Endovascular Interventions for Acute Pulmonary Embolism

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Abstract

Massive pulmonary embolism (PE) is a highly lethal condition with clinical manifestations of hemodynamic instability, acute right ventricular (RV) failure, and cardiogenic shock. Submassive PE, as defined by RV failure or troponin elevation, can result in life-threatening sequelae if treatment is not initiated promptly. Current treatment paradigm in patients with massive PE mandates prompt risk stratification with aggressive therapeutic strategies. With the advent of endovascular technologies, various catheter-based thrombectomy and thrombolytic devices are available to treat patients with massive or submassive PE. In this article, a variety of endovascular treatment strategies for PE are analyzed. The authors' institutional experience with ultrasound-accelerated thrombolytic therapy as well as catheter-directed thrombolytic therapy in patients with acute massive PE during a recent 10-year period is discussed. Finally, clinical evidence on the utilization of catheter-based interventions in patients with massive and submassive PE is also analyzed.

Keywords

pulmonary embolism, deep vein thrombosis, mechanical thrombectomy, ultrasound-accelerated thrombolysis, catheter-directed thrombolysis, thrombolytic therapy, catheterizations

Introduction

Pulmonary embolism (PE) is a life-threatening condition, which is responsible for more than 300 000 deaths every year in the United States. It is estimated that more than 600 000 patients develop symptomatic PE annually.[1,2] The mortality rate in the first 3 months following the diagnosis of PE has been shown to range from 15% to 18%.[3,4] Massive PE, characterized by circulatory collapse or hemodynamic instability from acute PE, is a highly lethal condition, which is associated with a 3-fold increased inpatient mortality compared with conditions without hemodynamic instability.[5,6] The majority of deaths in patients with PE are a result of acute massive PE, which typically occurs within 1 hour of presentation.[7] Submassive PE, on the other hand, is defined as PE-related right ventricular (RV) dysfunction and troponin elevation despite normal arterial pressure. Without prompt treatment, patients with submassive PE may progress to the massive category with a potentially fatal outcome. It is noteworthy that although the lethality data of PE are comparable with those of acute myocardial infarction, the overall mortality rate associated with this devastating condition has not improved significantly over the past 3 decades.[3,8-10]

The optimal treatment strategies for patients with acute PE has been a subject of controversy because no randomized controlled trials exists to support an ideal therapeutic modality. For patients with hemodynamic instability caused by massive PE, systemic thrombolysis is considered to be the standard of care.[2,11-15] Clinical evidence for utilizing catheter-directed thrombolysis in patients with massive PE remains scarce. In fact, the only randomized controlled trial in patients with massive PE that compared systemic streptokinase thrombolytic therapy versus heparin treatment enrolled only 8 patients.[16] The trial was stopped as a result of ethical concerns because all 4 patients receiving thrombolytic therapy survived, whereas those receiving heparin suffered fatal outcomes. The use of thrombolytic agents in acute PE was first reported more than 3 decades ago.[17] Since then, clinical studies, experimental models, and case series have consistently demonstrated the efficacious outcome of catheter-directed thrombolytic therapy (CDT) on hemodynamic and angiographic variables of patients with symptomatic or massive PE. It has been accepted beyond a reasonable doubt that thrombolytic therapy is superior to conventional

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systemic anticoagulation with either unfractionated or low-molecular-weight heparin with regard to early resolution of pulmonary artery embolism and restoration of RV function.[15,18,19]

CDT enables a high concentration of thrombolytic agents to be infused directly into the thrombus, resulting in shorter infusion times and reduced doses of the thrombolytic drug needed for thrombus resolution, which theoretically decreases the risk of hemorrhagic complications compared with systemic thrombolysis. In recent years, interest has risen in a variety of endovascular strategies involving catheter-based technologies for thrombus removal in patients with massive PE. Various mechanical devices based on fragmentation or rheolytic thrombectomy principles have shown clinical efficacy in radiographic thrombus resolution as well as symptomatic improvement in patients with PE.[20-26] In this article, we evaluate various interventional treatment strategies for PE. Clinical evidence for utilizing endovascular treatment modalities, based on our institutional experience as well as a literature review, is also examined.

Treatment Strategies for Pulmonary Embolism

Since the introduction of unfractionated heparin more than 4 decades ago, anticoagulation with systemic heparin has become the mainstay treatment for venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and PE. Administration of heparin anticoagulation is effective in preventing thrombus propagation, which triggers endogenous fibrinolysis to allow thrombus dissolution over a period of weeks and months.[27] During the past decade, low-molecular-weight heparin has been shown to be as effective as or superior to intravenous administration of unfractionated heparin.[28,29] Another important treatment strategy for VTE includes thrombolytic therapy, in which plasminogen activator is administered to convert plasminogen to plasma. This enzymatic reaction degrades thrombus-bound fibrinogen, resulting in rapid thrombus dissolution. Thrombolysis may result in faster and more complete thrombus degradation, thus, producing a more rapid improvement in pulmonary flow with oxygenation as well as RV performance. Consequently, thrombolysis could result in lower morbidity and mortality compared with systemic heparin therapy.[30]

For patients with massive PE who have major contraindications for thrombolysis, such as recent operation, trauma, or stroke, urgent pulmonary embolectomy has been described as a viable treatment option in experienced tertiary care institutions. Operative steps of a surgical embolectomy for PE include a median sternotomy incision, circulatory arrest with cardiopulmonary bypass, vascular control of the main pulmonary artery, followed by surgical removal of thromboembolism in the pulmonary artery. In a large clinical study, the International Cooperative Pulmonary Embolism Registry (ICOPER), which included 304 patients with PE, surgical pulmonary embolectomy was performed in only 1% of patients with massive PE who experienced cardiogenic shock.[3] This surgical treatment option was associated with a high complication and fatality rate—the in-hospital mortality rate following surgical embolectomy was 30%.[3]

Another treatment alternative for rapidly dissolving a pulmonary thrombus and reversing PE-related RV failure or cardiogenic shock is endovascular intervention with either catheter-directed thrombolysis or percutaneous mechanical thrombectomy.[31] Several recent studies have shown that CDT can serve as an effective treatment alternative in patients with cardiogenic shock or hemodynamic instability caused by massive PE.[2,13,16,31-34] In contrast, percutaneous mechanical thrombectomy devices may provide a useful alternative in patients who cannot receive thrombolysis because of contraindications or because they are not suitable candidates to undergo surgical pulmonary embolectomy as a result of cardiopulmonary comorbidities. Although a recent review article showed favorable outcome using a variety of percutaneous mechanical thrombectomy devices in patients with massive PE,[35] there have been no controlled clinical studies that compare the efficacy of mechanical thrombectomy therapy with other treatment modalities such as surgical embolectomy or catheter-directed thrombolysis.

Indications for Advanced Therapy for Acute Pulmonary Embolism

In the 2008 publication by the American College of Chest Physicians (ACCP), *Evidence-Based Clinical Practice Guidelines Regarding Treatment of PE*, therapeutic strategies of advanced interventions, including anticoagulation, thrombolysis, percutaneous embolectomy, and/or inferior vena cava (IVC) filter placement, were recommended based on appropriate risk stratification in highly selected patients who have PE-related hemodynamic instability.[36] A separate consensus guideline by the 2008 European Society of Cardiology Task Force regarding PE management shared many similar diagnostic criteria and therapeutic recommendations in patients with massive PE who experienced cardiogenic shock. Table 1 highlights the treatment recommendation from these 2 consensus guidelines regarding patients with PE-related hemodynamic compromise.

Based on clinical evidence,[37-40] clinical parameters that warrant early and aggressive catheter-based interventions for acute massive PE require one or more of the following conditions:

Table 1. Treatment Guidelines for Advanced Therapy in Patients With Acute Pulmonary Embolism

Treatment Variable	2008 ACCP Guidelines[36]	2008 ESC Guidelines[19]
Risk stratification	All patients should undergo rapid risk stratification	All patients should undergo risk stratification based on the presence of shock and hypotension, as well as further stratification based on imaging or biochemical markers of right ventricular dysfunction and myocardial injury
Thrombolysis	Use if hemodynamic compromise, unless contraindications. If high-risk without hypotension, use depends on clinician's assessment of PE severity, prognosis, and bleeding risk	First-line treatment for cardiogenic shock or persistent arterial hypotension. Consider in selected intermediate-risk patients after assessing bleeding risk
Catheter embolectomy	Selected highly compromised patients with too high bleeding risk for thrombolysis or insufficient time for systemic thrombolysis to be effective	Consider as an alternative to surgical treatment in high-risk patients when thrombolysis is absolutely contraindicated
Surgical embolectomy	Selected highly compromised patients with too high bleeding risk for thrombolysis or insufficient time for systemic thrombolysis to be effective	Valuable therapeutic option in patients with high-risk PE in whom thrombolysis is absolutely contraindicated or has failed
Vena caval filter	Place if anticoagulation is not possible because of the risk of bleeding. If the bleeding risk resolves, administer a conventional course of anticoagulant therapy	Use when there are absolute contraindications to anticoagulation and a high risk of PE recurrence. Remove retrievable filters as soon as it is safe to use anticoagulants

Note: ACCP = American College of Chest Physicians; ESC = European Society of Cardiology.

- arterial hypotension, as defined by systolic arterial pressure of ≤90 mm Hg, a drop in systolic arterial pressure of ≥40 mm Hg for ≥15 minutes, or ongoing administration of catecholamine for the treatment of systemic arterial hypotension;
- cardiogenic shock with peripheral hypoperfusion and hypoxia;
- circulatory collapse, including syncope or need for cardiopulmonary resuscitation;
- echocardiographic findings indicating RV dilation and/or pulmonary hypertension;
- subtotal or total filling defect in the left and/or right main pulmonary artery determined by chest CT scan or by conventional pulmonary angiography; and
- widened arterial–alveolar O_2 gradient (>50 mm Hg).

Endovascular Treatment Strategies for Pulmonary Embolism

A variety of endovascular treatment strategies, including catheter-based thrombolysis, percutaneous pulmonary embolectomy, and IVC filter placement have been reported in the literature for patients with acute PE.[1,2,8,11,22,32-34,41-43] The reported mortality rates based on these various endovascular techniques vary from 0% to 25%.[1,2,8,11,22,32-34,41-43] Many of these percutaneous mechanical thrombectomy devices were used in conjunction with pharmacological thrombolysis, a technique also known as pharmacomechanical thrombectomy, which is a commonly adapted interventional technique in iliofemoral DVT interventions.[44-46] Partly because of the heterogeneity of these endovascular treatment strategies, it is difficult to determine the most efficacious treatment strategy because no controlled trial is available. Nonetheless, brief overviews of these various treatment strategies are provided below.

Catheter-Directed Thrombolytic Therapy

The efficacy of CDT with intrapulmonary thrombolytic infusion in patients with acute massive PE has been reported in several studies with an overall remarkable treatment success.[8,16,20,31-34,47] This treatment strategy requires selective infusion catheter placement in the pulmonary artery within the embolus, followed by continuous infusion of thrombolytic drugs over a period of time. The treatment objective is to accelerate thrombus dissolution and achieve rapid reperfusion of the pulmonary arteries. In an ideal scenario, this catheter-directed intervention results in hemodynamic improvement with restoration of RV hypokinesis, normalization of RV size, and reduction of abnormally high pulmonary arterial pressures. Intrapulmonary administration of thrombolytic agents may potentially promote intravascular fibrinolysis elsewhere in the pelvis or lower extremity, thereby, reducing the likelihood of recurrent VTE. Another therapeutic advantage of this intervention

includes potential reduction of chronic elevations of pulmonary vascular resistance by improving pulmonary capillary blood flow, which might theoretically lower the incidence of long-term pulmonary hypertension.

Although CDT offers many theoretical benefits and therapeutic advantages in patients with PE, several major limitations must be acknowledged with this treatment approach. First, the risk of hemorrhagic complications, including intracranial or gastrointestinal bleeding, increases significantly with the treatment duration and thrombolytic dosage. This is a particular concern in elderly patients in whom catastrophic intracranial bleeding has been reported in clinical thrombolytic trials of arterial thrombosis.[48,49] Second, there has been only 1 single randomized trial, with only 8 patients, of whom 4 received streptokinase plus heparin and 4 received anticoagulation alone, which demonstrated survival advantage with thrombolytic therapy.[16] The survival benefit of CDT in PE remains to be proven in other clinical investigations. In contrast, findings from the ICOPER suggested that patients with massive PE treated with thrombolysis might not experience any survival advantage or reduction in major cardiovascular adverse events.[3]

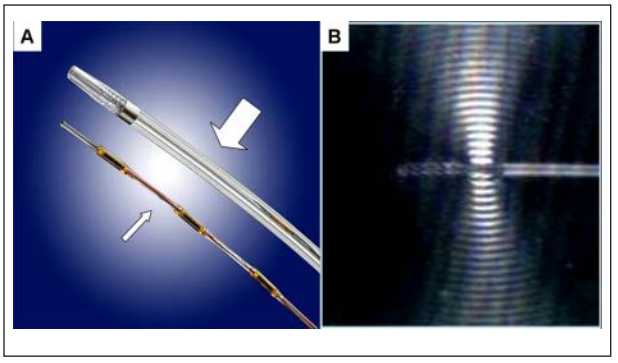

Figure 1. A. The EkoSonic endovascular system consists of a multiple-lumen infusion catheter (larger arrow) with a removal coaxial ultrasound transducer core (smaller arrow), which is connected to a control unit that delivers lower-energy high-frequency ultrasound energy with concomitant thrombolytic drug infusion into the thrombus. B. Schlieren photograph of an EkoSonic catheter, which emits ultrasound energy. The acoustic streaming energy dissociates the fibrin and increases the fibrin porosity without causing distal embolization, which also facilitates the penetration of thrombolytic agent into the thrombus for receptor binding

Ultrasound-Accelerated Thrombolytic Therapy

Ultrasound-accelerated catheter-directed thrombolysis is a novel treatment strategy in which pulmonary artery thrombolytic therapy is delivered through an infusion catheter, which emits ultrasound energy to accelerate thrombolytic cascade. This treatment strategy is achieved using the EkoSonic Endovascular System (EKOS, Seattle, WA), which is approved by the Food and Drug Administration (FDA) for pulmonary artery infusion. The system is a 5.2-F multilumen side-port infusion catheter, with infusion lengths of 6 to 50 cm depending on the length of the thrombotic occlusion. Once the EkosSonic catheter is positioned in the pulmonary artery over a 0.035-inch guidewire, the guidewire is exchanged for a matching ultrasound core wire containing a series of ultrasound transducer elements (2.2 MHz, 0.45 W), which are distributed approximately 1.0 cm apart along its leading tip to evenly deliver ultrasound energy radially along the coaxial infusion zone (Figure 1). A control unit provides continuous monitored variables, including temperature and ultrasound energy power output in the treatment zone, by means of thermocouples incorporated in the catheter and automatically adjusts power to optimize lysis of the intravascular thrombosis. The acoustic streaming energy dissociates the fibrin and increases the fibrin porosity without causing distal embolization, which also facilitates the penetration of thrombolytic agents into the thrombus for receptor binding. Two recent clinical reports, including our own institutional experience, on patients with acute massive PE who were treated with ultrasound-accelerated thrombolytic therapy showed promising clinical outcomes with dramatic hemodynamic improvement.[33,47]

Catheter Thrombus Fragmentation Technique

Percutaneous pulmonary thrombus fragmentation using a rotating pigtail catheter followed by catheter-directed thrombolysis is a useful method for treating patients with massive PE and has been widely described.[8,31,32] A common technique in using this approach is to use a rotatable pigtail catheter (Cook, Bloomington, IN), which is a modified 5F pigtail catheter with a radiopaque tip, with 10 side holes for contrast material injection. An oval side hole in the outer aspect of the pigtail loop allows direct passage of a 0.035-inch guidewire through the hole to act as a central axis around which the catheter rotates. The catheter is rotated bimanually to break apart large fresh clots. The pigtail tip of the catheter disrupts the clot in multiple smaller fragments, which embolize distally in the pulmonary circulation. Simple thrombus fragmentation using an angiography pigtail catheter by vigorous manual catheter rotation may generate sufficient mechanical force to break the pulmonary thrombus causing RV outflow obstruction and consequent left ventricular failure. The thrombus fragmentation also effectively increases the available thrombus surface area for effective thrombolysis. Several in vivo hemodynamic studies have shown that, once a large pulmonary thrombus is fragmented into multiple smaller thrombi, the

redistribution of larger central clots into the peripheral pulmonary bed may immediately increase total pulmonary blood flow and relieve RV afterload, which can improve oxygenation and hemodynamic oxygen perfusion.[50,51]

In a study that examined 20 patients with massive PE on whom this endovascular technique was used, catheter intervention with the pigtail rotational catheter showed a 33% recanalization rate by thrombus fragmentation without thrombolytic therapy.[52,53] However, adjunctive infusion of thrombolytic therapy with recombinant tissue plasminogen activator significantly improved the thrombus dissolution and improved RV performance.[52,53] One disadvantage with this catheter device is the risk of macroembolization of pulmonary thrombus in smaller pulmonary artery branches.[54] Macroembolization may lead to hemodynamic deterioration and systemic hypotension when a large centrally located nonobstructive pulmonary thrombus is fragmented and embolized into a previously nonobstructed major pulmonary branch. Although numerous clinical studies using the pigtail catheter fragmentation technique have shown significant hemodynamic improvement in patients with massive PE,[8,31,32,50] these studies have not demonstrated survival benefits using this treatment approach.

AngioJet Rheolytic Thrombectomy Catheter

The AngioJet Xpeedior thrombectomy device (Possis/Medrad; Minneapolis, MN) is a 6F over-the-wire catheter, which creates thrombus aspiration force based on Venturi's principle.[55,56] The device permits a concomitant infusion of the thrombolytic agent, which creates a pharmacomechanical thrombectomy technique of thrombus dissolution by both thrombolysis and mechanical thrombectomy. The pharmacomechanical thrombectomy technique using this device is widely adapted in DVT interventions.[45] Short-acting, newer-generation fibrinolytic drugs, such as alteplase (10 to 20 mg), reteplase (2.5 to 5 U), or tenecteplase (5 to 10 mg), may be used for the pharmacomechanical thrombectomy approach. However, because the AngioJet Xpeedior is not designed to treat vessels greater than 12 mm in diameter, its therapeutic efficacy in the treatment of massive PE remains limited.[57-59] Procedural-related complications and deaths have been reported using this device in PE interventions. In one study, the rheolytic AngioJet device was associated with a high rate of complications, including 5 procedure-related deaths. Several additional deaths related to the AngioJet have been recorded in the FDA Manufacturer and User Facility Device Experience database.[60] Because of these reported complications, the FDA has issued a block-box warning on the device label.[61] Based on safety concerns, the AngioJet device should not be used as the initial mechanical treatment in patients with acute massive PE.

Greenfield Embolectomy Catheter

The Greenfield embolectomy device (Boston Scientific, Watertown, MA) was the first percutaneous thromboembolectomy device approved by the FDA for PE intervention. The device is 10F in caliber, containing a steerable catheter with a 5-mm or 7-mm plastic suction cup at the tip. One device-related drawback is that it has to be inserted through a venotomy via the femoral or jugular vein without a guidewire. The device removes the centrally located fresh embolus by manual suction with a large syringe and requires the retrieval of the device and the thrombus as a unit through an open femoral or jugular venotomy. Because of its introduction in the 1970s, clinical reports have shown that more than 100 patients with massive PE have been successfully treated using this device.[62-64] Clinical success using this device in extracting pulmonary thrombus was as high as 83% of patients with massive PE, with the majority of them experiencing immediate hemodynamic improvement.[37,62,65,66] The 30-day mortality rate ranged from 5% to 30%.[37,62,65,66]

Aspirex Pulmonary Embolism Catheter

The Aspirex catheter thrombectomy device (Straub Medical, Wangs, Switzerland) is an 11F percutaneous thrombus removal system specifically designed for interventional treatment of PE. The device ranges from 6 mm to 14 mm in caliber, with the central part of the catheter system containing a high-speed rotational coil (40 000 revolutions per minute) within the catheter body. The rotational movement of the coil creates thrombus removal mechanisms by (*a*) creating negative pressure through an L-shaped aspiration port at the catheter tip, (*b*) macerating the aspirated thrombus, and (*c*) aspirating thrombus fragments.[67-69] A recent clinical study that included 13 patients with acute massive PE revealed successful thrombus aspiration in the pulmonary arteries without cardiovascular deaths or recurrent PE during a mean follow-up period of 12 months.[69] This device is ideally suited for patients with massive PE with contraindications for thrombolysis. Because of the large device caliber, this device can also be used for thrombus extraction in conditions such as IVC filter thrombosis, iliofemoral DVT, or thrombosis of the intrahepatic portosystemic shunts.[68]

IVC Filter Placement

Since the approval of retrievable IVC filters by the FDA in the past decade, the clinical applications of IVC filter placement have been widely expanded partly as a result of IVC filter retrievability.[70,71] For patients with hemorrhagic conditions or contraindications to anticoagulation, placement of a retrievable IVC filter may be appropriate.

Retrievable filters can be left in place for months or remain in place indefinitely if clinically indicated, because of persistent contraindication to anticoagulation or presence of a trapped large filter thrombus.[72] The 2 primary indications for IVC filter are the following: (*a*) major hemorrhage that precludes anticoagulation and (*b*) recurrent PE despite anticoagulation. Multiple randomized controlled trials have convincingly demonstrated the efficacy of IVC filters in the reduction of PE recurrence.[72-74] Although recurrence of clinically symptomatic PE following IVC filter placement is uncommon, it can occur in 2% to 5% of patients.[72,73] The filter insertion is a relatively low-risk procedure, which can be accomplished through the jugular vein, basilic vein, or femoral vein. Complications of IVC filter placement are uncommon and are primarily associated with long-term device implantation, including filter migration, IVC perforation, and IVC thrombosis.[73-75] The relative and absolute indications for IVC filter placement are listed in Table 2.

Table 2. Indications for Inferior Vena Cava Filter Placement

- Absolute indications
  - Patients with pulmonary embolism (PE) who have contraindications to anticoagulation, which include the following conditions
    - Hemorrhagic stroke
    - Recent neurosurgical procedures or other major surgery
    - Major or multiple trauma
    - Active internal bleeding (eg, upper- or lower-gastrointestinal bleeding, hematuria, hemobilia)
    - Intracranial neoplasm
    - Bleeding diathesis (eg, secondary thrombocytopenia, idiopathic thrombocytopenic purpura, hemophilia)
    - Pregnancy
    - Unsteady gait or tendency to fall (as seen in patients with previous stroke, Parkinson's disease)
    - Poor patient compliance with medications
  - Recurrent PE despite adequate anticoagulation
- Relative indications
  - Massive or submassive PE with hemodynamic compromise
  - Large, free-floating iliocaval thrombus
  - Poor compliance with medications
  - History of PE disease with upcoming surgery
  - Chronic thromboembolic pulmonary disease (before surgery)
  - Prophylaxis for PE prevention in patients at high risk for thromboembolic event. This may include the following patient cohorts:
    - Patients scheduled to undergo major surgery, including lower-extremity orthopedic operation, major abdominal operation, and neurosurgical operation
    - Patients with chronic pulmonary hypertension and a marginal cardiopulmonary reserve
    - Patients with traumatic injury, including the following conditions:
      - Severe head injury with prolonged ventilator dependence
      - Major abdominal or pelvic penetrating venous injury
      - Spinal cord injury with or without paralysis
      - Severe head injury with multiple lower-extremity fractures
      - Pelvic fracture with or without lower-extremity fractures

Baylor College of Medicine Experience

Clinical experience of interventional treatment in patients with acute massive PE at the Baylor College of Medicine was recently reported.[33] Briefly, a total of 25 patients underwent 33 catheter-directed interventions for massive PE during a recent 10-year period. Interventional treatment strategies in these patients included CDT (CDT group, n = 11) or ultrasound-accelerated thrombolytic therapy using the EkoSonic system (EKOS group, n = 15). Preinterventional and postinterventional pulmonary angiography (Figure 2) was analyzed for evidence of thrombus removal based on the published criteria as reported by Miller and associates.[76] The Miller score (MS) was calculated based on the degree of pulmonary artery obstruction and perfusion indexes, which ranges from 0 (*best*) to 34 (*worst*). A diagnosis of massive PE was confirmed with an MS >17. Preinterventional and postinterventional MS and relative MS improvement, defined as the pre-MS score minus the post-MS score divided by the pre-MS score, were calculated for each patient.

Relevant clinical factors, including hypercoagulable risk factors for PE, thrombolytic dose, infusion time, percentage lysis based on angiographic analysis, and treatment complications were compared between the 2 treatment groups. Complete thrombolysis was defined as more than 90% thrombus removal, near-complete lysis was defined as 75% to 90% thrombus removal, and partial lysis was defined as 50% to 75% thrombus removal. Follow-up interval pulmonary angiography was performed 12 to 48 hours after the initiation of catheter-based interventions to determine the need to either continue or stop thrombolysis. Helical CT angiogram of the chest was performed whenever clinical indications were present (Figure 3).

Our clinical experience showed that successful catheter-based interventions were initiated as the infusion catheter was positioned appropriately within the thrombus in all patients in both groups. In the EKOS group, tPA was used in all patients with a mean tPA dose rate of 0.86 ± 0.16 mg/h, for a mean total tPA dose of 17.2 ± 2.36 mg (range 8 mg-28 mg). The mean infusion time was 17.4 ± 5.23 hours (range 13-38 hours). There were no hemorrhagic complications in this patient group. The preinterventional MS was 18.65 ± 3.25, which decreased to a postinterventional MS level of 5.84 ± 1.57 (Table 2). In the CDT group, 5 patients received urokinase, whereas 10 patients received tPA as thrombolytic agents. The mean infusion time was

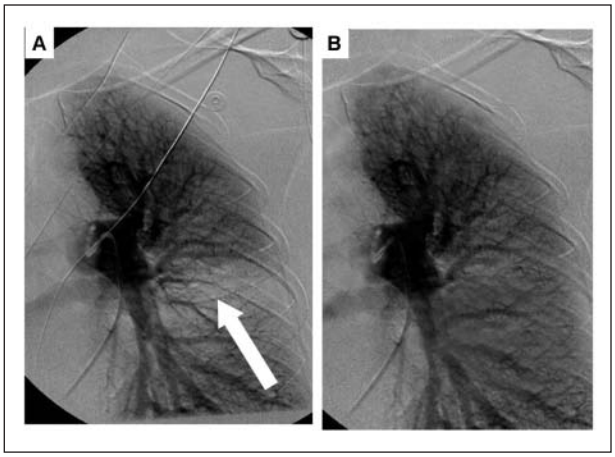

Figure 2. A. Selective angiography of the left main pulmonary artery demonstrated a pulmonary embolism in the inferior branch of the left pulmonary artery with contrast-filling defect in the left pulmonary parenchyma (arrow). B. Successful treatment with ultrasound-accelerated thrombolytic therapy restored pulmonary arterial flow with improved opacification of the left dorsal inferior pulmonary artery

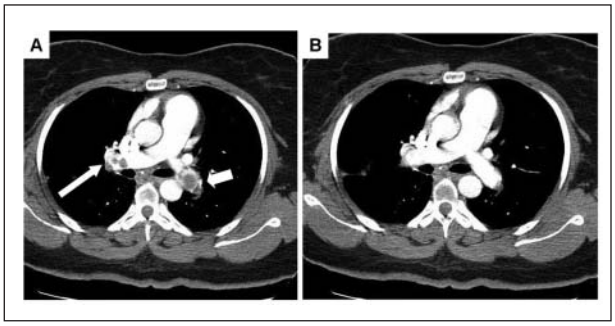

Figure 3. A. Helical computed tomography (CT) angiogram showed emboli in bilateral pulmonary arteries with large thrombus in the left main pulmonary artery (short arrow) and multiple thrombi in the right main pulmonary artery (long arrow) prior to ultrasound-accelerated thrombolytic therapy. B. Follow-up CT angiogram performed 5 days after successful thrombolytic therapy using the EkoSonic device demonstrated complete resolution of bilateral pulmonary embolism

26.7 ± 8.64 hours (range 14-46 hours). The mean tPA dose rate was 0.93 ± 0.22 mg/h for a mean total tPA dose of 25.43 ± 5.27 mg (range 16-45 mg). For those who received urokinase thrombolytic therapy, the mean starting dose was 60 000 U/h, which was increased at 6 hours to a mean dose of 90 000 U/h. The mean total urokinase dose was 2.04 ± 0.56 million U (range 1.65-2.87) delivered over a mean period of 25.3 ± 7.35 hours (range 17-39 hours). Complete thrombus resolution was achieved in 7 patients (50%), whereas partial thrombolysis was achieved in 2 patients (14.3%).[33]

Comparative analysis between the 2 treatment groups based on thrombus removal showed that the EKOS group had an improved treatment success compared with the CDT group ($P < .02$). The preinterventional MS was 17.29 ± 3.86, which was decreased to 7.38 ± 2.26 following CDT (Table 3). Specifically related to the tPA dosage and infusion time, there was a reduction in the tPA dosage and infusion time in the EKOS group when compared with the CDT group ($P < .001$). The MS scores were statistically significant in both the EKOS and CDT groups following respective interventional treatments ($P < .002$). No significant difference in relative MS improvement was observed between groups.[33]

This study demonstrated remarkable therapeutic efficacy of both catheter-directed thrombolysis and ultrasound-accelerated thrombolytic therapy in patients with acute massive PE. The treatment success of catheter-directed thrombolysis and EKOS interventions is evidenced by the 30-day survival rates, which were 86% and 91%, respectively.[33] The findings of this study underscored the beneficial role of endovascular interventions in patients with acute massive PE.

Clinical Evidence for Thrombolytic Therapy in Pulmonary Embolism

Several researchers have examined treatment outcomes in an unselected group of patients with PE who were treated with either thrombolysis or heparin.[77,78] In a meta-analysis that included 11 randomized controlled trials, the treatment outcome of thrombolysis versus heparin anticoagulation for PE was analyzed.[16,78-87] This pooled data set included a total of 748 patients with PE treated with either thrombolysis or heparin administration. The authors reported no difference in survival between the 2 treatment groups because the mortality rates were 4.3% and 5.9%, respectively.[16,78-87] In a Cochrane systematic review published in 2006, which analyzed 8 randomized controlled trials, a total of 679 patients with PE were analyzed regarding treatment outcome of thrombolytic therapy and heparin anticoagulation.[77] In this unselected patient population, the number of patients who underwent thrombolytic therapy and heparin anticoagulation were 333 and 340, respectively. No difference in the mortality rates between the thrombolytic and heparin groups was found: they were 4.5% (n = 15) and 4.7% (n = 16), respectively.[77] Based on these pooled data with an unselected patient population, it can be seen that administration of thrombolytic agents does not confer any survival advantage compared with heparin treatment. However, because of the relatively low adverse event rate following PE interventions, it has been estimated that future trials should include a sample size of at least 1000 patients to achieve adequate statistical power to detect treatment significance.[88]

Although the majority of these research findings suggest that thrombolytic therapy in unselected patients with PE

Table 3. Treatment Outcome in the EKOS and CDT Treatment Groups From Baylor College of Medicine[33]

Variable	EKOS Therapy	CDT Therapy	*P* Value
No. of patients	11	14	n/a
No. of PE lesions	15	18	n/a
Mean age	59 ± 17 years	62 ± 18 years	NS
Male (%)	5 (45%)	7 (50%)	NS
Complete thrombolysis	11 (100%)	7 (50%)	.01
Partial thrombolysis	0	2 (14.3%)	.03
Mortality	1 (9.1%)	2 (14.2%)	NS
Hemorrhagic complications	0	3 (21.4%)	.02
Thrombolytic dosage (Urokinase, U × 10^6)	n/a	2.04 ± 0.56	n/a
Thrombolytic dose rate (tPA, mg/h)	0.86 ± 0.16	0.93 ± 0.22	.04
Thrombolytic dose (tPA, mg)	17.2 ± 2.36	25.43 ± 5.27	.03
Thrombolytic infusion (hours)	17.4 ± 5.23	26.7 ± 8.64	.03
Preintervention MS	18.65 ± 3.25	17.29 ± 3.86	NS
Postintervention MS	5.84 ± 1.57[a]	7.38 ± 2.26[b]	NS
Relative MS improvement	0.63 ± 0.18	0.68 ± 0.26	NS

Note: EKOS = EkoSonic Endovascular System; CDT = catheter-directed thrombolytic therapy; PE = pulmonary embolism; MS = Miller score.
[a]Comparison of preintervention and postintervention MS within EKOS group showed a significant difference with $P < .002$.
[b]Comparison of preintervention and postintervention MS within CDT group showed a significant difference with $P < .002$.

does not confer survival benefits,[78-87] one might postulate that patients with acute massive PE who present with hemodynamic instability or cardiogenic shock may benefit from rapid thrombotic resolution and hemodynamic improvement as provided by prompt thrombolytic therapy. It is estimated that approximately 10% of patients who develop PE suffer from acute massive form with clinical manifestations of hemodynamic instability or cardiogenic shock.[15,27,89] The clinical devastation of acute massive PE is evidenced by the findings of the ICOPER, in which researchers noted that the mortality rate for patients with acute massive PE with hemodynamic instability was as high as 60%.[3] It is noteworthy that the current ACCP treatment guidelines support the use of thrombolytic therapy in hemodynamically unstable patients with acute massive PE.[36]

To further delineate the therapeutic role of thrombolytic therapy in patients with acute massive PE, Jerjes-Sanchez and colleagues[16] conducted a randomized trial of thrombolytic therapy and heparin alone specifically in patients with hemodynamic instability caused by PE. The authors randomized 8 patients to either a one-time bolus of streptokinase followed by a heparin infusion (n = 4) or heparin infusion alone (n = 4). All 4 patients who received streptokinase all survived to 2 years of follow-up. In contrast, all 4 patients who received heparin alone died within a few hours of presentation. In another randomized controlled trial, which included 30 patients with hemodynamic instability who were treated with either thrombolytic or anticoagulation therapy, there was no fatality in 13 patients who received intrapulmonary streptokinase whereas 1 out of 17 patients who received intrapulmonary heparin suffered a fatal outcome.[87] The major bleeding complications between the thrombolysis and heparin group were similar—7.7% and 5.9%, respectively. The therapeutic benefit of thrombolytic therapy in acute massive PE was similarly highlighted in a large clinical review, which included 33 studies of patients with acute massive PE who were treated with catheter-directed aspiration, fragmentation, or rheolytic thrombectomy, with or without local or systemic thrombolytic therapy.[35] In this article, which examined treatment outcomes of 348 patients with acute massive PE, the authors reported remarkable clinical success, as defined by improvement in hemodynamic parameters immediately after the procedure, in 71% to 100% of patients who underwent catheter-directed embolectomy with adjunctive systemic and local thrombolysis and 67% to 88% of patients who underwent catheter embolectomy alone. The authors emphasized the availability of skilled interventionalists, and their clinical experience should influence whether patients with acute massive PE undergo catheter-directed intervention. Taken together, the outcome of these studies underscored a potential therapeutic benefit of thrombolytic therapy in patients with hemodynamic instability.[16,87]

The therapeutic benefit of thrombolysis in patients with acute submassive PE, in contrast, remains a subject of debate. It has been shown that patients with submassive PE who developed acute RV dysfunction have a 3-fold increase in PE-related mortality compared with those without cardiac dysfunction.[90] Geibel and associates[91] reported their findings regarding treatment outcomes of 719 patients with submassive PE from a prospective multicenter registry (Management Strategy and Prognosis of Pulmonary Embolism Trial [MAPPET]). This study compared heparin plus thrombolysis versus heparin alone within 24 hours in patients

with submassive PE. The 30-day mortality rate in patients who received heparin alone was 11%, which was in sharp contrast to 2.7% in male patients who received thrombolytic therapy ($P = .03$). However, thrombolytic therapy conferred no survival benefits in female patients with submassive PE. Regarding risk factor analysis, the study reported that syncope (odds ratio [OR] = 2.41; 95% confidence interval [CI] = 1.20-4.84) and chronic lung disease (OR = 3.5; 95% CI = 1.37-8.95) but not thrombolytic therapy (OR = 0.77; 95% CI = 0.30-1.97) were independent predictors of overall mortality in women.

Konstantinides and colleagues[83] conducted a randomized study in 256 patients with submassive PE who had pulmonary hypertension or RV dysfunction. These patients were randomly assigned to receive thrombolytic therapy with recombinant tPA plus heparin or heparin treatment alone. The primary end point was in-hospital death or clinical deterioration requiring treatment escalation (eg, catecholamine infusion, secondary or rescue thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency surgical embolectomy or catheter fragmentation). The risk of the combined end points was significantly reduced in patients treated with thrombolysis than heparin (11.0% vs 24.6%). However, the risk of in-hospital death was similar in the 2 groups (3.4% vs 2.2%), which underscored the observation that the difference in the primary end point was driven entirely by a significant difference in the requirement for treatment escalation (10.2% vs 24.6%), especially the need for secondary thrombolysis (7.6% vs 23.2%). Nonetheless, these findings suggested a therapeutic advantage with thrombolytic therapy compared with heparin treatment in patients with submassive PE.[83]

Based on the recently published 2008 ACCP treatment guidelines for patients with PE, these patients should undergo rapid risk stratification. It recommends that selected high-risk patients without hypotension, who are deemed to have a low risk of bleeding, should receive thrombolytic therapy. Additionally, patients with hemodynamic instability should also be considered for thrombolytic therapy.[36] Specific ACCP treatment guidelines for advanced therapy in patients with PE are summarized in Table 1.

Conclusions

The results of multiple clinical reviews, along with our own institutional experience, highlight a potential therapeutic benefit in patients with acute massive PE whose hemodynamic instability or cardiogenic shock could be improved with prompted endovascular interventions. CDT is a viable treatment option in patients with acute massive PE who have contraindications to systemic thrombolysis, when there is no time to administer systemic thrombolytic agents, or when there is no improvement following standard intravenous thrombolytic administration. In contrast, catheter-based interventions should not be performed in hemodynamically stable patients with PE. The question of the therapeutic role of thrombolytic therapy in patients with acute submassive PE remains to be answered. Future studies are needed to examine the utility of combining various hemodynamic, angiographic, and echocardiographic risk factors to better estimate prognosis of patients with PE. Additionally, clinical investigations of endovascular treatment modalities, including catheter-directed thrombolysis or mechanical thrombectomy, should be performed in patients with acute submassive PE. Based on current best evidence as well as available treatment guidelines, catheter-based thrombolytic therapy should be considered as a first-line treatment strategy for patients with acute massive PE in institutions with appropriate clinical expertise.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

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