# Aggressive Management of Pulmonary Embolism

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## Abstract

Pulmonary embolism (PE) and deep vein thrombosis are two elements of the same pathophysiological process referred to as venous thromboembolism. PE occurs when a thrombus migrates from a deep vein to the pulmonary arteries. Although the true incidence of PE is not known, it is estimated that 530,000 cases of PE occur annually in the United States. Clinical presentation varies from asymptomatic (incidentally diagnosed) to fatal. Development of symptoms depends on the embolic burden and the severity of any underlying cardiopulmonary disease. Several treatment options are available for patients diagnosed with PE. The mainstay of treatment is anticoagulation, but given the high mortality associated with some presentations of symptomatic PE, some advocate more aggressive therapy. In this article we discuss such therapies and their potential and appropriate use.

**Keywords**

- pulmonary embolism
- thrombolysis
- catheter-directed thrombolysis
- pharmaco-mechanical thrombolysis

**Objectives:** Upon completion of this article, the reader should be able to identify the indications for aggressive management of pulmonary embolism, and the technical considerations of using catheter-directed therapy in this patient population.

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Pulmonary embolism (PE) and deep vein thrombosis are two elements of the same pathophysiologic process referred to as venous thromboembolism.[1] PE occurs when a thrombus migrates from a deep vein to the pulmonary arteries.[2] Although the true incidence of PE is not known, it is estimated that 530,000 cases of PE occur annually in the United States.[3,4] Clinical presentation varies from asymptomatic (incidentally diagnosed) to fatal.[5] Development of symptoms depends on the embolic burden and the severity of any underlying cardiopulmonary disease.[6] The initial PE event has an associated mortality rate of 10%.[5,6] The diagnosis of PE is never made in ~70% of those who survive the initial event; the mortality rate in such individuals is ~30%.[5,6]

There are several treatment options available for patients diagnosed with PE. The mainstay of treatment is anticoagulation, but given the high mortality associated with some presentations of symptomatic PE, some individuals advocate more aggressive therapy.[6] In this article we discuss such therapies and their potential and appropriate use.

## Management

Making a diagnosis of PE can sometimes be challenging.[5] However, once a diagnosis of PE is made, patients should receive appropriate treatment without delay. The treatment should be tailored to the individual patient and his or her clinical condition. This can be achieved by risk stratification and an associated escalation of the degree of aggressiveness of treatment. The following are some of the therapeutic options that are available for use.

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## Anticoagulation

The mainstay of PE treatment is systemic anticoagulation.[2,6,7] This should be initiated immediately after the diagnosis of PE is made, but caution should be taken to ensure that the patient does not have a contraindication to anticoagulation.[8] The use of systemic anticoagulation alone is typically suitable for patients who are hemodynamically stable.[7] The use of systemic heparin prevents propagation of thrombus and reduces the risk of recurrent fatal PE,[2,8] and the use of unfractionated or low molecular weight heparin may be used.[2,6,7] Heparin reduces mortality related to PE from 30% if untreated to 8%.[2,9–13] Initiation of oral anticoagulation with warfarin should be made in conjunction with parenteral anticoagulation to allow for overlap between the two forms of anticoagulation, at least until the anticoagulant effect of the oral medication is within the therapeutic range. This process is termed *bridging*.[2]

Limitations for the use of heparin are heparin-induced thrombocytopenia (HIT) and contraindication to anticoagulation. Alternative parenteral anticoagulation medications such as argatroban or lepirudin are available for use in patients with HIT. However, patients who are not suitable candidates for any form of anticoagulation are more challenging to treat.

## Inferior Vena Cava Filter Placement

The routine use of inferior vena cava (IVC) filters in patients with PE is not recommended by the American College of Chest Physicians (ACCP).[9] Patients who have failed anticoagulation or have contraindications to anticoagulation are candidates for IVC filter placement, and the Food and Drug Administration (FDA) has approved use of IVC filters in such circumstances.[2] Some investigators suggest that IVC filters decrease the rate of recurrent PE but increase the rate of DVT, with no significant impact on the mortality rate.[2]

In both massive and submassive PE, there is compromised cardiopulmonary circulation. Submassive PE is characterized by right ventricular dysfunction without systemic arterial hypotension, whereas in massive PE there is associated systemic hypotension and shock.[14] Additional PE in a patient with an already compromised cardiopulmonary circulation may have dire consequences. Caval filtration with an IVC filter may be a prudent measure to take in this patient population because it likely decreases mortality in such compromised patients.[2] However, this remains an area of controversy with no evidence-based data to substantiate their use. Retrievable filters may play a key role until this debate is settled. They have the appeal of being optional; they can potentially be retrieved after the patient recovers from the acute episode or left in place as a permanent filter.

## Systemic Thrombolysis

The ACCP recommends the systemic infusion of thrombolytics intravenously through a peripheral vein, administered over a 2-hour period in patients with PE and hemodynamic compromise.[2,10] Thrombolytic drugs have been shown to be more effective at reducing the thrombus burden than systemic anticoagulants alone.[7] The use of thrombolytics in this manner has a major bleeding risk of up to 20%, with intracranial hemorrhage accounting for 3 to 5%.[2,15,16] Whether or not systemic thrombolytic therapy has a positive effect on mortality is still a subject for debate because some studies have shown a positive effect compared with systemic anticoagulation alone[2,17,18] and some have shown no significant difference.[2,19,20] These are nonrandomized studies, and the actual effect has yet to be determined in a randomized study.[2]

Patients should be screened for appropriateness of thrombolytic therapy. One of the contraindications to the use of thrombolytic drugs is an allergic reaction to such drugs. This is more of a concern with streptokinase, where allergic reactions have been reported in up to 26% of patients.[7] Currently, the agent most commonly used is tissue-type plasminogen activator (tPA), which carries a lower allergic reaction risk than streptokinase. The use of thrombolytic drugs in patients at high risk for bleeding is also contraindicated. Some of these conditions include an active bleeding source, recent major surgery (within 10 days), recent stroke (within 3 months), and metastatic disease to the brain.

## Catheter-Directed Interventions

The use of catheter-directed interventions (CDIs) in the treatment of PE is the next level of aggressive management of this condition. There have been multiple reports about the use of CDI in the treatment of PE, with varying results.[5]

### Early Thrombus Removal in Pulmonary Embolism

The two main problems that PE causes is mechanical obstruction of blood flow that results in decreased perfusion of the lung. The obstruction component has implications on the hemodynamics of pulmonary arterial flow. With significant thromboembolism, there is an increase in pulmonary capillary resistance resulting in a rapid rise in pulmonary arterial pressures.[7] A cascade of hemodynamic and respiratory changes ensue, including vasoconstriction, pulmonary arterial hypertension, right heart failure, decreased cardiac output, bronchoconstriction, increased dead space, and a decrease in pulmonary surfactant levels.[7]

The main predictor of mortality associated with PE is right ventricular failure.[21] The rapid removal of thrombus restores blood flow to the pulmonary circulation, with subsequent improvement in the strain on the right heart.

### Stand-Alone Catheter-Directed Pharmacological Thrombolysis

Catheter-directed thrombolysis is delivery of the thrombolytic drug through a catheter placed selectively within the thrombus.[22] The delivery of the drug through a catheter placed proximal to the clot in the main pulmonary artery has not been shown to have any advantage over peripheral administration of the drug.[7,23] Delivery of the drug directly into the thrombus has the advantage of increasing the surface area of thrombus subjected to the drug, thereby improving efficacy of thrombolysis and using smaller doses of the drug.[7] Additionally, because tPA needs thrombus-bound plasminogen to activate plasmin, placing the catheter directly into the thrombus improves this effect.

The choice of drug varies by availability and operator preference; currently the drug used most frequently is tPA. Infusion of the thrombolytic drug is continued for 12 to 24 hours. During this time, the patient is maintained on anticoagulation (full or partial, depending on operator preference) to prevent pericatheter thrombus formation and propagation of preexisting thrombus.[7]

The major disadvantages to catheter-directed infusions is the amount of time it may take for the drug to work. This is particularly important if the patient is unstable.

### Stand-Alone Percutaneous Mechanical Thrombectomy

Fragmenting the thrombus into smaller fragments is useful because these are easier to aspirate than larger clots.[5] Fragments that are not immediately aspirated will embolize to the distal pulmonary branches, typically with few clinical sequelae.[7] Because the surface area of the peripheral pulmonary vasculature is many times that of the central vessels, simply fragmenting a central thrombus and allowing it to travel distally effectively increases perfusion to the lung, even if the thrombus volume is not affected.[5] In addition to improved perfusion, this allows for better blood flow so the strain on the right heart is relieved.[7] There are many devices that can be used to break up the clot in to smaller fragments, including commercially available mechanical devices, balloons, and even wire maceration.[5] A potential disadvantage of mechanical thrombectomy done in this fashion is that it increases procedure time and there is a risk of injuring the pulmonary arteries using aggressive techniques.[24]

### Pharmacomechanical Catheter-Directed Thrombolysis

Modern CDI techniques often combine mechanical thrombectomy with the administration of thrombolytic drugs.[24] These two techniques can be used concurrently or sequentially. This combination has the advantage of fragmenting the clot, which not only makes it easier to aspirate but provides a larger surface area for the residual fragments to come in contact with the thrombolytic drug. This has the dual effect of increasing the drug's effectiveness as well as lowering the dose of drug that is administered.[7,24] This CDI technique reduces pulmonary arterial pressures to near-normal levels in nearly half of all patients treated in such a fashion.[7]

### Patient Selection for Catheter-Directed Thrombolysis

To date, there is no consensus on the precise indications and optimal technique for catheter-direct treatment of patients with PE. The ACCP recommends against the routine use of CDI for PE management; however, it does advocate its use in patients in extremis from PE in whom systemic thrombolytic therapy is contraindicated or in whom it has failed to improve their clinical condition.

Patients who are not candidates for thrombolytic therapy stand are candidates for stand-alone mechanical thrombectomy.[7] Debulking of the central thrombus creates a channel to restore blood flow within and downstream from the occluded vessel. Although this in itself is advantageous, the use of adjunctive aspiration of the thrombus can further reduce the thrombus burden. As alluded to earlier, there are numerous commercially available catheters and devices that range from a simple pigtail catheter used in a rotating fashion to break up the central thrombus to sophisticated devices that have motorized parts and use fluid infusion and aspiration channels or even ultrasound technology. None of these, however, are FDA approved for CDI for PE.[4]

The high mortality rate in patients presenting with acute PE (30%) largely occurs within the first hour of presentation.[2,5,7] Due to this potential rapid deterioration of their clinical status, many patients do not have the luxury of time to allow for prolonged infusion of systemic thrombolytics (the standard bolus infusion occurs over 2 hours). This has given rise to the trend toward advocating for catheter-directed therapy in this subgroup of PE patients.

Zeni et al have recommended aggressive therapy for patients with occlusion or obstruction of two or more lobar arteries.[5] In this study, primary management entailed systemic thrombolytic infusion, but in those patients with a contraindication to thrombolytic therapy, CDI was the treatment of choice. The authors also suggested that even in patients who could receive thrombolytic therapy but had severe enough symptoms, CDI may be performed initially, followed by thrombolytic infusion. For this population, the severity of symptoms is not well defined; however, it is generally accepted that CDI is indicated in patients with "massive PE." In a different report, Uflacker et al recommended the use of CDI in patients exhibiting any of the following: (1) arterial hypotension ($<$90 mm Hg systolic or drop of $>$40 mm Hg); (2) cardiogenic shock, peripheral hypoperfusion, and hypoxia; (3) circulatory collapse with need for cardiopulmonary resuscitation (syncope); (4) echocardiographic findings indicating right ventricular afterload stress and/or pulmonary hypertension; (5) precapillary pulmonary arterial hypertension (mean partial arterial pressure $>$20 mm Hg in the presence of normal partial arterial pressure occlusion pressures; (6) widened arterial-alveolar oxygen gradient $>$50 mm Hg, and (7) clinically severe PE with a contraindication to anticoagulation or thrombolytic therapy.[6] In an effort to prevent right ventricular failure, Goldhaber has also recommended CDI in patients with submassive PE where there is right ventricular dysfunction but preservation of systemic arterial pressure without the need for pressors to support it.[4,25]

The major disadvantage of systemic thrombolytic therapy is severe hemorrhage. Even when patients are screened for risk factors that would place them at a higher risk for hemorrhage, the risk of hemorrhage is still high (20% overall, with the risk of intracranial hemorrhage at 3 to 5%).[4] CDI can potentially lower the dose of drug required for therapy and thus theoretically decrease the risk of major hemorrhage.

### Specific Catheter-Directed Intervention Considerations

CDI techniques continue to evolve. One of the newer CDI techniques involves the use of low-intensity, high-frequency ultrasound waves transmitted into the thrombus with the thrombolytic agent. The ultrasound waves separate fibrin strands in the clot and increase the surface area of the thrombus available to the thrombolytic drug.[24] The

ultrasound waves also help to disseminate the drug throughout the clot. In addition to less infusion time, the dose of thrombolytic agent is also reduced with this technique, which may in turn decrease the risk of bleeding complications.[24]

The end point of CDI is also a matter of debate. Some authors advocate for the termination of CDI as soon as hemodynamic stability is achieved.[4] However, this only applies to patients with massive PE. In patients who are undergoing CDI but are hemodynamically stable, an appropriate end point may be normalization of the pulmonary arterial pressures. A radiographic, such as a normal-appearing angiogram, end point is generally not an acceptable end point by itself.[4]

A meta-analysis in 2009 of CDI in patients with massive PE demonstrated a clinical success rate of 86.5%, with a complication rate of 2.4%.[4] These rates compare favorably to results with systemic thrombolysis of 77% success and 22% complication rates.[4] Finally, a potential but as yet undefined long-term benefit of CDI is the reduction of, or prevention of, secondary pulmonary hypertension due to chronic PE.[7]

### Surgical Intervention

Surgical embolectomy has been used to treat patients with massive PE who did not respond to systemic thrombolytic therapy or in those patients in which the use of anticoagulants and thrombolytics is contraindicated.[2,6] Advancement in surgical and anesthetic techniques has significantly reduced morbidity and mortality of surgical embolectomy, with a resultant increase in the survival rate to 85%.[2,6,26] In some centers surgical embolectomy remains a viable option[2,27,28]; however, with the advent of modern interventional equipment, development of new techniques, and more experienced interventionalists, I envision the role of surgery diminishing even further.

## Conclusion

Acute PE has various forms of presentation. Patients identified as possible candidates for CDI should undergo risk stratification in an expedited manner. In cases with known high morbidity and mortality rates, aggressive therapy with modern CDI techniques should be initiated without delay. Further studies are needed to define the subgroups in this patient population that are most likely to benefit from this more aggressive therapy.

### References


1 Key NS, Kasthuri RS. Current treatment of venous thromboembolism. Arterioscler Thromb Vasc Biol 2010;30(3):372–375
2 Banovac F, Buckley DC, Kuo WT, et al; Technology Assessment Committee of the Society of Interventional Radiology. Reporting standards for endovascular treatment of pulmonary embolism. J Vasc Interv Radiol 2010;21(1):44–53
3 Kuo WT, Sze DY, Hofmann LV. Catheter-directed intervention for acute pulmonary embolism: a shining saber. Chest 2008;133 (1):317–318; author reply 318
4 Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. J Vasc Interv Radiol 2009;20(11):1431–1440
5 Zeni PT Jr, Blank BG, Peeler DW. Use of rheolytic thrombectomy in treatment of acute massive pulmonary embolism. J Vasc Interv Radiol 2003;14(12):1511–1515
6 Uflacker R. Interventional therapy for pulmonary embolism. J Vasc Interv Radiol 2001;12(2):147–164
7 De Gregorio MA, Gimeno MJ, Mainar A, et al. Mechanical and enzymatic thrombolysis for massive pulmonary embolism. J Vasc Interv Radiol 2002;13(2 Pt 1):163–169
8 Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960;1(7138): 1309–1312
9 Hirsh J, Guyatt G, Albers GW, Harrington R, Schünemann HJ; American College of Chest Physicians. Executive summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6, Suppl): 71S–109S
10 Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. N Engl J Med 1992;326(19):1240–1245
11 Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979–1998: an analysis using multiple-cause mortality data. Arch Intern Med 2003;163(14): 1711–1717
12 Dismuke SE, Wagner EH. Pulmonary embolism as a cause of death. The changing mortality in hospitalized patients. JAMA 1986;255 (15):2039–2042
13 Dalen JE, Alpert JS. Natural history of pulmonary embolism. Prog Cardiovasc Dis 1975;17(4):259–270
14 Krichavsky MZ, Rybicki FJ, Resnic FS. Catheter directed lysis and thrombectomy of submassive pulmonary embolism. Catheterization and cardiovascular interventions. Cathet Cardiac Intervent 2011;77(1):144–147
15 Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353(9162):1386–1389
16 Fiumara K, Kucher N, Fanikos J, Goldhaber SZ. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. Am J Cardiol 2006;97(1):127–129
17 Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004;110(6):744–749
18 Agnelli G, Becattini C, Kirschstein T. Thrombolysis vs heparin in the treatment of pulmonary embolism: a clinical outcome-based meta-analysis. Arch Intern Med 2002;162(22):2537–2541
19 Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. J Am Coll Cardiol 2002;40 (9):1660–1667
20 Dong B, Jirong Y, Liu G, Wang Q, Wu T. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev 2006(2): CD004437
21 Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90. mm Hg or higher. Arch Intern Med 2005;165(15):1777–1781
22 Vedantham S, Grassi CJ, Ferral H, et al; Technology Assessment Committe of the Society of Interventional Radiology. Reporting standards for endovascular treatment of lower extremity deep vein thrombosis. J Vasc Interv Radiol 2006;17(3):417–434
23 Verstraete M, Miller GA, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation 1988;77(2):353–360
24 Chamsuddin A, Nazzal L, Kang B, et al. Catheter-directed thrombolysis with the Endowave system in the treatment of acute massive pulmonary embolism: a retrospective multicenter case series. J Vasc Interv Radiol 2008;19(3):372–376

25 Goldhaber SZ. Integration of catheter thrombectomy into our armamentarium to treat acute pulmonary embolism. Chest 1998;114(5):1237–1238
26 Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg 2005;129(5):1018–1023
27 Jamieson SW, Auger WR, Fedullo PF, et al. Experience and results with 150 pulmonary thromboendarterectomy operations over a 29-month period. J Thorac Cardiovasc Surg 1993;106(1):116–126; discussion 126–127
28 Archibald CJ, Auger WR, Fedullo PF, et al. Long-term outcome after pulmonary thromboendarterectomy. Am J Respir Crit Care Med 1999;160(2):523–528