

Endovascular Approaches to Pulmonary Thromboembolic Disease

Catheter-based therapies have been shown to be safe and effective adjunctive treatments in patients with submassive and massive pulmonary embolism.

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Pulmonary thromboembolic disease is a significant problem accounting for one-third of patients with venous thromboembolism. Approximately 600,000 people in the United States present with pulmonary embolism annually, resulting in 50,000 to 200,000 deaths per year.¹ Early mortality and adverse outcomes are linked to those with high- and intermediate-severity disease, and risk stratification plays a pivotal role in triaging patients for treatment. The two main factors predicting disease severity are the volume of pulmonary arterial occlusion and the presence of pre-existing cardiopulmonary disease. Patients with underlying conditions such as chronic obstructive pulmonary disease, ischemic heart disease, and pulmonary arterial hypertension have decreased cardiopulmonary reserve and can tolerate a lesser degree of pulmonary arterial occlusion before going into hemodynamic shock.

Low-risk, or nonmassive, pulmonary embolism accounts for the majority of cases (55%).² These patients are characterized by a low embolic burden

and are hemodynamically stable without evidence of myocardial dysfunction or injury. The standard of care is systemic anticoagulation, typically with warfarin or enoxaparin, but newer agents are increasingly available. Outcomes are promising with an early mortality rate of < 1%.³

On the opposite end of the spectrum, patients with high-risk disease, or massive pulmonary embolism, have more dismal outcomes, with 25% to 58% early mortality, typically within the first 2 hours.⁴⁻⁶ Due to impaired left ventricular contractility from a combination of both decreased preload and mass effect from right heart enlargement, these patients are hemodynamically unstable and are often on the verge of death. Clinical parameters defining massive pulmonary embolism include a sustained systolic blood pressure < 90 mm Hg, a sudden decrease in systolic blood pressure of ≥ 40 mm Hg in a hypertensive patient, or hemodynamic shock requiring vasopressor support. The goal for these patients is urgent revascularization, and treatment should be initiated immediately with both systemic anticoagu-

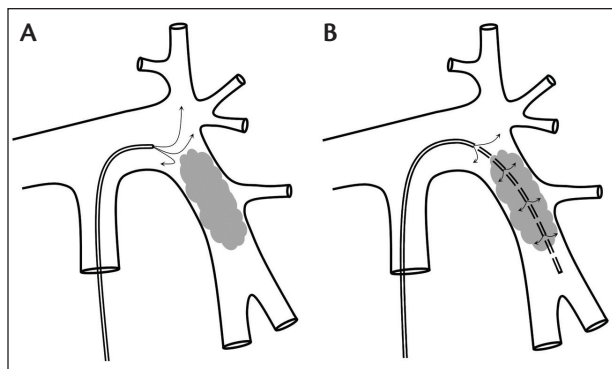


Figure 1. Infusion of a thrombolytic through a nonembedded catheter results in rapid dissipation of the drug through non-obstructed pathways (A). A multisidehole infusion catheter is embedded within an embolus in the left lower lobe, allowing thrombolytics to be infused directly into the clot (B).

lation and systemic thrombolysis. In patients with a contraindication to or failure of systemic thrombolysis, catheter-directed thrombolysis (CDT) to mechanically decrease clot burden or surgical embolectomy are viable alternatives.

Patients with intermediate-risk disease, or submassive pulmonary embolism, have a low early mortality rate of 5% to 10%.⁷ Unlike their low-risk counterparts, they have a potential to rapidly decompensate and also have an increased likelihood of developing chronic adverse outcomes including long-term right ventricular dysfunction and chronic thromboembolic pulmonary hypertension. These patients are clinically stable on presentation, but data from the past 10 to 15 years suggest that the presence of right heart dysfunction distinguishes them from those with low-risk disease. Transthoracic echocardiography best diagnoses and provides direct evidence for right ventricular dysfunction. An RV:LV end diastolic volume ratio > 0.9 on echocardiography or EKG-gated cardiac CT has been used as an objective sign of right heart strain and is supported by biomarkers such as increased troponins and BNP. Treatment is traditionally systemic anticoagulation, and there is currently no consensus on the role of CDT.

ROLE OF THE INTERVENTIONIST

Several societies, including the American College of Chest Physicians, the American Heart Association, and the European Society of Cardiology, provide guidelines predominantly on the medical management of pulmonary embolism. Although there has been recent interest in the role of CDT, little guidance has been provided on the interventionist's role.

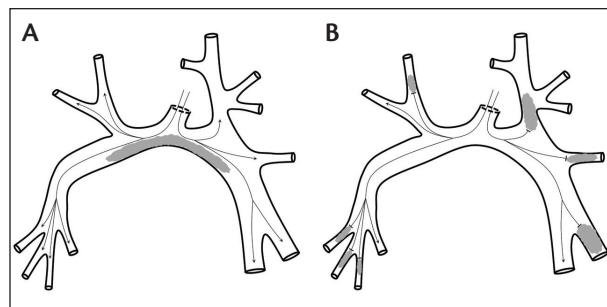


Figure 2. A saddle embolus bridges the right and left pulmonary arteries (A). Despite the central location, only a small portion of the total pulmonary arterial cross-sectional area is occluded, and blood flows into the distal branches. Following mechanical disruption of the embolism, multiple occlusive emboli are present distally in lobar and segmental pulmonary artery branches (B). In comparison to the saddle embolus in (A), there is occlusion of a larger cross-sectional area of the pulmonary arterial system. This limits blood flow, resulting in elevated right heart pressures and decreased preload to the left heart.

In our experience, patients with submassive embolism may benefit from endovascular therapies. Several trials have demonstrated a benefit of thrombolytic therapy in this subgroup. Data from the PEITHO trial demonstrate that patients who receive systemic thrombolysis have decreased early mortality rates as well as a lower risk of early hemodynamic decompensation.⁸ This study was a follow-up of the MAPPET-3 trial, which showed similar results.⁹ Additionally, Kline et al have proposed that patients receiving both tPA and heparin compared to heparin alone may have better long-term outcomes with a more significant decrease in right ventricular systolic pressures at 6 months.¹⁰

Although these findings favor treatment with systemic thrombolysis, they are tempered by the associated risk of hemorrhage in patients who are administered large systemic doses of thrombolytics (up to 100 mg tPA). In fact, the PEITHO trial reported an increased risk of significant bleeding (up to 20%) in patients who received systemic thrombolysis, most importantly hemorrhagic stroke (3%–5%), which is in keeping with the results of previous studies such as ICOPER.² Consequently, there was no significant difference in overall outcomes compared to those treated conservatively with anticoagulation alone.

Decreased rates of major hemorrhage were observed in the MOPETT trial, which compared a lower dose of thrombolytic (50 mg tPA) with heparin alone.¹¹ CDT has the potential to provide an effective alternative to systemic thrombolysis in this group of patients, while

decreasing the overall dose of thrombolytics and likely bleeding complications.

A meta-analysis by Kuo et al in 2009 reviewed the results of CDT encompassing both pharmacologic and mechanical thrombolysis and proposed that CDT is an effective adjunctive or even first-line therapy in submassive and massive pulmonary embolism.¹² Other recent trials, such as ULTIMA, SEATTLE II, and a study by Kennedy et al, have evaluated CDT as an alternative to systemic therapy.¹³⁻¹⁵ In these studies, an ultrasound-accelerated multisidehole infusion catheter was embedded into the clot, and thrombolytic was slowly infused through the catheter at a rate of 0.5 to 1 mg/hr per catheter for up to 24 hours in addition to full-dose systemic anticoagulation. Although sample sizes were small, these studies did show that CDT is both safe and efficacious with significant improvements in right heart strain and pulmonary arterial pressures after treatment. Importantly, these studies have shown a lower rate of major hemorrhage in comparison to studies in which full-dose systemic thrombolytics have been utilized.

Interventionists may also play a role in assisting the treatment of massive pulmonary embolism. These patients are critically ill and have a significant risk of imminent death. Society guidelines support full-dose thrombolytic therapy with 100 mg of intravenous tPA administered over 2 hours. After systemic thrombolysis has been initiated, endovascular techniques can serve as adjunctive treatments to improve pulmonary arterial perfusion. For example, thrombolytic therapy can

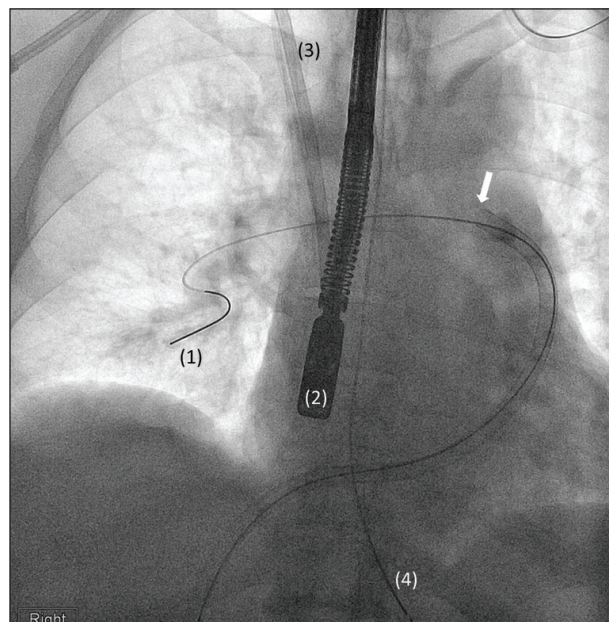


Figure 3. Fluoroscopic image demonstrates a 22-F AngioVac catheter positioned within the main pulmonary artery (arrow). Also present are (1) a guidewire positioned in a distal right pulmonary arterial branch, (2) a transesophageal ultrasound probe, (3) two right internal jugular catheters, and (4) a nasogastric tube.

be completed via a targeted catheter-directed infusion. Additionally, several instruments are available that allow for rapid mechanical clot debulking by maceration or aspiration of embolus.

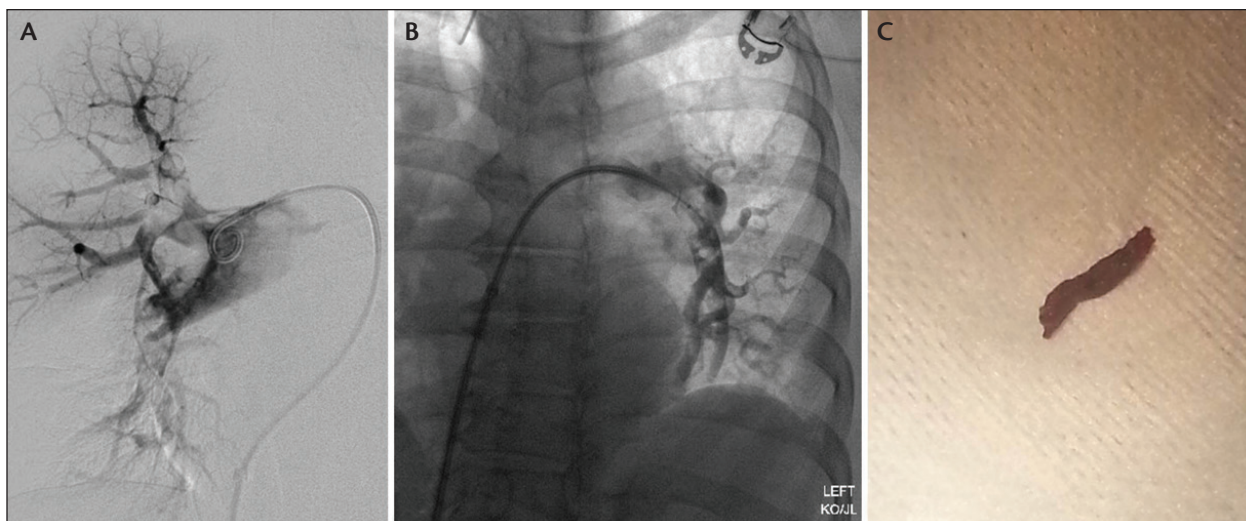


Figure 4. Pronto XL extraction device. Digital subtraction angiography is performed through a pigtail catheter positioned in the right interlobar artery (A). Note the numerous filling defects within the segmental branches. A Pronto straight catheter is positioned in the left lower lobar artery (B). Note the segmental filling defects. An embolus that was removed by manual aspiration through a Pronto catheter (C).

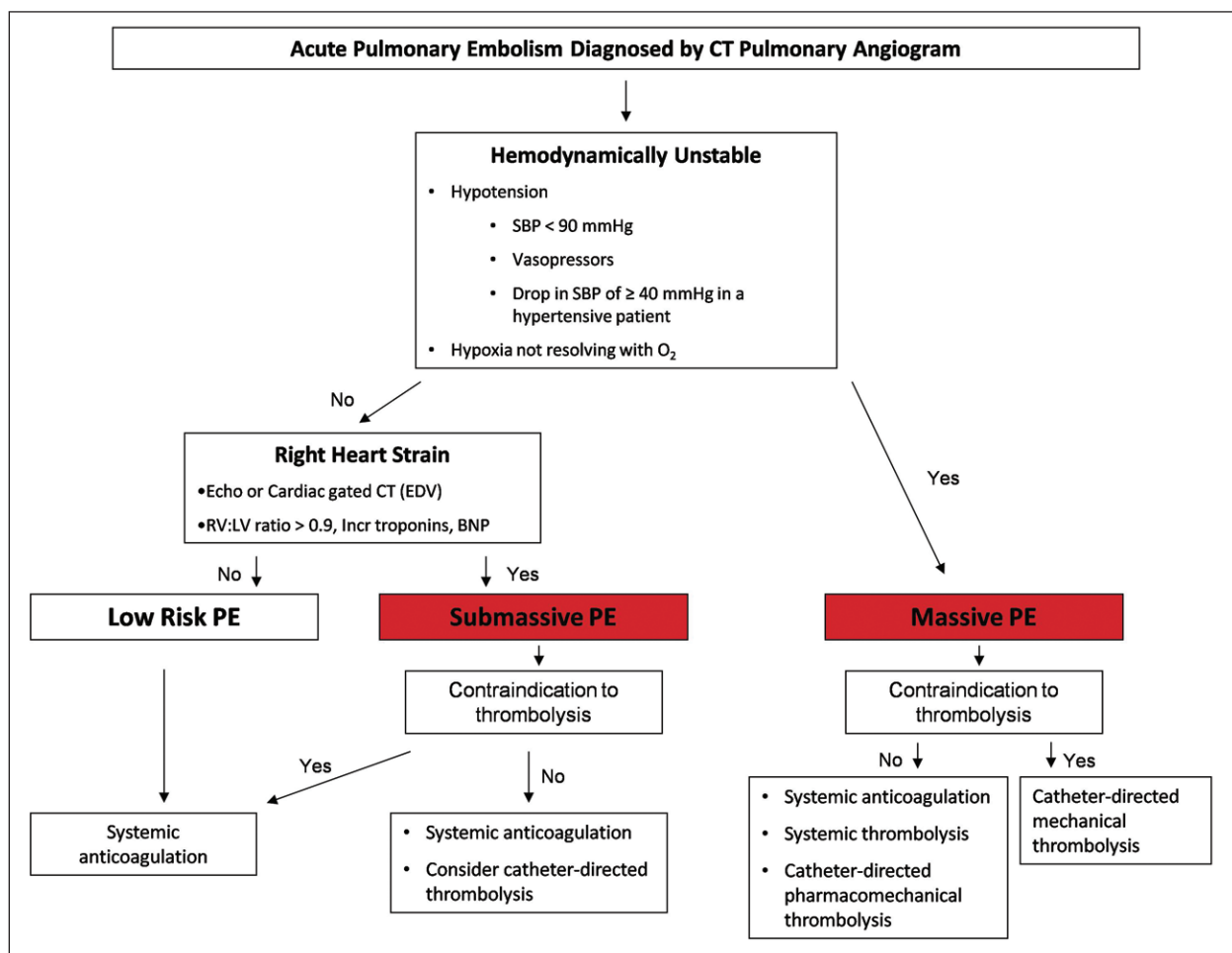


Figure 5. A proposed risk stratification algorithm for triaging patients diagnosed with pulmonary arterial embolism.

PRINCIPLES OF ENDOVASCULAR INTERVENTION

The objective of all endovascular therapy is to accelerate clearance of blood clot from the pulmonary arterial circulation in order to relieve strain on the right ventricle and atrium and to improve preload to the left heart chambers. In patients with massive pulmonary embolism, the immediate goal is to ensure adequate cardiac output to keep the patient alive. The goal of treatment in patients with submassive pulmonary embolism is to preserve the function of the right ventricle and to prevent the development of chronic thromboembolic pulmonary hypertension.

The physiological effect of the pulmonary embolism is determined by the degree of obstruction of the cross-sectional area of the pulmonary arterial tree, explaining why many patients with saddle emboli are hemodynamically stable and without right heart strain. As the pulmonary arteries are a high-flow system, any

infusion of thrombolytic must be given directly into the blood clot in order to be effective, as it will otherwise preferentially flow through the nonobstructed pathway without embolus (Figure 1). In the setting of submassive pulmonary embolism, slow infusion of thrombolytic through a multisidehole infusion catheter can be initiated quickly and easily.

Mechanical clot aspiration and maceration has the potential to reduce the degree of pulmonary artery obstruction quickly and without the administration of thrombolytic medication. Caution is recommended when treating submassive pulmonary embolism, as disruption of central thrombus has the potential to embolize and more significantly occlude distal pulmonary arterial branches (Figure 2).

DEVICES

Currently employed devices in endovascular treatment of acute pulmonary embolism include delivery

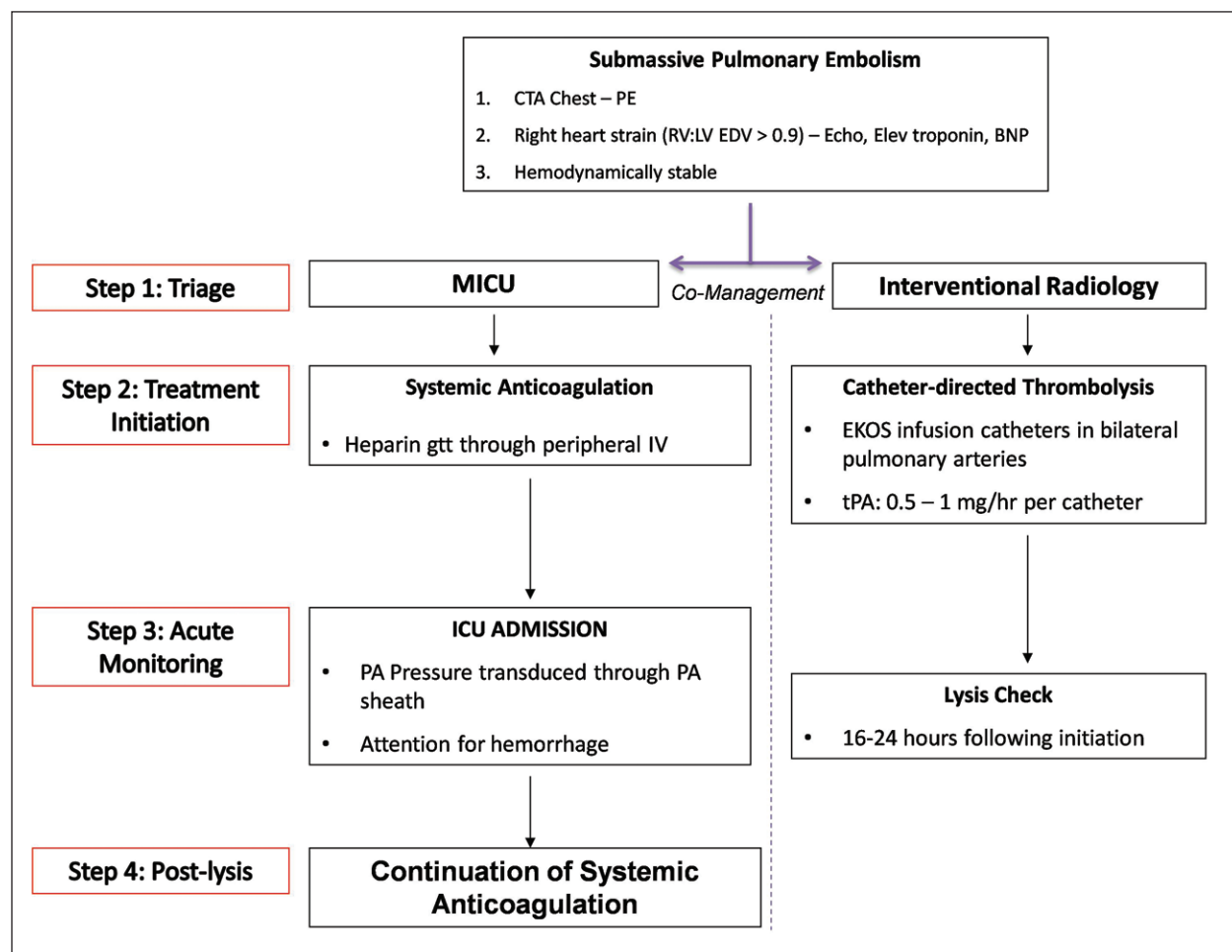


Figure 6. A flow chart demonstrating an algorithm for the comanagement of submassive pulmonary embolism.

devices for infusion of thrombolytic into the embolus and mechanical devices for disruption, maceration, and aspiration of blood clot. Traditionally used devices and techniques include multisidehole infusion catheters, suction aspiration catheters and sheaths, and rotating pigtail catheters. We will highlight several new devices that are promising in the management of pulmonary embolism.

The EkoSonic endovascular system or Ekos (Ekos Corporation, a BTG International Group) is a multisidehole infusion catheter combined with a high-frequency ultrasound transducer that is intended to improve penetration of the lytic agent during catheter-directed infusion thrombolysis. Several studies have recently been published demonstrating that infusion thrombolysis using the device for patients with submassive pulmonary embolism is effective in providing early reductions of angiographic clot burden, pulmonary arterial pressure, and right ventricular strain. In our practice, we

administer 0.5 to 1 mg tPA/h per catheter concurrent with full-dose anticoagulation, which is in line with the protocols of the published studies. In 2014, the device received an indication from the FDA for use in treatment of pulmonary embolism.

The AngioVac cannula (AngioDynamics) is a 22-F system that allows for en bloc aspiration of fresh clot (Figure 3). The patient must be placed on extracorporeal bypass. Two access sites are required, one for the AngioVac cannula and one for the reinfusion cannula. Any combination of the femoral or internal jugular veins can be used for access. This product is intriguing because of its ability to remove large volumes of blood clot rapidly. The primary drawback is the rigidity of the catheter, which makes positioning in the pulmonary arteries challenging and advancement beyond the main pulmonary artery limited.

The Pronto XL extraction catheter (Vascular Solutions) is available in 8 and 14 F and allows for large-

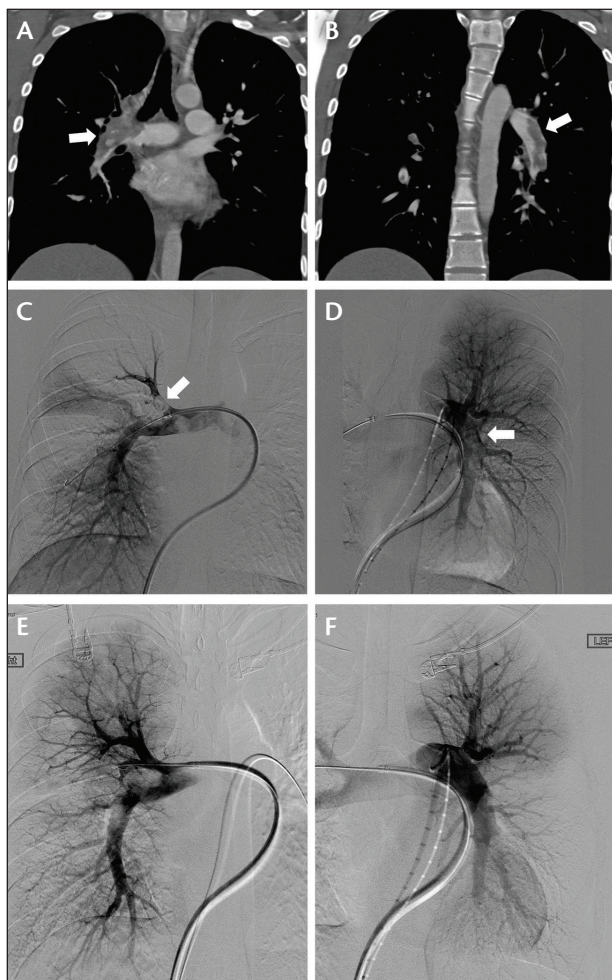


Figure 7. Coronal CT images demonstrate emboli in the right (A) and left (B) pulmonary arteries. Catheters were placed in the right (C) and left (D) pulmonary arteries. Initial DSA pulmonary angiograms demonstrate filling defects corresponding to the emboli noted on CT. Following Ekos infusion thrombolysis, right (E) and left (F) angiograms demonstrate clearance of the filling defects and improved blood flow, although perfusion defects remain.

vessel thrombus aspiration (Figure 4). The catheter is delivered over a 0.035-inch wire and comes in both straight and pigtail shapes. The catheters are flexible enough to be directed into the right and left pulmonary arteries. Manual aspiration of clot is performed through a syringe system.

A SYSTEMATIC APPROACH FOR TREATMENT

Based on the previously discussed data, we have developed a model for triaging patients presenting with pulmonary thromboembolic disease (Figure 5). After diagnosis of pulmonary embolism, patients are first

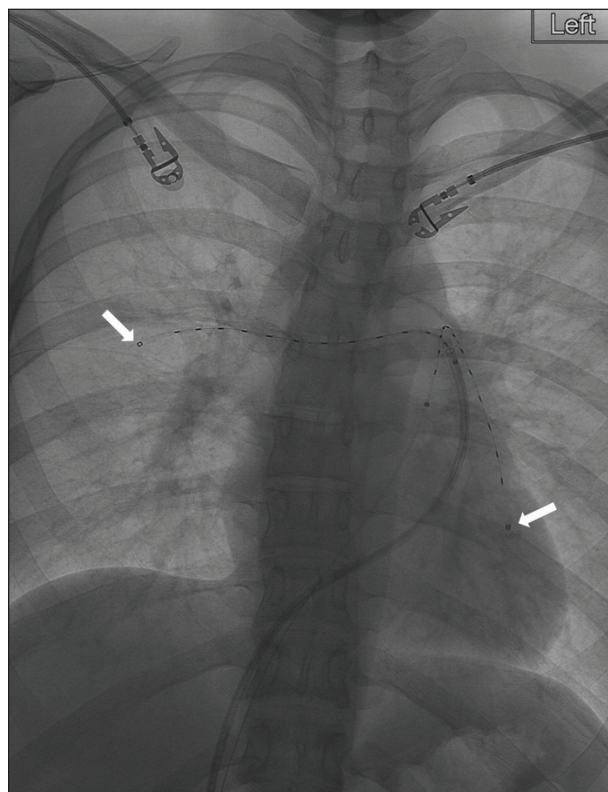


Figure 8. Ekos catheters (arrows) are positioned in the right and left pulmonary arterial systems. Note that the right catheter is placed through a sheath positioned in the main pulmonary artery to transduce pressures during lysis.

evaluated for hemodynamic stability. Clinically unstable patients have massive pulmonary embolism and require urgent revascularization without delay using a combination of systemic anticoagulation and systemic thrombolysis with catheter-directed pharmacomechanical thrombolysis used as an adjunctive measure in patients who can be rapidly mobilized to the interventional suite. We do not delay the initiation of systemic thrombolysis through a peripheral IV in these patients, but do advocate mobilization of our team either to complete the administration of the thrombolytic dose directly into the pulmonary embolism or to provide rapid mechanical clearance of embolic burden in patients who are not responding to thrombolytic therapy. Those with an absolute contraindication for thrombolysis can be treated with mechanical thrombolysis alone, but in practice, it is typically necessary to administer at least some thrombolytic to achieve an adequate early decrease in clot burden.

Patients who are deemed to be clinically stable undergo an echocardiogram or EKG-gated cardiac CT for evaluation of right ventricular dysfunction. If

right heart strain is detected, systemic anticoagulation should be administered with consideration for subsequent CDT. These patients have a relatively low risk of early clinical deterioration, which affords time for appropriate clinical evaluation and consultation of critical care services that will be involved in comanagement of the patient.

The clinically stable patient without evidence of right heart strain is diagnosed with low-risk pulmonary embolism and can be treated with systemic anticoagulation alone.

OUR EXPERIENCE

In our institution, patients with submassive pulmonary embolism are comanaged in conjunction with the medicine critical care team, who initiate IV heparin while resources are mobilized in preparation for endovascular intervention (Figure 6). These patients are treated with catheter-directed infusion thrombolysis via the Ekos ultrasound-assisted multisidehole catheter system (Figure 7).

Bilateral common femoral vein access is achieved with initial placement of 6-F sheaths. A pigtail catheter is advanced into the main pulmonary artery, and pressures are transduced. The catheter is advanced over a 0.035-inch Bentson wire (Cook Medical) into the right and left pulmonary arteries. Limited pulmonary angiography with hand injection is performed to get the lay of the land. Power contrast injection is avoided to prevent acute rise in pulmonary arterial pressure.

An 8-F sheath is placed in the main pulmonary artery via one of the access sites to transduce arterial pressures during infusion. Subsequently, two Ekos infusion catheters are placed into the involved right and left pulmonary arteries (Figure 8) and infused with alteplase at 0.5 to 1 mg/h per catheter with concurrent administration of full-dose heparin. Patients are admitted to the ICU after the procedure and brought back for a thrombolysis check-up 16 to 24 hours after initiation of treatment. Using the previously mentioned algorithm, we have treated 10 patients between 2012 and 2013. The average patient receives 23.5 mg of alteplase with a mean pulmonary arterial pressure reduction of 5 mm Hg at 24 hours. No hemorrhagic complications have been encountered.

CONCLUSION

Early mortality and chronic adverse outcomes are linked to the severity of pulmonary embolism, and risk stratification plays an important role in guiding therapy. Although guidelines are available for the medical management of pulmonary embolism, the role of the

interventionist remains to be defined. We believe that endovascular therapies, particularly CDT, can be an important adjunctive or even first-line therapy in both submassive and massive pulmonary embolism. ■

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