

Mechanical Interventions and Thrombolytic Therapy in Venous Thrombosis and Pulmonary Embolism

Rajesh Subramanian, MBBS; Christopher J. White, MD

Ochsner Heart and Vascular Institute, Department of Cardiology, Ochsner Clinic Foundation, New Orleans, LA

Venous thromboembolism is associated with significant morbidity and mortality. Anticoagulation with heparin and warfarin has favorably altered the natural history of untreated venous thromboembolism. The role of thrombolysis and interventional therapy in the management of venous thromboembolism is less well appreciated. This review evaluates the role of thrombolytic therapy and mechanical interventions in the management of deep vein thrombosis and pulmonary embolism.

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Venous thromboembolism encompasses a spectrum of disorders including deep vein thrombosis (DVT) and pulmonary embolism (PE). While the actual incidence of DVT and PE remains unknown, it has been estimated that PE contributes to over 200,000 deaths annually in the United States (1). The prognosis depends upon prompt recognition and treatment (2). Anticoagulation therapy with heparin and warfarin remains the mainstay of therapy (3).

The outcome of patients with PE depends largely on the size of the embolus and the presence of medical comorbidities, especially preexisting cardiopulmonary disease (4). Death after a massive PE usually results from hemodynamic compromise with right ventricular failure and a decreased cardiac output. Patients surviving massive PE continue to have high in-hospital mortality despite therapy with heparin (5). Right ventricular dysfunction in the setting of acute PE has been associated with increased mortality (6,7).

DVT is a common precursor of PE and is associated with significant morbidity from post-phlebotic syndrome (8). Manifestations of the post-phlebotic syndrome include edema,

hyperpigmentation, pain, and ulceration. These post-phlebotic changes may occur months to years following the index episode in up to 50% of patients with DVT (9). Strategies continue to evolve for the management of these patients in efforts to decrease both short- and long-term morbidity and mortality.

Thrombolytic Therapy in PE

Thrombolytic therapy has been used in the management of PE since the 1960s and has been shown to be more effective than heparin alone for PE under certain circumstances (10,11). Due to difficulties in establishing the diagnosis and misunderstanding the role of thrombolytic therapy in the management of PE, physicians underutilize thrombolytic therapy (12). The clearest indication for the use of thrombolytic therapy in PE is in the setting of hemodynamic collapse secondary to PE (3). In the only randomized trial of thrombolytic therapy versus heparin in massive PE with cardiogenic shock, four of four patients allocated to heparin died whereas all four patients allocated to thrombolytic therapy survived (13). This small study was stopped for ethical reasons.

Table 1. Thrombolytic therapy in pulmonary embolism.

Study	Design	No.	Thrombolytic agent and route	Outcome	Complications
UPET (16)	RCT	160	IV urokinase	2-week mortality similar [7% (urokinase) vs. 9% (heparin)]; Earlier improvement in lung perfusion scans with urokinase	Bleeding 45% (urokinase) vs. 27% (heparin)
Goldhaber et al. (18)	RCT	101	IV rt-PA and heparin vs heparin	rt-PA: Improved RV function; Improved perfusion scans; Decreased recurrent PE	Deaths- 2/55 (heparin) vs. 0/46 (rt-PA); Transfusion 3/46 (rt-PA), vs. 1/55 heparin
Dalla-Volta et al. (22)	RCT	36	IV rt-PA and heparin vs heparin	Improved perfusion with rt-PA	Major Bleed: 3/20 (rt-PA) vs. 2/16 (heparin); Any bleed:14/20 (rt-PA) vs. 6/16 (heparin); Death: 2 vs. 1 rt-PA vs. heparin
Tibbut et al. (23)	RCT	30	IV streptokinase vs heparin	Improved perfusion with streptokinase	Death 1/17 (heparin) vs. 0/13 (streptokinase); 7 patients withdrawn for adjuvant therapy
PIOPED Investigators (20)	RCT	13	IV rt-PA and heparin vs heparin	Trend towards improved angiographic score with rt-PA	Major bleed : 1/9 (rt-PA) vs. 0/4 (heparin)
Levine et al. (21)	RCT	58	IV rt-PA and heparin vs heparin	Improved perfusion with rt-PA	Death 1/25 (rt-PA) vs. 0/33 (heparin); No major bleed
Jerjes-Sanchez et al. (13)	RCT	8	IV urokinase vs heparin	Survival benefit with thrombolysis	Death 0/4 (urokinase) vs. 4/4 (heparin)
Ly et al. (24)	RCT	20	IV streptokinase vs heparin	Improved angiographic thrombolysis	30 day survival : 9/10 (streptokinase) vs. 8/10 (heparin); Major bleed: 4/10 (streptokinase) vs. 2/10 (heparin)
Konstaninides et al. (25)	Observational Registry	719	Thrombolysis vs heparin	Lower 30 day mortality with thrombolytic therapy (4.7% vs. 11.1%); Reduction in recurrent PE	Major bleeding 21.9% (thrombolysis) vs. 7.8% (heparin)
Hamel et al. (15)	Retrospective Cohort	128	Thrombolysis vs heparin	Improved perfusion but with increased bleeding and death with thrombolysis	Death 4/64 and major bleed 10/64 thrombolysis; No death or major bleed with heparin
McCotter et al. (28)	Case Series	26	IP urokinase	20/26 Clinical success	5/26 died; Bleeding 1/26
Krivec et al. (27)	Case series	13 (2 died before therapy)	IP streptokinase/ urokinase	9/11 receiving therapy survived to discharge	2/11 died; Bleeding –none reported
Leeper et al. (29)	Case series	7	IP streptokinase	Improved lung perfusion	Bleeding 2/7; Death – none

UPET = Urokinase Pulmonary Embolism Trial; RCT = Randomized controlled trial; IV = intravenous administration; rt-PA = recombinant tissue plasminogen activator; PE = pulmonary embolism; x/y: x = number of events and y = number in group; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; IP = intrapulmonary arterial administration;

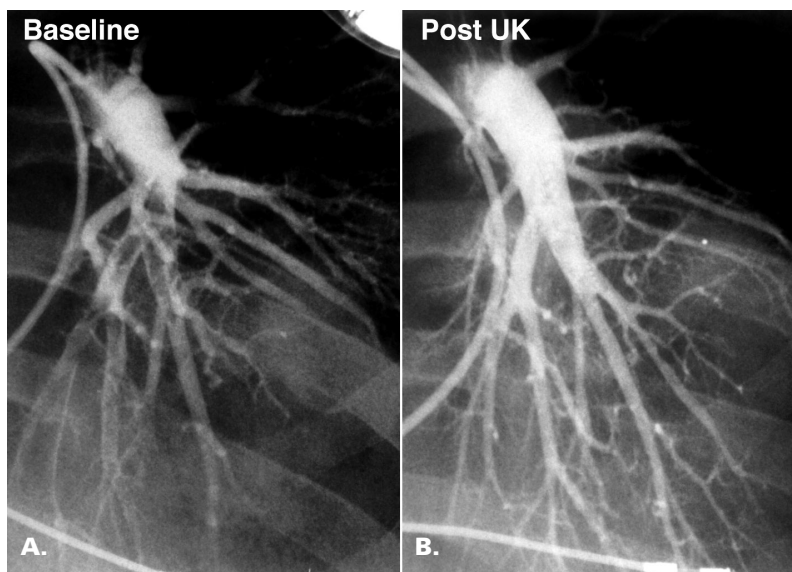


Figure 1. A Selective angiography of left pulmonary artery demonstrating filling defects with restriction of flow in the branches of the left pulmonary artery due to pulmonary embolism. **B:** Selective angiography of left pulmonary artery demonstrating resolution of filling defects with restoration of flow in the left pulmonary artery and its branches following local, catheter delivered thrombolysis. UK = urokinase.

The use of intravenous thrombolytic therapy in hemodynamically stable patients is more controversial (14,15). Thrombolytic therapy in massive PE has been shown to accelerate clot lysis, improve perfusion defects, and decrease right ventricular dysfunction (Table 1) (16-18). Thrombolytic therapy appears to improve lung perfusion and angiographic score of clot lysis up to 14 days after the onset of symptoms, although there is an inverse relationship between the duration of symptoms prior to therapy and the effectiveness of thrombolysis in PE (19). Thrombolytic therapy has not been shown to confer a survival benefit in hemodynamically stable patients, possibly because insufficient numbers of patients have been enrolled in studies designed to statistically evaluate this endpoint (20-24). However, analysis of the Management Strategy and Prognosis of Pulmonary Embolism Registry suggests that, compared with heparin therapy alone, thrombolytic therapy is independently associated with survival benefit in patients with PE and concomitant increased right ventricular afterload (25).

Currently urokinase (UK), streptokinase (SK), and recombinant tissue plasminogen activator (rt-PA) have been approved for intravenous use in PE. The thrombolytic agent may be administered via a peripheral vein or given locally via a catheter at the site of the thrombus in the pulmonary artery (Figure 1) (26). Local delivery of thrombolytic therapy into the pulmonary artery via a catheter has also been effective in dissolving thrombi and improving lung perfusion and has the advantage of requiring a lower total dose (27,28). Bleeding, particularly at the sites of arterial or venous puncture performed for venous access, arterial blood gases, or catheterization, is a frequent complication of thrombolytic therapy. Leeper et al reported bleeding requiring transfusion in two of seven patients treated with intrapulmonary thrombolytic therapy and

similar rates of major bleeding have been reported when thrombolytic therapy is used in conjunction with mechanical thrombus disruption (Table 2) (29). The incidence of intracranial hemorrhage following thrombolytic therapy for PE is low. Pooled analyses of systemic thrombolytic therapy in PE have estimated the incidence of intracranial hemorrhage to be 1%-2% (14).

Thrombolytic Therapy in DVT

While thrombolytic therapy accelerates clot lysis compared with unfractionated heparin in acute DVT, its use is tempered by the potential for serious bleeding, including intracranial bleeding (30). The potential benefits of thrombolytic therapy include prevention of PE and a decreased incidence of the post-phlebotic syndrome. Thrombolytic therapy has been shown to decrease swelling, venous valvular dysfunction, and the post-phlebotic syndrome associated with DVT (31-34). Patients with extensive DVT who are at high risk for post-phlebotic syndrome are potential candidates for thrombolytic therapy. Systemic thrombolytic therapy, when compared with conventional therapy, has been shown to improve venous patency and decrease the degree and incidence of post-phlebotic syndrome (35).

Semba and Dake demonstrated the feasibility of catheter-directed thrombolysis in iliofemoral DVT by achieving lysis in 23 of 27 patients without major complications (Figure 2) (36). The technique involves obtaining venous access via the ipsilateral popliteal vein, contralateral common femoral vein, or the internal jugular vein. The thrombolytic agent is delivered directly into the occluded venous segment by means of a coaxial catheter system. A prospective multicenter registry confirmed the efficacy of catheter-directed thrombolysis with a low mortality rate (Table 3) (37). Data from this registry suggest that a higher rate of lysis is achieved in patients with DVT of less than 10 days' duration. Grossman and McPherson reviewed 15 published reports of catheter-directed thrombolysis in iliofemoral DVT and noted a successful outcome of 84% (range 67%-100%) with a low rate of major complications (38). Comerota et al administered a health-related quality of life (HRQOL) questionnaire to patients

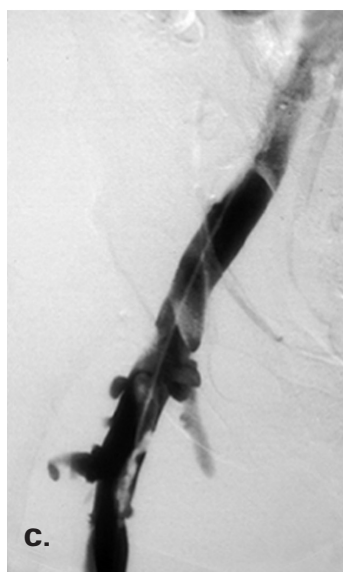
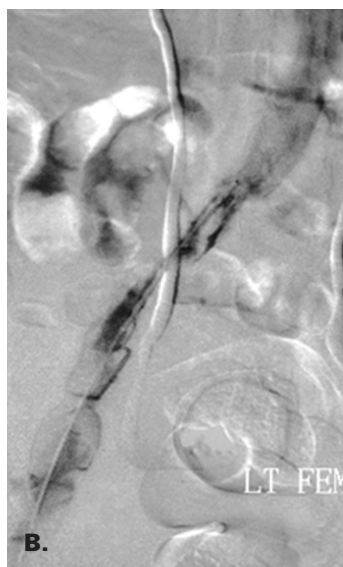
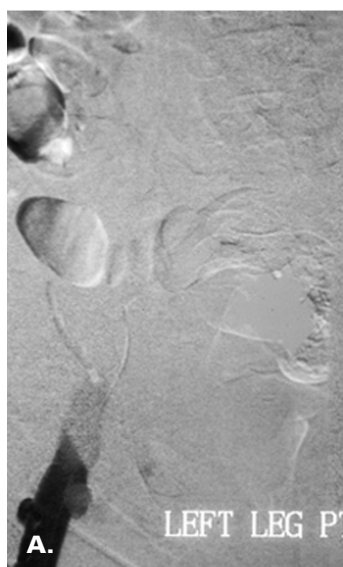


Table 2. Thrombolytic therapy in deep vein thrombosis.

Study (Ref.)	No. Pts.	Location of DVT	Acute Outcome	Long-term Outcome	Complications
Mewissen et al. (37)	287	Iliofemoral DVT- 71%; Femoro-popliteal DVT- 25%	Complete lysis-31% 50%-99% lysis-52% < 50% lysis-17%	Primary patency at 1 year - 60%	Major bleeding - 11% Minor bleeding 16% PE- 1% Neurological complications-0.4% Death - 0.4%
Grossman and McPherson (38)	263	Iliofemoral	84% success*	-	Bleeding requiring transfusion:4.9% PE - 0.8 % Death: 0.4%

*Success defined as either of the following: Complete thrombolysis of clot; technical restoration of normal venous blood flow, and less than 50% residual luminal narrowing; or partial thrombolysis of clot that allowed adjunctive methods to restore flow.

Table 3. Mechanical interventional therapy in pulmonary embolism.

Study (Ref.)	No. Pts.	Device Success	Technical Outcome	Acute and Death	Complications
Greenfield et al. (41)	46	Greenfield embolectomy catheter	76%	30 day survival - 70%	Hematoma-15% Pulmonary infarct - 11% Recurrent PE - 4% Death - 30%
Timsit et al. (40)	18	Greenfield embolectomy catheter	56%	72 % survival	Death - 28%
Fava et al. (42)	16	Grollman catheter*	87.5%	94% survival	Bleeding - 19% Death - 6.25%
Schmidt-Rode et al. (43)	10	Rotatable pigtail catheter*	70%	80% survival	Death - 20%
Essop et al. (50)	5	Guidewire/ catheter fragmentation*	100%	80% survival	Major bleed - 20% Death - 20%
Koning et al. (45)	2	Angiojet thrombectomy catheter	50%	100%	None

*Adjuvant pharmacologic thrombolysis

Figure 2. A. Selective venography of the left iliac vein demonstrating a filling defect and absence of flow due to thrombus. **B.** Partial restoration of flow with persistence of filling defect following local thrombolysis. **C.** Restoration of flow in the left iliac vein following stent placement.

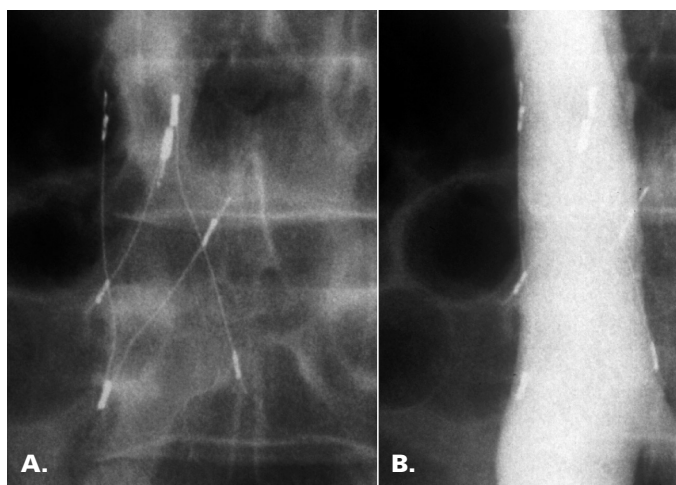


Table 4. Indications for thrombolytic therapy or mechanical interventions in venous thromboembolism.

Definite

Hypotension secondary to pulmonary embolism

Relative

Right ventricular dysfunction secondary to pulmonary embolism

Severe hypoxemia

Lobar or larger perfusion defect

Iliofemoral deep vein thrombosis

Figure 3. A: Fluoroscopic image of a Birds' Nest Filter in the inferior vena cava. **B:** Angiographic demonstration of flow across the Birds' Nest Filter in the inferior vena cava.

at a mean of 16 months following treatment of iliofemoral DVT (39). Patients who underwent catheter-based thrombolytic therapy reported a better sense of well-being and fewer post-phlebotic symptoms compared with patients who underwent conventional anticoagulation therapy. Furthermore, successful lysis was directly correlated with HRQOL and patients with failed lysis had outcomes similar to those patients receiving anticoagulation alone.

Mechanical Therapy in PE

Mechanical therapy consists of catheter-based embolectomy or emboli fragmentation. Mechanical interventions may be used alone (in patients with contraindications to thrombolysis) or in conjunction with thrombolytic therapy. The rationale for mechanical therapy is to relieve the central obstruction to flow that is the basis for hemodynamic collapse in PE. As with thrombolytic therapy, this form of therapy is generally reserved for patients with acute massive PE and evidence of hemodynamic collapse or compromise.

A variety of devices are now available which have been used successfully in massive PE. The devices are designed to relieve the obstructing thrombus by either aspiration or fragmentation. The largest experience is with the Greenfield transvenous pulmonary embolectomy catheter (Boston Scientific, Watertown, MA) (40). The technique involves introducing the catheter via either an internal jugular or common femoral vein. The catheter is advanced into the pulmonary artery and captures emboli with a cup device while applying suction. The emboli are then removed by withdrawing the catheter. Procedural success is more likely in acute PE compared with those suffering recurrent chronic

PE. Procedural success correlated with survival with improved survival, with a 30-day survival of 83% among patients undergoing successful embolectomy compared with 27% for those who failed (41).

Mechanical fragmentation of the pulmonary embolus with a Grollman catheter (Cook, Bloomington, IN) or a rotatable pigtail catheter (Cook, Bloomington, IN) with adjuvant thrombolysis to restore flow in PE has also been successful (42, 43). Additionally, guidewires have also been used to fragment the thrombus (44). Rheolytic thrombectomy with the Angiojet® Thrombectomy System (Possis, Minneapolis, MN), which uses a Venturi effect to disrupt and fragment the thrombus and then aspirate the debris, has been utilized in PE. The ability to guide this device over a wire gives it an advantage over other systems in that it can be precisely placed in the pulmonary circulation (45).

Mechanical Therapy in DVT

Mechanical therapy in DVT consists of devices directed towards prevention of proximal propagation or embolization of the thrombus into the pulmonary circulation, or involves the removal of the thrombus. The most common source of pulmonary emboli is the deep veins of the lower extremities (46). Mechanical prevention of embolization of thrombus from the lower extremity veins has been achieved with the use of vena caval filter devices (Figure 3) (47). Inferior vena caval filters are indicated in DVT in the presence of contraindications to anticoagulation, recurrent PE, large mobile proximal DVT, or as primary prophylaxis in patients at high risk for PE with contraindications for anticoagulation (3).

Patients with extensive DVT, especially iliofemoral DVT may benefit from thrombectomy. Kasirajan et al performed thrombectomy using rheolytic thrombectomy with the Angiojet® System in 17 patients with DVT, using adjuvant thrombolysis and balloon angioplasty (48). They reported clinical improvement with decreased swelling in 82% of the patients. Delomez et al performed thrombectomy with the Amplatz Thrombectomy Device (Microvena, White Bear Lake, MN) in 18 patients and obtained successful recanalization in 15 patients. There was one in-hospital death from recurrent caval thrombosis, and at a mean follow-up of 29.6 months only one patient with successful recanalization developed post-phlebotic changes (49).

Summary

Significant progress has been made in the management of venous thromboembolism, particularly with regard to interventions including thrombectomy and local thrombolysis. While anticoagulation with heparin and warfarin remains the cornerstone of care, adjuvant therapy with thrombolytic and mechanical interventional therapies can be very helpful in a select group of patients with venous thromboembolic disease (Table 4). By far the most critical element in the successful treatment of patients with venous thromboembolism remains early recognition, which requires a high index of suspicion. Clinicians need to remain alert to the early signs and symptoms of this disease in order to obtain the highest therapeutic success rates.

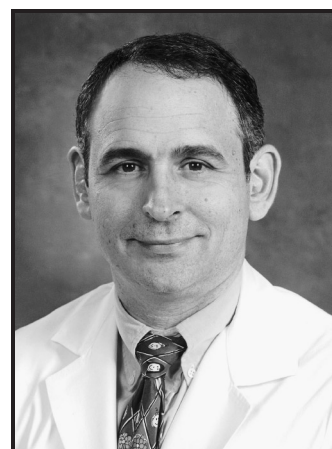
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Dr. Subramanian is a fellow at the Ochsner Heart and Vascular Institute.



Dr. White is the Chairman of Ochsner's Department of Cardiology.