

Percutaneous mechanical thrombectomy combined with catheter-directed thrombolysis in the treatment of acute pulmonary embolism and lower extremity deep venous thrombosis: A novel one-stop endovascular strategy

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Abstract

Objective: This study was performed to evaluate the efficacy and feasibility of percutaneous mechanical thrombectomy (PMT) combined with catheter-directed thrombolysis (CDT) in patients with acute pulmonary embolism (APE) and lower extremity deep venous thrombosis (LEDVT).

Methods: In total, 20 consecutive patients with APE and LEDVT were prospectively selected for PMT combined with CDT. Mechanical thrombus fragmentation and aspiration using a pigtail rotation catheter followed by CDT was performed in each patient. Details regarding the patients' clinical presentation and outcome, pulmonary status parameters (pulmonary arterial pressure, partial pressure of oxygen in arterial blood, Miller score, thigh and calf circumference, and shock

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index), and lower extremity parameters (thrombus-lysis grade and Villalta scale score) were recorded.

Results: All 20 patients' clinical manifestations significantly improved. Both the clinical success rate and technical success rate were 100%. No major adverse events occurred during hospitalization. Four patients developed iliac vein compression syndrome and underwent stent implantation in the iliac vein. No pulmonary embolism recurred within 16.5 ± 6.8 months of follow-up.

Conclusions: The combination of PMT and CDT is a safe and effective treatment for APE and LEDVT with good short- and intermediate-term clinical outcomes.

Keywords

Acute pulmonary embolism, deep venous thrombosis, percutaneous mechanical thrombectomy, catheter-directed thrombolysis, post-thrombotic syndrome, endovascular therapy, venous stenosis

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Introduction

Venous thromboembolism, which includes deep venous thrombosis (DVT) and acute pulmonary embolism (APE), is a major contributor to the global disease burden and is the third most common cardiovascular pathology after coronary artery disease and stroke.¹ APE may cause chest pain, dyspnea, hypoxia, hypotension, and shock, while lower extremity DVT (LEDVT) can block the venous lumen and lead to venous congestion, swelling, and lower extremity venous valve function damage resulting in post-thrombotic syndrome (PTS). The rate of long-term complications of venous thromboembolism including chronic thromboembolic pulmonary hypertension after APE² and PTS from DVT, may reach 40%.³ Patients with these complications are more likely to develop lifelong adverse clinical consequences and are the most frequently hospitalized for treatment. In contemporary clinical practice, a focus should always be placed on relieving APE symptoms because of the lethality of this condition. In most cases, treatment of thrombi in the lower

extremity is initiated only after completion of thrombolysis in the pulmonary artery. Inherently, such management prolongs the lysis time, lowers the treatment efficacy, and may miss the best therapeutic window for LEDVT (normally 14 days), resulting in a distinct increase in the incidence of PTS. For the treatment of venous thromboembolism, systemic thrombolysis alone ineffectively removes thrombi of the deep venous system; hence, catheter-directed thrombolysis (CDT) with or without percutaneous mechanical thrombectomy (PMT) is becoming the standard of medical care in the treatment of acute and subacute proximal DVT.^{4,5} The present prospective study was performed to evaluate the feasibility, efficacy and safety of PMT+CDT for concurrent management of APE and LEDVT.

Materials and methods

Study population

The present study was conducted as an open noncomparative prospective cohort over a time span of 1 year (Jan 2015–Dec

2015) in the Department of Vascular Surgery at The Affiliated Hospital of Qingdao University, HuangDao District, Shandong, China. Approval for the study was obtained from the ethics committee of the institute, and all patients provided written informed consent. The American College of Chest Physicians Guidelines 9th edition⁶ and the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology⁷ were used to define whether the diagnoses of LEDVT and APE were established.

Inclusion criteria

The inclusion criteria for the present study were as follows:

- a. dyspnea, hypoxia, or hemodynamic instability
- b. evidence of APE by computed tomographic pulmonary angiography or pulmonary arteriography
- c. diagnosis of LEDVT by duplex ultrasound (DUS) or venography
- d. overwhelming symptoms of lower extremity swelling, incapacitating pain, or phlegmasia dolens, indicating an extensive ilioacaval or iliofemoral thrombus that is compromising lower limb blood flow
- e. APE and LEDVT onset of <14 days

Exclusion criteria

The following patients were excluded from the study:

- a. patients with asymptomatic LEDVT who underwent conventional anticoagulation treatment at our institution
- b. patients with contraindications to anticoagulation or thrombolytic therapy, such as a history of major bleeding, recent delivery or major surgery (up to 10 days

before study onset), neurosurgical intervention (up to 3 months), recent significant trauma, or a disease with a known risk of hemorrhagic complications

- c. patients who refused to participate in follow-up
- d. patients with no APE but with only isolated infrapopliteal thrombosis, recurrent ipsilateral LEDVT, pre-existing leg ulcers, a short life expectancy, or contraindications for the use of contrast media

All patients who met the inclusion criteria were included in this study. Patients who showed a rapid deterioration of their cardiopulmonary condition underwent oxygen supplementation with noninvasive pressure support or intubation. Positive inotropic and vasoactive support with catecholamines was also performed according to the patient's hemodynamic condition prior to right heart catheterization and pulmonary angiography.

Definitions and outcomes

Primary outcomes. The primary outcomes of this study were evaluation of safety by calculation of the major adverse events rate and in-hospital death rate and evaluation of efficacy by calculation of the clinical success rate and technical success rate.

Clinical success was defined as improvement in the clinical manifestations or a decrease in the vasopressor requirement and hemodynamic decompensation in patients with APE as well as alleviation of lower limb swelling in patients with LEDVT, without major adverse events or in-hospital death. Digital subtraction pulmonary angiograms obtained at baseline and after PMT+CDT of the pulmonary arteries and lower extremity were reviewed by two vascular surgeons and two radiologists. Technical success was defined as successful placement and withdrawal of the devices and completion of the procedure

without major complications such as perforation of the pulmonary artery or cardiac structures, tamponade, cerebral vascular accident, or death.

Major adverse events were defined as treatment-related events requiring surgery or transfusion, the need for dialysis, worsening pulmonary artery hypertension, and any stroke, hypoxia or shock, and/or perioperative death. Minor adverse events were defined as transient catheter-induced arrhythmia, mild contrast reactions, catheter-related infection, and small hematomas not requiring transfusion. A major hematoma was defined as a hematoma requiring one or more blood transfusions.

Secondary outcomes. Secondary outcomes were the pulmonary arterial pressure (PAP), partial pressure of oxygen in arterial blood, Miller score (MS), thigh and calf circumference, shock index, thrombus-lysis grade, and Villalta scale (VS) score.

The variation in the pulmonary artery indicating the thrombus burden from baseline to postoperative digital subtraction arteriography was assessed by the MS,⁸ the use of which was shifted in the present study from the traditional emphasis on radiological imaging to managing treatment based on physiologic measurements of cardiac function obtained from echocardiogram reading as well as the patient's clinical condition.⁹ The MS was calculated by two blinded reviewers. As previously described,¹⁰ the right and left main pulmonary arteries are considered to have nine and seven major branches, respectively, and an embolism in any of these branches is scored as 1 point. Each lung is considered to have an upper, middle, and lower zone, and in each of these three zones, the absence of pulmonary artery flow is scored as 3 points; severely reduced flow, 2 points; mildly reduced flow, 1 point; and normal flow, 0 points. Therefore, the MS ranges from 0 to 34. We did not classify

massive or submassive APE into subgroups. We followed the reporting standard of a national multicenter registry¹¹ that assessed the pre- and post-lysis thrombus effect in the extremity by grading the portion of thrombolysis at the completion of treatment as follows: complete (Grade III, >90% clearance), near complete (Grade II, 50%–90% clearance), or partial (Grade I, <50% clearance). We used DUS to investigate venous patency during follow-up. Other variables that were analyzed to evaluate the effect of therapy were the PAP, partial pressure of oxygen in arterial blood, and thigh and calf circumference before and after treatment. We calculated the mean circumference by measuring the thigh circumference 15 cm above the knee joint and that of the calf 10 cm below the tibial tuberosity. Hemodynamic measurements were obtained before diagnostic angiography was performed and after the procedure. Hemodynamic decompensation was in turn defined as new-onset sustained hypotension, a new requirement for inotropes or vasopressors, or continued or worsening hypotension despite treatment.

Procedures

All procedures included four sequential steps: venography, implantation of the inferior vena cava (IVC) filter, treatment for APE, and treatment for LEDVT. The procedures were performed in a hybrid operating room with a fixed angiography suite, and punctures were performed under DUS guidance.

Venography. Before the procedure, the patients were diagnosed with LEDVT via DUS. The superficial veins were blocked by a tourniquet on the ipsilateral ankle, and Ultravist (Bayer Schering Pharma, Berlin, Germany) diluted 1:1 with saline was manually injected into the ipsilateral dorsalis pedis vein at the speed of 2 ml/s

while performing digital subtraction venography. This standard procedure was performed in all patients to determine the proximal and distal extent of the thrombus and estimate the overall clot burden.

Implantation of IVC filter. All patients underwent IVC filter implantation using a standard protocol as previously described.¹² After sterilizing the contralateral inguinal area and perineum, a 6-French sheath was placed into the common iliac vein through a puncture in the common femoral vein, and 20 ml of contrast medium (Ultravist 300 mg; Bayer Schering Pharma) was injected at a speed of 10 ml/s. A 5000-U intravenous bolus dose of unfractionated heparin (UFH) (Changzhou Qianhong Bio-Pharma Co. Ltd., Changzhou, China) was administered followed by continuous intravenous infusion of UFH at the rate of 1000 U/h through the side port of the sheath. The long sheath was then advanced to the level of the inferior renal vein, and the IVC filter (OptEase filter; Cordis, Miami, FL, USA) was released below the infrarenal level. The accurate positioning of the filter was reconfirmed with venography after completion of the procedure. The filter was inserted via the right jugular route in one patient with LEDVT in the bilateral lower limbs. Under fluoroscopic guidance, the filters were retrieved following the standard protocol¹² after completion of the thrombolytic infusion procedure.

Treatment for APE. Under local anesthesia, a 6-French, 10-cm vascular sheath (Terumo Medical Corporation, Elkton, MD, USA) was inserted in the ipsilateral femoral vein through a puncture, and then a 6-French curved pigtail catheter (Cordis Corporation, Miami Lakes, FL, USA) was passed by the IVC filter with deliberate calibration and advanced into the main pulmonary artery for pulmonary angiography (Figure 1). Digital subtraction

arteriography was subsequently performed to confirm the amplitude and magnitude of the thrombus (Figure 1(a)). The intraluminal PAP was measured with a Swan-Ganz catheter (Baxter Healthcare, Irvine, CA, USA) after a satisfactory pulmonary artery waveform was recorded. Following the American College of Cardiology paradigm,¹³ a 6-French pigtail catheter (12-mm diameter) was used in the central portion of the pulmonary artery, whereas a 5-French catheter (8-mm diameter) was used in the peripheral part of the pulmonary vascular tree. Once the embolic occlusion of the pulmonary artery had been passed with the wire, the catheter was manually rotated around the axis of the guidewire (Figure 1(b)). While rotating, it was repeatedly moved back and forth over several centimeters within the clot. This was followed by manual clot aspiration via a 20-ml syringe with a Luer Lock connector until sufficient fragmentation of the embolus was achieved. After the embolus had been fragmented with the rotating pigtail catheter, percutaneous transluminal angioplasty (PTA) was performed through the larger sheath if significant thrombosis (>50% of the lumen) was found. During this session, the thromboembolism in the pulmonary artery or branches was incompletely dilated using one or two 3- to 6-mm balloon catheters (Admiral Xtreme; INVATEC/Medtronic, Minneapolis, MN, USA) based on the diameter of the target pulmonary artery (Figure 1(c)). A balloon catheter was utilized to crush the thrombus attached to the vessel wall. The patient then received an intrapulmonary pulse spray thrombolysis injection of urokinase (200×10^3 U) via the thrombolytic catheter (Unifuse, 240 cm; Angiodynamics, Latham, NY, USA), and the catheter was retained in the artery for subsequent adjuvant infusion therapy. Pulmonary angiography and PAP measurement were repeated and recorded (Figure 1(f)).

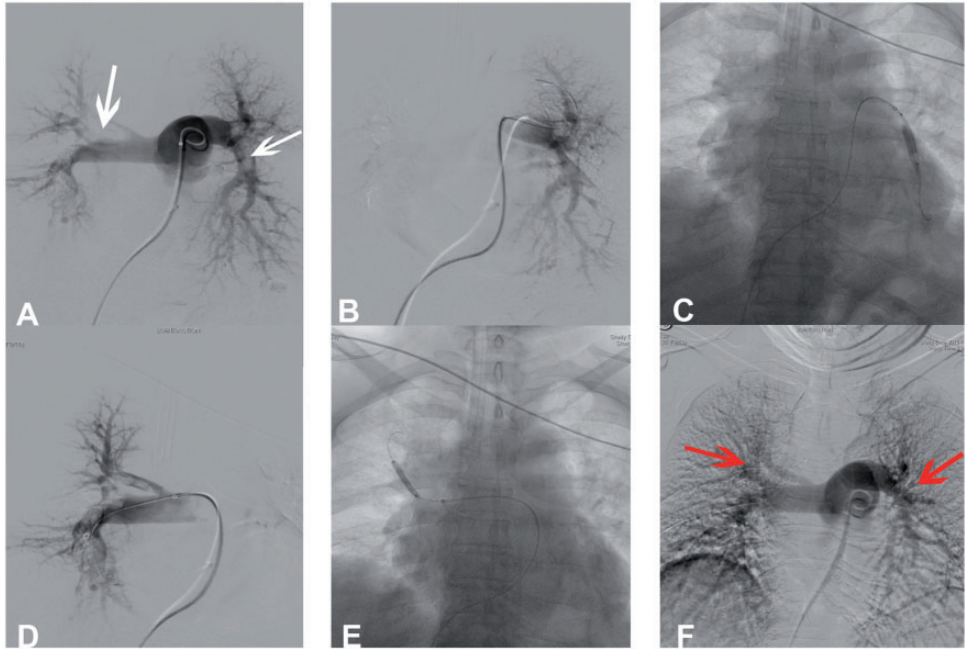


Figure 1. Images from a 66-year-old man with acute pulmonary embolism and bilateral deep vein thrombosis. (a) Preoperative pulmonary angiography shows massive emboli in the upper and intermediate section of a left lobe artery (white arrow) and in the intermediate section of a right lobe artery (white arrow). The pulmonary arterial pressure was 52/22 (mean, 37) mmHg, and the Miller score was 18. (b) After initial catheter fragmentation of the right lobe artery via a 6-French pigtail catheter, the embolus dislodged and partially diminished. (c) A balloon catheter (Admiral Xtreme; INVATEC/Medtronic, Minneapolis, MN, USA) was placed and dilated through the embolus to crush the thrombus attached to the artery wall. (d and e) The same procedures were performed on the left side. (f) Post-thrombolysis angiogram shows considerable recanalization and improved perfusion after the therapy (red arrows) compared with the initial situation, although some thrombi remained in the branches of pulmonary artery. The post-treatment pulmonary arterial pressure was 28/8 (mean, 18) mmHg, and the Miller score was 9.

Treatment for LEDVT. After venography, we punctured the contralateral common femoral vein or the mildly thrombosed vein if both lower extremities were thrombosed (Figure 2(a)). A 6-French Balkin sheath (Cook Medical Inc., Bloomington, IN, USA) was introduced to cross the bifurcation of the IVC and placed in the ipsilateral iliac vein. If severe iliac vein stenosis (>70%) was found, an Admiral Xtreme balloon catheter (6–8 × 120 mm/130 cm; INVATEC/Medtronic) was used to predilate the lesion. After placement of a 0.035-inch guidewire (Terumo Medical, Tokyo,

Japan), a 4-French vertebral catheter (Angiodynamics) was retrogradely advanced via the iliac vein, femoral vein, popliteal vein, and calf vein to penetrate the thrombus. We performed contrast venous angiography to reconfirm the edge of the thrombosis (Figure 2(b)). The vertebral catheter was then exchanged for an Admiral Xtreme balloon catheter (4–6 × 120 mm/130 cm; INVATEC/Medtronic). The balloon catheter was used to pre-dilate the venous lumen (Figure 2 (c)). Next, a 4- or 5-French multi-side hole thrombolytic catheter (Unifuse;

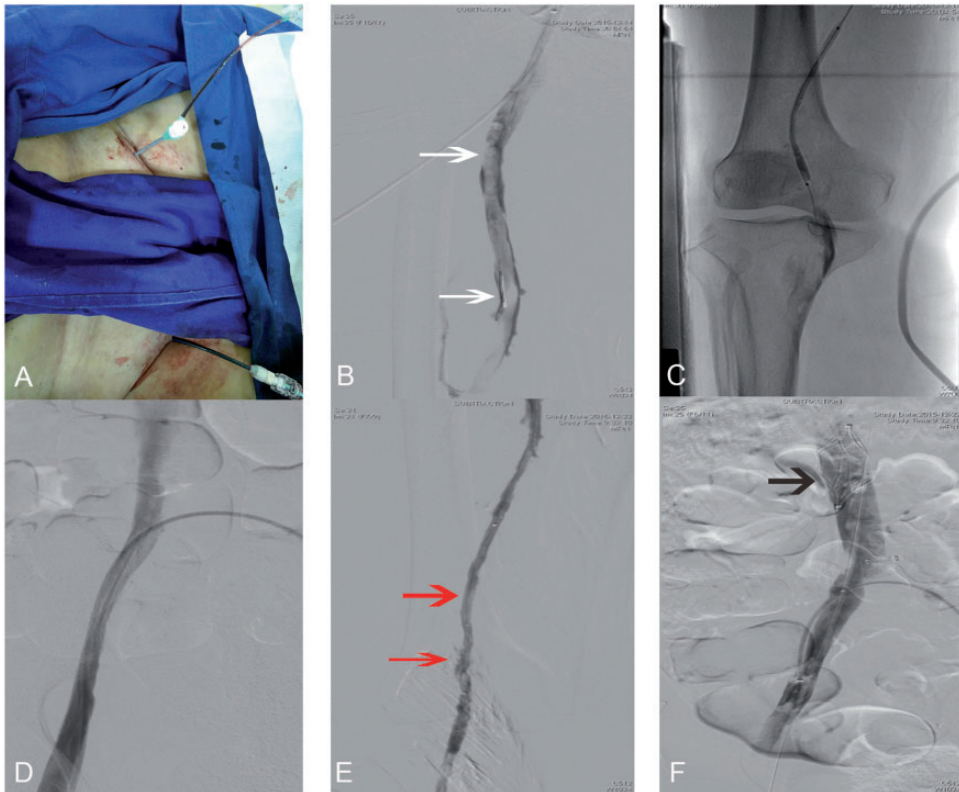


Figure 2. Low extremity venogram images from the same patient as in Figure 1. (a) A typical picture of bilateral common femoral vein puncture for establishing pulmonary and lower extremity access for intervention via a 6-French vascular sheath. (b) Prograde venography via the ipsilateral dorsalis pedis vein confirmed the presence of a thrombus (white arrow) in the popliteal vein. (c) A balloon catheter (4–6 mm \times 120 mm/130 cm; INVATEC/Medtronic) with a 120-mm treatment length was placed into the thrombus and predilated in the venous lumen. (d) A multi-side hole catheter (Unifuse; Angiodynamics, Latham, NY, USA) was then introduced across the heaviest part of the clot, and a urokinase spray infusion was started for initial standard catheter-directed thrombolysis. (e) Post-thrombolysis showed complete resolution of the thrombus after a 20-hour infusion (red arrow). (f) A final venogram was evaluated to verify that the vena cava filter (black arrow) was in a good position before all thrombolysis devices were withdrawn.

Angiodynamics) was then advanced across the most severely clotted veins (unilateral or bilateral), and infusion was initiated with urokinase (200 \times 103 U) for standard CDT (Figure 2(d)). The thrombolytic catheter was repositioned via the guidewire to ensure that the treatment zone traversed the entire clot and the tip exited the thrombus. The catheter was retained in the veins for adjuvant infusion therapy, and we typically

obtained a final venograph to reconfirm that the clot burden had been alleviated before all instruments were withdrawn (Figure 2(e), (f)).

Postoperative and follow-up management

In the clinical ward, each patient was instructed to move the ankle joint at regular intervals. The patients' medical records

were reviewed and evaluated for demographics, risk factors for thromboembolism, comorbidities, symptomatic improvement or resolution after treatment, hemodynamic parameters, thrombus clearance, length of hospital stay, survival to discharge, and complications.

The total dose of urokinase (average of 800×10^3 U/day) was administered to the patient through two infusion catheters. One was located in the pulmonary arteries and the other was located in a deep lower extremity vein: each was used to deliver a dose of 200×10^3 U/day via pulse spray injection and 200×10^3 U/day via continuous intravascular pumping. A total of 12,500 IU of UFH (Changzhou Qianhong Bio-Pharma Co. Ltd.) was given through the side port of the two sheaths (each 6250 IU) via continuous intravascular pumping to bathe the clot along the catheter. An angiogram was obtained every 24 hours to assess the clot burden and treatment efficacy. Blood samples were taken every 12 hours to measure the hematocrit level, hemoglobin level, active partial thromboplastin time, fibrinogen level, and platelet count to adjust the UFH dose and detect blood loss.

Dose adjustment was performed accordance with the laboratory results: a thrombolytic dose reduction was performed when the fibrinogen level was <1.5 g/L, and thrombolysis was discontinued when the fibrinogen level was <1 g/L. After thrombolysis, additional adjunctive procedures (angioplasty or stent implantation) were performed if an underlying vein stenosis of $>70\%$ was present. Postprocedure venography was performed before removing the introducer. All patients continued to receive anticoagulation therapy (low-molecular-weight heparin followed by warfarin) to preserve an international normalized ratio of 2 to 3. Low-dose aspirin was prescribed for three months for patients who underwent stent implantation. All filters were

removed within 4 weeks. After discharge, oral anticoagulation with warfarin was continued concomitant with the use of graduated elastic compression stockings. Clinical follow-up by the referring physician included physical examination, color Doppler DUS, and measurement of the international normalized ratio in all patients. Evaluation of PTS was performed in compliance with the modified VS.¹⁴ The clinical evaluation outcomes were classified as follows: severe PTS was defined as a total score of >14 points or a venous ulcer, mild PTS was defined as 5 to 14 points, and no PTS was defined as <5 points.¹⁵ Venous patency was classified as complete recanalization for a 95% to 100% restoration of patency, partial recanalization for 50% to 95%, and minimal recanalization for $<50\%$ due to residual stenosis or an organized thrombus.¹⁶

Statistical analysis

Standard statistical tests were used to analyze discrete data. Discrete variables are reported as numbers with percentages, and continuous data are reported as mean and standard deviation. Paired t-tests were used to analyze continuous data, and the chi-square test or Fisher's exact test was used to compare nominal variables. Statistical significance was set at $P < 0.05$. The Kaplan–Meier method was used to analyze time-to-event survival data. All statistical tests were performed using GraphPad InStat (version 11.5; GraphPad Software, Inc., La Jolla, CA, USA).

Results

Baseline demographic profile

Twenty consecutive patients diagnosed with APE and LEDVT were enrolled in this study. The baseline characteristics of these 20 patients are detailed in Table 1.

Table 1. Baseline clinical data and demographics

Variable	Value
Age (years)	61.4±13.5
Sex (male:female)	7:13
Duration of symptoms (hours)	126±114
APE laterality	
Left pulmonary artery	5
Right pulmonary artery	7
Bilateral	2
Branch pulmonary arteries	6
DVT-affected limbs	
Left	12
Right	7
Bilateral	1
Risk factors for APE and DVT	
Tumor	1 (5)
Trauma	3 (15)
Iliac vein compression	4 (20)
No specific cause found	12 (60)
IVC filter use	20 (100%)
Symptoms	
Dyspnea	20 (100)
Chest pain	11 (55)
Syncope	4 (20)
Palpitation	7 (35)
Cramps	3 (15)
Heaviness	8 (40)
Clinical presentation	
Shock	9 (45)
Hypotension	15 (75)
Limb swelling	20 (100)
Venous ectasia	14 (70)

Data are presented as mean±standard deviation, n, or n (%). APE=acute pulmonary embolism, DVT=deep vein thrombolysis, IVC=inferior vena cava.

The patients comprised 7 men and 13 women with a mean age of 61.4±13.5 years (range, 39–82 years). The duration of symptoms prior to emergency presentation was 126±114 hours. APE was observed in all 20 patients as follows: 2 (10%) in the main pulmonary artery, 5 (25%) in the left pulmonary artery, 7 (35%) in the right pulmonary artery, and 6 (30%) in the segmental pulmonary arteries), and LEDVT was present in 21 limbs (12 left limbs, 7 right

limbs, and 1 bilateral limbs) of the 20 patients. The clinical presentation and predisposing factors are shown in Table 1. Among the predisposing factors for thromboembolism, 3 (15%) patients had a history of traumatic fracture, 1 (5%) patient was diagnosed with a tumor, 4 (20%) patients were diagnosed with iliac vein compression syndrome via intraoperative angiography, and 12 (60%) patients had no definite cause of the LEDVT and APE.

Short-term clinical outcome

All patients received CDT along with mechanical thrombofragmentation and PTA during thrombolytic therapy. No in-hospital death or major adverse events occurred. The overall technical and clinical success rates were 100% for APE and LEDVT.

Outcome of APE treatment. In terms of APE results, there was a highly significant decrease in the mean PAP from 35.5±6.5815 to 19.7±4.943 mmHg ($P<0.0001$) (Figure 3), in the shock index from 1.089±0.177 to 0.678±0.088 ($P<0.0001$), and in the MS from 18.05±2.502 to 9.05±2.929 ($P<0.0001$). Complete circulatory restitution (return of systemic blood pressure to normal, shock index of <1, and mean PAP of <25 mmHg) before removing the introducer was achieved in 17 of the 20 patients, whereas PAP remained elevated in 3 patients (Table 2). The partial pressure of oxygen in arterial blood significantly increased from baseline levels (35.9±5.036 to 63.1±3.538 mmHg, $P<0.0001$). The infusion time was 30.10±21.77 hours (range, 15–116 h).

Outcome of LEDVT treatment. In the treatment of LEDVT, an abrupt decrease in the mean circumference of the thigh and calf was also noted when the CDT therapeutic scheme had been accomplished

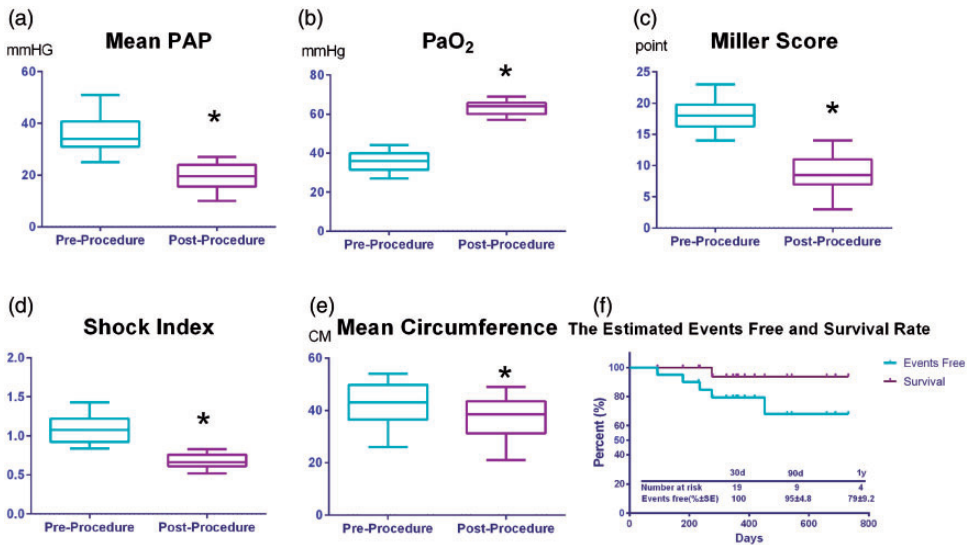


Figure 3. Hemodynamic changes in the mean (a) pulmonary arterial pressure (PAP), (b) partial pressure of oxygen in arterial blood (PaO₂), (c) Miller score, (d) shock index, and (e) mean circumference of the thigh and calf. All hemodynamic parameters were significantly improved after the procedure. (f) Kaplan–Meier curve for the estimated adverse event-free and survival rates. Bars denote medians, boxes denote inter-quartile ranges, and whiskers denote ranges from maximum to minimum. *P<0.0001 versus baseline.

(42.75±7.759 to 37.15±7.876 cm pre-procedure, P< 0.0001) (Table 2 and Figure 3). Besides this, four patients with iliac vein compression syndrome underwent successful venous stenting (Bard Luminexx, 12–14 mm in diameter, 80 mm in length; C. R. Bard, Inc., Murray Hill, NJ, USA) followed by immediate relief of the obstruction with good venous run off. The degree of thrombolysis was calculated after completion of treatment: 7 (35%) patients had Grade III lysis, 8 (40%) of patients had Grade II lysis, and 5 (25%) of patients had Grade I lysis at the end of intraluminal thrombolysis.

Adverse events

No major adverse events occurred during hospitalization, but minor adverse events not requiring intervention or transfusion were observed in the form of hemoptysis

in one patient with Grade II lysis and a hematoma in one patient with Grade I lysis. The dosages of urokinase and UFH were both decreased in these two patients. Additionally, the dosage of urokinase was reduced for another two patients with fibrinogen diminution. In one of these patients, the amount of UFH was increased (intravascular pumping) because the activated partial thromboplastin time was not up to standard. No patient developed intracranial hemorrhage, thrombocytopenia, or recurrence of APE during hospitalization.

Follow-up

The mean follow-up time for the cohort was 16.5±6.8 months. Echocardiography and DUS venography parameters were measured at baseline, postoperatively, and at the latest follow-up visit. No patient developed APE recurrence during the follow-up

Table 2. Perioperative changes in diameters and in-hospital and follow-up outcomes

Patient no.	Age/sex	Mean PAP		PaO ₂ (mmHg)		Miller score		Shock index		Shock index Post	Infusion time (h)	Mean circumference (cm)		Procedural outcome Grade	Complementary procedures	Follow-up Grade	Adverse events N/A
		Pre	Post	Pre	Post	Pre	Post	Pre	Post			Pre	Post				
1	48/M	31	11	30	68	16	13	1.03	0.75	18	54	49	II	PTA	Complete	N/A	
2	39/F	25	10	44	64	17	3	0.91	0.52	25	47	41	III	PTA+IVS	Recurrent DVT	N/A	
3	82/F	27	18	27	58	17	8	0.86	0.68	24	38	34	II	PTA	Died	N/A	
4	61/F	34	26	34	66	23	11	1.38	0.76	23	45	42	III	PTA	Complete	N/A	
5	70/M	51	25	41	65	18	11	0.97	0.62	19	50	44	III	PTA	Complete	N/A	
6	55/M	31	15	31	65	14	6	0.84	0.59	42	51	42	I	PTA	PTS	N/A	
7	78/F	33	24	33	63	17	9	1.13	0.64	30	36	21	II	PTA+IVS	Complete	N/A	
8	43/M	42	19	42	69	15	7	0.93	0.61	21	47	40	III	PTA	Complete	N/A	
9	69/F	37	24	37	60	16	8	1.07	0.59	15	35	32	II	PTA	Complete	N/A	
10	70/F	42	23	36	61	18	8	1.25	0.77	20	35	31	I	PTA	Complete	N/A	
11	63/M	46	27	44	61	18	10	1.08	0.72	22	40	31	II	PTA+IVS	Recurrent DVT	N/A	
12	46/F	29	14	36	64	18	7	0.89	0.55	27	51	44	III	PTA	Complete	N/A	
13	47/F	36	22	29	57	21	14	1.23	0.80	116	39	36	I	PTA	Partial	N/A	
14	81/F	31	20	30	60	20	12	1.36	0.78	29	33	30	II	PTA	Complete	N/A	
15	78/M	34	23	33	65	19	6	1.05	0.63	24	41	37	III	PTA+IVS	Complete	N/A	
16	55/F	30	15	39	66	21	14	1.43	0.74	21	49	44	II	PTA	Complete	N/A	
17	46/F	33	17	37	59	23	11	1.19	0.83	32	46	41	I	PTA	Partial	N/A	
18	60/F	41	19	40	59	15	8	0.92	0.70	25	38	33	III	PTA	Complete	N/A	
19	71/F	40	24	40	64	17	6	1.09	0.65	49	26	22	I	PTA	Partial	Hematoma	
20	66/M	37	18	35	68	18	9	1.16	0.63	20	54	49	II	PTA	PTS	N/A	

M = male, F = female, PAP = pulmonary arterial pressure, SpO₂ = partial pressure of oxygen in arterial blood, Mean circumference (cm) = mean circumference of thigh and calf, IVS = iliac vein stent, PTA = percutaneous transluminal angioplasty, DVT = deep venous thrombosis, PTS = post-thrombotic syndrome
 Procedural outcome (thrombolysis) grades: complete (Grade III, >90% clearance), near complete (Grade II, 50%–90% clearance), and partial (Grade I, <50% clearance).

period. One patient died of a tumor approximately 9 months after hospital discharge. Ten patients (50% of all of patients) had complete patency of the lower limb veins as shown by DUS venography, while five (25%) patients had partial patency. PTS diagnosed using the VS¹⁷ (VS score of >5) was seen in two patients (10%) prior to the intervention. Two patients (10%) developed mild to moderate PTS during follow-up that mainly manifested as pain, heaviness, and edema of the affected limbs after activity. These four patients were treated with additional PTA and venous stenting. Among them, two had patent veins during follow-up, and the other two were diagnosed with recurrent LEDVT due to stent restenosis.

The estimated overall adverse event-free and death-free rates were 100% and 100% at 30 days, 95% and 100% at 90 days, and 79.4% and 93.8% at 1 year, respectively (Figure 3(f)).

Discussion

The general purpose of APE and LEDVT management is to restore flow by early recanalization of the obstructed venous segment and avoiding phlebostenosis caused by thrombus organization, thus reducing the risk and severity of pulmonary hypertension and PTS. In the present study, we demonstrated the following. First, PMT combined with CDT rapidly improved the patients' hemodynamic parameters and clinical manifestations and provided a satisfactory outcome for patients with APE associated with LEDVT. Second, this one-step endovascular strategy involving simultaneous treatment of thrombi in the pulmonary arteries and lower extremity deep veins is a novel but feasible and efficient algorithm, and it may have a potential role in preventing long-term sequelae of pulmonary hypertension or chronic venous obstruction. However, to the best of our

knowledge, no previous reports have described one-step treatment of APE complicated with LEDVT using PMT+CDT or pharmacomechanical therapy.

Despite the improvement in diagnostic and therapeutic modalities, contemporary in-hospital mortality of patients with APE is still approximately 20%.¹⁸ Similarly, PTS or chronic thromboembolic pulmonary hypertension develops in 20% to 50% of patients with LEDVT or APE.^{19,20} However, the treatments for APE and LEDVT are separate in most studies. APE is typically secondary to exfoliation of an embolus that originally colonized a peripheral deep vein, but physicians usually take APE into consideration first because of its highly lethal nature. LEDVT must then be treated in the second step, and the patient may therefore miss the best treatment time window and develop an organized thrombus. We performed the herein-described one-step pharmacomechanical therapy to reduce venous pressure overload in the early period and minimize the risk of long-term complications. Inherently, more effort is required to lyse a chronic thrombus than a fresh one, and early recanalization reduces the incidence of chronic thromboembolic pulmonary hypertension or PTS.^{2,19,21} However, not all cases of LEDVT require early treatment. We perform interventions for LEDVT when the thrombus is found mainly above the knee (femoral venous thrombosis) because a clot in this part of the body often leads to phlebostenosis²² after discharge. If the thrombus is just located in the veins below the knee, we simply perform intravenous thrombolysis and anticoagulation. The standard CDT procedure we applied in this study was described in a previously published article.^{23,24} We also used a balloon catheter to crush large clots into smaller ones during the thrombolytic therapy. Based on our experience, monitoring fibrinogen every 12 hours is sufficient, and

we achieved a good cost-effective outcome. There still no generally accepted protocol for monitoring fibrinogen, but some scholars have recommended a frequency of every 8 hours.²⁵

PMT is used to relieve pulmonary thromboembolic lesions and was first reported about two decades ago, initially using a pigtail rotation catheter.^{13,26} The main concept of this technique is to crush the clots in the pulmonary arteries, causing fragmentation and distal migration of the smaller fragments. The fragments have a greater surface area that is exposed to the thrombolytic agent, thus improving the results of lytic activity and allowing for reductions in the dose and infusion time. More recent case series have demonstrated that outcomes have been improving as the technique has been refined.^{27–29} Piazza et al.²⁷ evaluated a cohort of 150 patients with APE who were treated with an ultrasound-facilitated system (EKOS EndoWave®; EKOS Medical, Bothell, WA) and CDT. Fifteen (10% of all) major bleeding events occurred in their series, whereas only two cases of moderate bleeding (10% of all) occurred in the present study. This result may have been due to the fact that two baseline indexes, the mean PAP (51.4–36.9 mmHg, $P < 0.0001$) and the MS (22.5–15.8, $P < 0.0001$), were both higher in their study than in ours, indicating more severe embolism. In our study, seven (35%) patients had Grade III lysis, eight (40%) had Grade II lysis, and 5 (25%) had Grade I lysis after infusion, which is in agreement with the results found in the literature.^{30,31} Few studies have reported on patency after 6 months. According to a Cochrane review,³² the patency rates vary from 65% to 98%, major bleeding complications range from 0% to 11%, and the rate of PTS ranges from 3% to 48%. We identified a low PTS rate (10%) and low major bleeding rate (0%) in our study, which may be attributed to the decrease in the

thrombolysis dose due to prompt thrombus fragmentation (PMT+PTA); however, this conclusion is limited by the small study sample. Compared with CDT alone, PMT has been shown to result in similar levels of clot removal but with a significant reduction in the infusion time and total dose of thrombolytic, thus potentially reducing adverse bleeding events and low-dose thrombolysis; it has also been shown to reduce PTS recurrence.^{4,5} This is why we conducted PMT+CDT in our study.

Although numerous devices have been recently developed for pharmacomechanical thrombolysis, we performed mechanical thrombectomy by manual rotation and aspiration using pigtail catheters. This is a relatively elementary practice. Newly developed catheters such as the rotating motorized system (CLEANER XT; Argon Medical Devices, Plano, TX, USA), rheolytic instruments (AngioJet system; Boston Scientific, Marlborough, MA, USA), or ultrasound-facilitated systems (EKOS EndoWave) are not available to us. However, Lin et al.³³ demonstrated no significant difference in the thrombus removal rate during pharmacomechanical thrombolysis between the AngioJet system and CDT in the management of LEDVT. Indeed, multiple devices are available to perform PMT. We believe that these new and specially designed pharmacomechanical thrombolysis devices may surpass manual mechanical thrombus fragmentation. However, the most effective strategy ultimately relies on the physician's knowledge of each device and specific patient characteristics to determine which device offers the best risk–benefit ratio. Mechanical thrombus fragmentation still plays a role in APE and LEDVT management because it is readily available and has a high cost–benefit ratio.

The IVC filter plays a small but crucial role in the procedure because it prevents recurrence of APE. The advantage of the

IVC filter remains controversial, however. We inserted the IVC filter with this consideration. First, all of the patients in this study had been diagnosed with APE, which is the indication for implantation of an IVC filter as recommended by established guidelines.^{7,34} Second, the incidence of the thrombus falling off during percutaneous CDT is high; thus, an IVC filter is rationally placed to prevent APE recurrence. However, it must be emphasized that misplacement or malpositioning of the filter may cause IVC perforation, and the IVC filter itself can cause recurrent thrombogenesis.³⁵ We therefore choose the OptEase filter because of its olive-like shape and lack of a sharp claw configuration rather than filters such as the Gunther Tulip (Cook Medical Inc.). We placed the filter with extraordinary precaution. All motions were as slight as possible to confirm that the filter had been placed in the optimal position when the catheter passed it.

We did not use venous stents because the only available venous stent in our institution is the Wallstent (Boston Scientific), which has a steel weave helical design, is soft in structure, and is not suitable for stiff chronic venous stenosis such as that in patients with iliac vein compression syndrome. However, we used a Luminexx stent (Bard, Inc.) because this stent is made by laser cutting and provides a better braced force with which to prop the stenosis. We have performed 300 Luminexx stent implantations in patients with venous stenosis with patient follow-up every 6 months. The outcome is very promising: 90% of patients maintained patency, and >70% of them had complete patency (>90% true luminal cavity) at the 1-year follow-up. However, the need for a specially designed stent in the treatment of phlebostenosis is obvious. We anticipate the future development of more effective venous stents.

Limitations

The major limitation of our study was the lack of a comparator group. Because we did not include a comparator group, we cannot directly compare on the efficacy or safety of PMT+CDT versus CDT in APE or LEDVT alone. In addition, the number of patients enrolled was not large.

Conclusion

Our prospective study has demonstrated the successful treatment of patients with APE and LEDVT via PMT and CDT. The results showed significant improvements in hemodynamics and respiratory parameters, good short- and long-term patency, and a low PTS rate, indicating that this is a low-risk and promising strategy for treatment of acute venous thromboembolism. A large-scale collaborative prospective study is needed to confirm the efficacy and safety of this one-step treatment algorithm.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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