventricle (RV) dysfunction demonstrated on imaging studies or elevated cardiac biomarkers (6). Several catheter-directed therapies for submassive PE have been explored, including conventional catheter-directed thrombolysis (CDT), ultrasound-assisted CDT (UACDT), and various types of mechanical thrombectomy.

UACDT has been the subject of multiple investigations and is effective in reducing pulmonary artery pressure (PAP) and right ventricular to left ventricular (RV/LV) ratio in pa-

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tients with submassive or massive PE (7–9). Despite the recent focus on UACDT, conventional CDT remains an effective treatment option and several authors have demonstrated no differences between UACDT and conventional CDT in terms of thrombolytic dose, bleeding complications, PAP reduction, follow-up echocardiographic findings, or mortality (7, 10–12). Mechanical thrombectomy devices are of particular interest in treating PE since they reduce PAP, RV/LV ratio, and thrombus burden with a low risk of bleeding events (13, 14).

Currently there is little in the literature to recommend the routine use of CDT for submassive PE, and endpoints evaluating the effectiveness of CDT in this indication have been inconsistent (15). Several studies have used reductions in PAP or RV/LV ratio as endpoints, while others have focused on improvement of clinical symptoms (8, 9, 16–18). The goal of this study was to describe a single-center experience treating submassive PE with conventional CDT while utilizing repeat angiography to determine treatment effectiveness. In addition, this study attempted to contribute to the standardization of terms that describe angiographic resolution of thrombus burden.

Methods

Study design

This retrospective study was conducted at a large university medical center and was approved by the institutional review board with a waiver of informed consent under protocol number 1911183851. Patients who underwent CDT for PE from December 2012 to June 2019 were identified through a local radiological information system. A total of 156 patients were found who presented with acute PE and were recommended for CDT intervention. Eleven of these patients were excluded since they met criteria for massive PE at the time of hospital presentation. Five patients with submassive PE were excluded: three underwent UACDT, one died prior to CDT initiation, and one suffered hemodynamic compromise requiring systemic thrombolysis instead of the planned CDT intervention. Ultimately, 140 patients who presented with submassive PE and underwent conventional CDT were included in this study.

Main points

- In patients undergoing catheter-directed thrombolysis (CDT) for submassive pulmonary embolism (PE), higher degrees of thrombus clearance are associated with higher rates of clinical improvement.
- In this study, CDT for submassive PE was associated with a 5.7% bleeding event rate and 30-day mortality of 1.4%.
- Repeat angiography is a directly observable method of determining procedural success in patients undergoing CDT for submassive PE.
- Pulmonary artery pressures are heavily influenced by underlying cardiopulmonary disease and do not reliably correlate with the degree of angiographic improvement after CDT in patients with submassive PE.

Patient population

All patients included in this study were diagnosed with PE by multidetector contrast-enhanced computed tomography (CT) or ventilation-perfusion scan. Patients met criteria for submassive PE if they had evidence of RV dysfunction or myocardial necrosis in the absence of persistent hypotension (systolic blood pressure < 90 mmHg for >15 minutes). RV dysfunction was defined by the presence of one of the following findings on CT or echocardiography: right ventricle to left ventricle (RV/LV) ratio > 0.9, RV dilatation or hypokinesia, septal bowing or flattening, or RV pressure >35 mmHg. Additionally, brain natriuretic peptide (BNP) levels >90 pg/mL were considered indicative of RV dysfunction. Myocardial necrosis was defined as an elevation in troponin-I level >0.03 ng/mL. All treatment decisions were made by a multidisciplinary pulmonary embolism response team (PERT) comprised of an emergency medicine physician, intensivist, and an interventional radiologist.

Demographic, clinical, and serologic data were collected for all patients who presented with submassive PE and underwent conventional CDT. Symptoms of PE at the time of presentation were recorded as well as risk factors for PE and personal history of deep vein thrombosis (DVT) or PE. The imaging modality used to diagnose PE was documented for each patient, and echocardiogram results were collected if available. Laboratory values including BNP and troponin-I levels were also noted.

CDT procedure

CDT was accomplished using Unifuse (Angiodynamics) or Cragg-McNamara (Medtronic) conventional infusion catheters. After venous access was obtained using ultrasound guidance, initial pulmonary artery manometry and angiography were performed to assess thrombus burden and location. Infusion catheters were then placed in the pulmonary arteries under direct fluoroscopic guidance. Patients with single catheter placement received recombinant tissue plasminogen activator (rtPA) (Activase; Genentech) at 0.5–1 mg/hr while patients with two catheters received 1.0 mg/hr divided between catheters. Systemic anticoagulation with heparin was achieved using a low-dose thrombostabilizer protocol with a target activated partial thromboplastin time (aPTT) of 53–68 seconds. Follow-up pulmonary artery manometry and angiography were performed at 12 or 24 hour intervals after initiation of CDT at the discretion of the interventional radiologist. All characteristics of the CDT procedure including vascular access site, duration of CDT, dose of rtPA, and number of infusion catheters used were recorded.

Outcomes

The primary endpoint was angiographic resolution of thrombus burden after CDT, which was reported as high (>75%), moderate (51%–75%), low (26%–50%), or insignificant (≤25%). Angiographic resolution of thrombus burden was determined by two board-certified interventional radiologists who examined pre-treatment and post-treatment pulmonary angiograms and scored them independently. Any scoring discrepancies were then resolved by consensus agreement. Secondary endpoints included reduction in PAP, clinical improvement, clinical decompensation, bleeding complications, and 30-day mortality. Clinical improvement was defined as patient-reported relief from symptoms following CDT and overall improvement in the patient's respiratory or hemodynamic status. Clinical decompensation was defined as the worsening of hemodynamic or respiratory status necessitating use of vasopressor agents, mechanical ventilation, cardiopulmonary resuscitation, systemic thrombolysis, or surgical pulmonary embolectomy. Bleeding complications were classified according to the Society of Interventional Radiology (SIR) adverse event criteria; moderate and severe bleeding events were recorded.

Statistical analysis

Statistical analyses were performed using the IBM SPSS 26 (IBM Corporation) statistical software package. The Wilcoxon signed

rank test was used to evaluate the differences in pre-treatment and post-treatment PAP. The Kruskal-Wallis test was used to determine whether there were statistically significant differences in PAP among patients with varying levels of angiographic resolution of thrombus burden. Categorial variables were analyzed using chi-square testing. Normally distributed variables were reported using mean and standard deviation, while non-normal variables were reported using median and range. Two-sided *p* values ≤0.05 were considered statistically significant.

Results

The mean patient age was 56.6 years (range, 17–89 years); 50.7% of patients were male, and 49.3% were female. The most common presenting symptom of PE was dyspnea, and 84.3% of patients required supplemental oxygen at the time of presentation. Thirty-seven patients (26.4%) had a history of PE or DVT, 40.7% had recent operations or periods of immobility including extended automobile or air travel, and 8.6% had a known malignancy.

Myocardial necrosis (troponin-I > 0.03 ng/mL) was present in 118 patients (84.3%), and signs of RV dysfunction were present on echocardiography or CT in all patients. Echocardiography detected RV dysfunction in 127 patients (90.7%) and CT was positive for signs of RV dysfunction in 94 patients (67.1%). In 81 patients (57.9%), both CT and echocardiography showed evidence of RV dysfunction. Overall, 132 patients (94.3%) had an elevated troponin-I or brain natriuretic peptide (BNP) level in addition to having imaging findings suggestive of RV dysfunction. All patient characteristics and clinical data are summarized in Table 1.

Table 1. Patient characteristics and clinical data

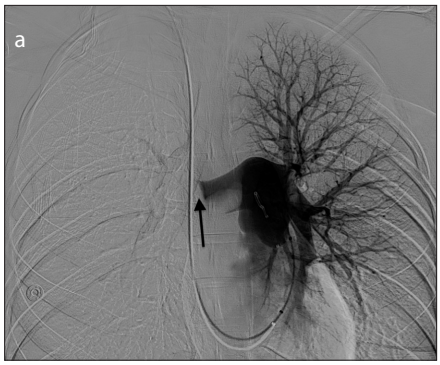
Age (years)	56.6±15.8
% Male/% Female	50.7/49.3
Symptoms at presentation	
Dyspnea	132 (94.3)
Increased oxygen requirement	118 (84.3)
Tachycardia	110 (78.6)
Chest pain	94 (67.1)
Lower extremity pain/edema	63 (45.0)
Cough	49 (35.0)
Syncope/presyncope	41 (29.3)
Symptom duration (days)	2.9 ± 3.1
Risk factors for PE	
History of PE	26 (18.6)
History of DVT	24 (17.1)
Obesity	106 (75.7)
Active malignancy	12 (8.6)
Immobility in last 30 days	30 (21.4)
Operation in last 3 months	27 (19.3)
Oral contraceptives/estrogen	10 (7.1)
Imaging to diagnose PE	
CT	139 (99.3)
V/Q scan	1 (0.7)
RV dysfunction	140 (100.0)
CT	94 (67.1)
Echocardiography	127 (90.7)
Elevated troponin-I	118 (84.3)
Troponin-I level (ng/mL)	0.42±0.42
Elevated BNP (>90 pg/mL)	88 (62.9)
BNP level (pg/mL)	463.43±342.1
Elevated troponin-I or BNP	132 (94.3)

Percentages may not add to 100 due to rounding. Data are presented as mean ± standard deviation or n (%).
PE, pulmonary embolism; DVT, deep vein thrombosis; CT, computed tomography; V/Q, ventilation-perfusion; RV, right ventricle; BNP, brain natriuretic peptide.

CDT was technically successful in all 140 patients with a mean treatment time of 26.0 hours and a mean rtPA dose of 25.3 mg. A total of 272 conventional infusion catheters were placed and 92.1% of patients underwent bilateral CDT. Follow-up pulmonary angiography was performed in 138 patients. In two patients (1.4%) repeat angiography could not be accomplished; one patient died shortly after initiation of CDT, and another patient suffered a cardiac arrest requiring cessation of CDT and administration of systemic rtPA. High (>75%) or moderate (51%–75%) resolution of thrombus burden was achieved in 89.3% of patients. Pre-treatment and post-treatment pulmonary angiograms depicting high and moderate thrombus clearance following CDT are shown in Figs. 1 and 2.

On initial manometry, 68 patients (48.6%) had mean PAP ≥30 mmHg and 23 (16.4%) had mean PAP ≥40 mmHg. After CDT, both systolic PAP (47 vs. 35 mmHg, $p < 0.001$) and mean PAP (25 vs. 21 mmHg, $p < 0.001$) were reduced. According to a Kruskal-Wallis analysis, patients with differing levels of angiographic resolution of thrombus burden (high, moderate, low, insignificant) did not have statistically significant differences in their absolute systolic PAP reduction ($H = 1.616$, df 3, $p = 0.656$) or absolute mean PAP reduction ($H = 0.233$, df 3, $p = 0.972$). Similarly, no statistical significance was observed in the percent systolic PAP reduction ($H = 2.203$, df 3, $p = 0.531$) or percent mean PAP reduction ($H = 0.912$, df 3, $p = 0.822$). Data pertaining to the CDT procedure and follow-up angiography and manometry are shown in Table 2.

Clinical improvement occurred in 119 of 125 patients (95.2%) with high or moderate thrombus clearance, while 10 of 13 patients (76.9%) with low or insignificant thrombus clearance showed clinical improvement ($\chi^2=6.4522$, $p = 0.011$). Overall clinical improvement was 92.1%. Ten patients (7.1%)



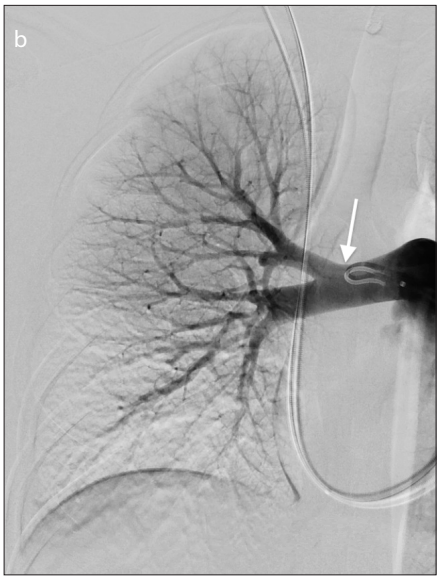
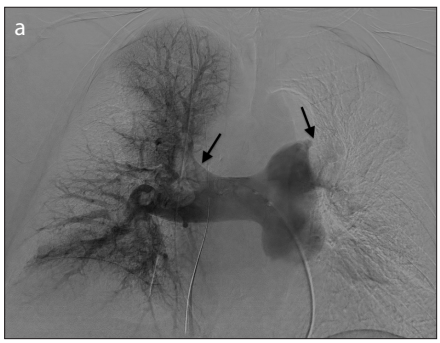


Figure 1. a, b. Pre-treatment digital subtraction angiography **(a)** shows absence of flow in the right pulmonary artery due to pulmonary embolus *(black arrow)*. Post-treatment digital subtraction angiography **(b)** shows "high" (>75%) resolution of thrombus burden with restored perfusion of the right pulmonary artery *(white arrow)*.



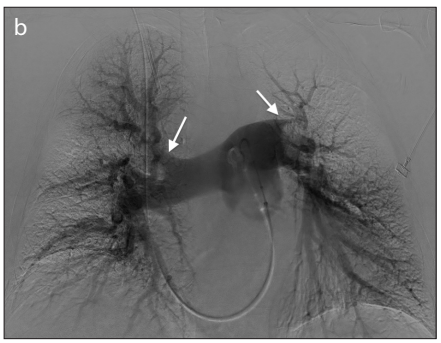


Figure 2. a, b. Pre-treatment digital subtraction angiography **(a)** shows near-absence of flow in the left pulmonary artery and a large perfusion defect in the right pulmonary artery due to bilateral pulmonary emboli *(black arrows)*. Post-treatment digital subtraction angiography **(b)** shows increased perfusion of the both pulmonary arteries with "moderate" (51%–75%) resolution of total thrombus burden *(white arrows)*.

Table 2. CDT procedural characteristics and outcomes

Vascular access site, n (%)	
Right internal jugular	188 (69.1)
Right femoral	77 (28.3)
Left femoral	4 (1.5)
Other	3 (1.1)
Number of catheters placed, n (%)	
One	8 (5.7)
Two	132 (94.3)
Catheter placement, n(%)	
Unilateral	11 (7.9)
Bilateral	129 (92.1)
Duration of CDT (hours), mean±SD	26.0±9.8
rtPA dose administered (mg), mean±SD	25.3±11.0
Angiograms per patient, n (%)	
One	2 (1.4)
Two	94 (67.1)
Three	43 (30.7)
Four	1 (0.7)
Resolution of thrombus burden, n (%)	
High (>75%)	98 (70.0)
Moderate (51%–75%)	27 (19.3)
Low (26%–50%)	8 (5.7)
Insignificant (≤25%)	5 (3.6)
No follow-up angiography	2 (1.4)
Systolic PAP (mmHg)	
Pre-procedure median	47
Pre-procedure range	15–94
Post-procedure median	35
Post-procedure range	17–76
Mean PAP (mmHg)	
Pre-procedure median	25
Pre-procedure range	4–57
Post-procedure median	21
Post-procedure range	4–42

Percentages may not add to 100 due to rounding. CDT, catheter-directed thrombolysis; SD, standard deviation; rtPA, recombinant tissue plasminogen activator; PAP, pulmonary artery pressure.

had post-procedural clinical decompensation attributed to the natural progression of PE. None of these complications were deemed to be due to the procedure itself or to bleeding events. All cases of clinical decompensation are shown in Table 3.

Eight patients (5.7%) experienced bleeding complications categorized as moderate or severe according to the SIR adverse event criteria, and all bleeding events occurred within 50 hours of CDT initiation. The single severe bleeding event occurred in a patient with metastatic ovarian cancer who developed severe gastrointestinal bleeding during CDT. CDT was immediately discontinued and two units of packed red blood cells were transfused. At this point, it was decided that the patient would be transitioned to comfort care and aggressive treatment would not be pursued; the patient died shortly thereafter. No patients in this study experienced intracranial hemorrhage. Following CDT, the mean length of hospital stay was 6.9 days and 30-day mortality was 1.4%. All bleeding events and outcomes are shown in Table 4.

Discussion

Multiple treatment options for submassive PE have been investigated, but there is little consensus in the literature on what constitutes the optimal approach. Data regarding the use of conventional CDT for submassive PE are limited; most studies have concentrated on UACDT and few have focused solely on patients with submassive PE. While several past studies have quantified angiographic resolution of thrombus burden after CDT, follow-up angiography has not been routinely employed as a procedural endpoint. Other metrics previously used to assess the effectiveness of CDT include reduction in PAP, reduction RV/LV ratio, and clinical outcomes.

Nearly all studies examining CDT, including this study, report reduction in PAP as an endpoint. PAP is of interest since systolic PAP >50 mmHg in acute PE is associated with the development of chronic thromboembolic

Table 3. Cases of clinical decompensation after initiation of CDT

Patient no.	Complication	Intervention	Outcome
5	Cardiac arrest	Cessation of CDT, cardiopulmonary resuscitation, 100 mg systemic rtPA	Survived to discharge
6	Respiratory failure	Intubation and mechanical ventilation	Survived to discharge
14	Cardiogenic shock, respiratory failure	Intubation and mechanical ventilation, vasopressors	Survived to discharge
21	Cardiac arrest	Cessation of CDT, cardiopulmonary resuscitation, 50 mg systemic rtPA	Survived to discharge
51	Insignificant angiographic improvement with CDT, respiratory failure	Open surgical embolectomy	Survived to discharge
56	Respiratory failure	Intubation and mechanical ventilation, bronchoscopy	Survived to discharge
86	Cardiac arrest	Cessation of CDT, cardiopulmonary resuscitation, 50 mg systemic rtPA	Died
88	Respiratory failure	Intubation and mechanical ventilation	Survived to discharge
119	Insignificant angiographic improvement with CDT, respiratory failure	Open surgical embolectomy	Survived to discharge
121	Cardiac arrest, myocardial infarction	Cardiopulmonary resuscitation	Survived to discharge

CDT, catheter-directed thrombolysis; rtPA, recombinant tissue plasminogen activator.

Table 4. Bleeding events and outcomes

Patient no.	Bleeding event	SIR adverse event classification	Baseline Hgb (mg/dL)/Hct (%)	Lowest Hgb (mg/dL)/Hct (%)	Intervention	Outcome
12	Anemia of unknown origin	Moderate	8.4/24.3	7.2/21.7	2U PRBC	Survived to discharge
38	Anemia of unknown origin	Moderate	9.5/30	6.6/20.9	1U PRBC	Survived to discharge
93	Anemia of unknown origin	Moderate	9.9/30.0	5.6/17.9	1U PRBC	Survived to discharge
5	Vaginal bleeding	Moderate	10.8/32.5	6.8/20	2U PRBC	Survived to discharge
7	Epistaxis, hemoptysis	Moderate	9.4/29.0	7.2/22.1	1U PRBC	Survived to discharge
119	Gastrointestinal bleeding	Moderate	7.3/24.3	6.9/22.5	1U PRBC	Survived to discharge
100	Intraperitoneal bleeding	Moderate	12.2/37.0	6.5/19.1	4U PRBC	Survived to discharge
61	Gastrointestinal bleeding	Severe	10.5/33.8	6.5/20.8	2U PRBC	Transitioned to comfort care, died

Hgb, hemoglobin; Hct, hematocrit; PRBC, packed red blood cells; U, units; SIR, Society of Interventional Radiology.

pulmonary hypertension (CTEPH) (19, 20). Although CDT reduces PAP, it has not yet been shown to reduce rates of CTEPH development (21). The utility of PAP reduction as an endpoint for CDT is unclear. There appears to be a modest correlation between PAP and clot burden visualized on CT, but mean PAP does not rise until 25%–30% of the pulmonary arterial tree is occluded and is heavily influenced by underlying cardiopulmonary disease (22–24). In this study, 68 patients (48.6%) had mean PAP ≥30 mmHg and 23 patients (16.4%) had mean PAP ≥40 mmHg. Mean PAP ≥40 mmHg in acute PE is indicative of underlying cardiopulmonary disease (24). In those without cardiopulmonary disease, mean PAP ≥30 mmHg in acute PE suggests severe pulmonary hypertension (24). The inherent difficulties in accounting for underlying cardiopulmonary disease make PAP an imprecise tool for evaluating the severity of PE or the effectiveness of CDT. In this study, reductions in systolic PAP and mean PAP were similar among all patients and were not significantly related to angiographic resolution of thrombus burden. It is unlikely, then, that serial PAP measurements give a precise representation of the degree of thrombus resolution with CDT.

Improvement in RV/LV ratio has been used by several authors to describe the effectiveness of CDT (8, 9, 17, 25). Increased RV/LV ratio in patients with PE is associated with increased all-cause mortality, increased PE-related mortality, and adverse outcomes (26). CDT quickly improves RV/LV ratio and does so faster than anticoagulation alone, but it is unknown if this confers a clinical benefit (8, 21, 25). Two studies with 30-day and 90-day echocardiographic follow-up failed to demonstrate long-term differences in RV/LV ratio between patients undergoing CDT and those receiving standard anticoagulation (8, 25). RV/LV ratio is correlated with initial thrombus burden in patients with PE, but it is unknown if reductions in RV/LV ratio accurately predict resolution of thrombus burden after CDT (27, 28). Baseline RV/LV ratio may also be affected by underlying cardiopulmonary disease or may be elevated in patients without acute PE (27). For these reasons, reduction in RV/LV ratio is not currently a reliable endpoint for determining procedural success.

Thrombus burden resolution after CDT has been described in several studies, but it is not typically used as the primary effec-

tiveness outcome. In a retrospective study of 19 patients with submassive PE, Gaba et al. (16) used angiographic resolution of thrombus burden as a key endpoint for conventional CDT. Procedural success was defined as complete (≥90%) or near complete (70%–90%) clearance of thrombus burden; this goal was achieved in 18 patients with 90-day survival of 94%. Another study of 60 patients undergoing UACDT for submassive or massive PE defined thrombus clearance as complete (>90%), near-complete (50%–90%), or partial (<50%), and found complete or near-complete clearance in 57% and 41% of patients, respectively. Ninety-day survival was 93%, and three of the four patients that did not survive to 90 days presented with massive PE (29). In this study, high or moderate resolution of thrombus burden occurred in 125 patients (89.3%), and within this group the clinical improvement rate was 95.2%. Thirteen patients (9.3%) with low or insignificant thrombus burden resolution had a clinical improvement rate of 76.9%. The differences in clinical improvement rates between these groups reached statistical significance, but further research is needed to verify the utility of repeat angiography and to determine if long-term clinical outcomes, including the development of CTEPH, are impacted or improved.

In an attempt to more thoroughly describe the clinical severity of submassive PE, the European Society of Cardiology (ESC) divided intermediate-risk PE into "intermediate low-risk" and "intermediate high-risk" groups. Intermediate high-risk PE is characterized by signs of RV dysfunction and elevated cardiac biomarkers (troponin I or T, BNP) (30). By the ESC criteria, 132 of the patients in this study would have been categorized as intermediate high-risk (30). One study examining patients with intermediate high-risk PE found that death or hemodynamic decompensation occurred in 5.6% of those receiving standard anticoagulation with 7-day mortality of 1.8% (3). In this study, six patients (4.3%) died or experienced hemodynamic decompensation with 7-day mortality of 1.4%. To date there has not been a demonstrated mortality benefit for patients with intermediate-risk PE who undergo CDT, but it is possible that the ESC criteria will aid in the further stratification and identification of patients likely to benefit from this therapy (21).

A recent meta-analysis by Pei et al. (31) found that UACDT for PE is associated with a 5.4% major bleeding rate. Patients with submassive PE receiving standard anticoagulation have a major bleeding rate of 2.4% (3). In this study, SIR moderate or severe bleeding events occurred in 8 patients (5.7%) (32). Although this bleeding event rate is higher, it should be noted that three of these patients required transfusions due to anemia and were anemic prior to CDT initiation.

This study has several important limitations. The retrospective nature of the study and lack of control group may limit the application of the findings. Conventional CDT appears to be an effective treatment for submassive PE, but this study provides no direct comparison to UACDT. While angiographic resolution of thrombus burden after CDT was independently scored by two interventional radiologists, this methodology was limited by angiograms which differed in quality and the subjective nature of the thrombus burden assessment. Although it is postulated that RV/LV ratio is limited in its ability to accurately determine procedural success, patients in this study did not undergo repeat echocardiography or CT on a routine basis. Without these measurements, the true relationship between angiographic resolution of thrombus burden and reduction in RV/LV ratio is unknown. Finally, 9 patients were lost to follow-up at 30 days which could have introduced attrition bias into the calculated mortality rate.

In conclusion, angiographic resolution of thrombus burden is a safe and directly observable metric that can be used to determine procedural success in patients undergoing CDT for submassive PE. In this study, high or moderate thrombus clearance was associated with a clinical improvement rate of 95.2%. Overall, the bleeding event rate was 5.7% and 30-day mortality was 1.4%. Further research is needed to elucidate the relationship between post-CDT angiographic improvement and long-term clinical outcomes.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Office of the Surgeon G, National Heart L, Blood I. Publications and Reports of the Surgeon General. The Surgeon General's call to action to prevent deep vein thrombosis and pulmonary embolism. Rockville (MD): Office of the Surgeon General (US); 2008.
2. Busse LW, Vourlekis JS. Submassive pulmonary embolism. Crit Care Clin 2014; 30:447–473. [Crossref]
3. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014; 370:1402–1411. [Crossref]
4. Kearon C. Natural history of venous thromboembolism. Circulation 2003; 107:I22–30. [Crossref]
5. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000; 101:2817–2822. [Crossref]
6. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011; 123:1788–1830. [Crossref]
7. Kuo WT, Banerjee A, Kim PS, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): Initial results from a prospective multicenter registry. Chest 2015; 148:667–673. [Crossref]
8. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014; 129:479–486. [Crossref]
9. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: The SEATTLE II Study. JACC Cardiovasc Interv 2015; 8:1382–1392. [Crossref]
10. Rothschild DP, Goldstein JA, Ciacci J, Bowers TR. Ultrasound-accelerated thrombolysis (USAT) versus standard catheter-directed thrombolysis (CDT) for treatment of pulmonary embolism: A retrospective analysis. Vasc Med 2019; 24:234–240. [Crossref]
11. Liang NL, Avgerinos ED, Marone LK, Singh MJ, Makaroun MS, Chaer RA. Comparative outcomes of ultrasound-assisted thrombolysis and standard catheter-directed thrombolysis in the treatment of acute pulmonary embolism. Vasc Endovascular Surg 2016; 50:405–410. [Crossref]
12. Tafur AJ, Shamoun FE, Patel SI, Tafur D, Donna F, Murad MH. Catheter-directed treatment of pulmonary embolism: A systematic review and meta-analysis of modern literature. Clin Appl Thromb Hemost 2017; 23:821–829. [Crossref]
13. Pieraccini M, Guerrini S, Laiolo E, et al. Acute massive and submassive pulmonary embolism: preliminary validation of aspiration mechanical thrombectomy in patients with contraindications to thrombolysis. Cardiovasc Intervent Radiol 2018; 41:1840–1848. [Crossref]
14. Tu T, Toma C, Tapson VF, et al. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: The FLARE study. JACC Cardiovasc Interv 2019; 12:859–869. [Crossref]
15. Chiarello MA, Sista AK. Catheter-directed thrombolysis for submassive pulmonary embolism. Semin Intervent Radiol 2018; 35:122–128. [Crossref]

16. Gaba RC, Gundavaram MS, Parvinian A, et al. Efficacy and safety of flow-directed pulmonary artery catheter thrombolysis for treatment of submassive pulmonary embolism. AJR Am J Roentgenol 2014; 202:1355–1360. [Crossref]
17. Bagla S, Smirniotopoulos JB, van Breda A, Sheridan MJ, Sterling KM. Ultrasound-accelerated catheter-directed thrombolysis for acute submassive pulmonary embolism. J Vasc Interv Radiol 2015; 26:1001–1006. [Crossref]
18. McCabe JM, Huang PH, Riedl L, Eisenhauer AC, Sobieszczyk P. Usefulness and safety of ultrasound-assisted catheter-directed thrombolysis for submassive pulmonary emboli. Am J Cardiol 2015; 115:821–824. [Crossref]
19. Korkmaz A, Ozlu T, Ozsu S, Kazaz Z, Bulbul Y. Long-term outcomes in acute pulmonary thromboembolism: the incidence of chronic thromboembolic pulmonary hypertension and associated risk factors. Clin Appl Thromb Hemost 2012; 18:281–288. [Crossref]
20. Yang S, Yang Y, Zhai Z, et al. Incidence and risk factors of chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. J Thorac Dis 2015; 7:1927–1938.
21. Furfaro D, Stephens RS, Streiff MB, Brower R. Catheter-directed thrombolysis for intermediate-risk pulmonary embolism. Ann Am Thorac Soc 2018; 15:134–144. [Crossref]
22. Rodrigues AC, Guimaraes L, Guimaraes JF, et al. Relationship of clot burden and echocardiographic severity of right ventricular dysfunction after acute pulmonary embolism. Int J Cardiovasc Imaging 2015; 31:509–515. [Crossref]
23. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 1971; 28:288–294. [Crossref]
24. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002; 121:877–905. [Crossref]
25. Avgerinos ED, Liang NL, El-Shazly OM, et al. Improved early right ventricular function recovery but increased complications with catheter-directed interventions compared with anticoagulation alone for submassive pulmonary embolism. J Vasc Surg Venous Lymphat Disord 2016; 4:268–275. [Crossref]
26. Meinel FG, Nance JW, Jr., Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: Systematic review and meta-analysis. Am J Med 2015; 128:747–759.e742. [Crossref]
27. Wong LF, Akram AR, McGurk S, Van Beek EJ, Reid JH, Murchison JT. Thrombus load and acute right ventricular failure in pulmonary embolism: correlation and demonstration of a "tipping point" on CT pulmonary angiography. Br J Radiol 2012; 85:1471–1476. [Crossref]
28. Furlan A, Aghayev A, Chang CC, et al. Short-term mortality in acute pulmonary embolism: clot burden and signs of right heart dysfunction at CT pulmonary angiography. Radiology 2012; 265:283–293. [Crossref]
29. Kennedy RJ, Kenney HH, Dunfee BL. Thrombus resolution and hemodynamic recovery using ultrasound-accelerated thrombolysis in acute pulmonary embolism. J Vasc Interv Radiol 2013; 24:841–848. [Crossref]
30. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014; 35:3033–3069. [Crossref]
31. Pei DT, Liu J, Yaqoob M, et al. Meta-analysis of catheter directed ultrasound-assisted thrombolysis in pulmonary embolism. Am J Cardiol 2019; 124:1470–1477. [Crossref]
32. Khalilzadeh O, Baerlocher MO, Shyn PB, et al. Proposal of a new adverse event classification by the Society of Interventional Radiology Standards of Practice Committee. J Vasc Interv Radiol 2017; 28:1432–1437.e1433. [Crossref]