

Endovascular Treatment of Acute Pulmonary Embolism

Tod C. Engelhardt, MD, discusses the rationale and potential for treating acute massive and submassive pulmonary embolism using ultrasound-enhanced thrombolysis. Clinical trials are underway to evaluate the device in this setting.



What is the current standard of care for the treatment and management of pulmonary embolism (PE)?

The current standard of care for all PE patients in most institutions is anticoagulation. But, the American College of Chest

Physicians (ACCP) 2008 publication of Evidence-Based Clinical Practice Guidelines¹ suggested that in the absence of contraindications, patients with massive PE should be treated using thrombolytics—specifically, a systemic administration of recombinant tissue-plasminogen activator (rt-PA), which is usually given in a 100-mg 2-hour infusion. The same publication stated that in submassive PE patients, thrombolytics should be considered, although the recommendation was not as firm.

However, using a systemic 100-mg dose of lytic can carry a 22% chance of major bleeding complications and a greater than 3% risk of intracranial hemorrhage.² Additionally, many of these patients have had recent surgery, which often is why some have PE in the first place, due to their immobility. In these patients, the risk of bleeding is too high to administer systemic thrombolysis in my opinion. Based on my experience using ultrasound-enhanced thrombolysis, we do not need to administer a 100-mg thrombolytic dose to achieve the desired effect.

What options are there to treat patients with acute PE?

There are currently no US Food and Drug Administration-approved interventional devices for treating acute PE. However, some devices are being used off-label in this setting in the United States and also now with CE Mark approval in Europe, in the case of the EkoSonic ultra-

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sound-accelerated thrombolysis device (Ekos Corporation, Bothell, WA). In my early experience with the Ekos device as a means of treating acute PE, I have seen favorable results using a miniscule dose of rt-PA (20 mg over 12 hours). This is an attractive option to me because it allows me to treat massive and submassive PE without a substantially increased risk of bleeding. Other potential options include devices that remove clot mechanically.

The ACCP considers such therapies “pharmacomechanical means,” distinguishing them from traditional medical therapy with anticoagulation.

What are the characteristics that distinguish massive and submassive PE from one another, and how do these affect your treatment decisions?

Serious PEs are broken down into the categories of massive and submassive. The distinction is very important, particularly in the context of the decision on how to treat the patient. Patients with massive PEs present with hemodynamic instability or cardiogenic shock. These patients are quite literally dying due to PE, which is likely why the ACCP recommended a more active form of treatment than simply administering anticoagulants to stop more clot from forming. Massive PE warrants

aggressive treatment aimed at removing existing clot. But, massive PE accounts for only approximately 5% of the PE patients we see, while 40% to 45% of PE patients present with submassive PEs. Many of these patients are currently receiving anticoagulation alone.

Submassive PEs are large, but the distinguishing factor is that the patients are hemodynamically stable. These are the PEs in which many US physicians do not believe it is necessary to introduce any potential risks of thrombolytic treatment because the patients are stable. However, these patients still demonstrate right heart strain or enlargement of the right ventricle on echocardiogram or computed tomography scan. If the right heart is dilated and the patient is treated with the current standard of care (anticoagulation), it has been shown that a significant number may develop chronic pulmonary hypertension and potentially right heart failure. One study has shown that 44% of patients with right heart dysfunction at the time of diagnosis had chronic pulmonary hypertension at 1-year follow-up.³ Another study subsequently showed that patients with unresolved right ventricular dysfunction at the time of discharge are eight times more likely to have a recurrent PE and have a four times higher mortality rate than patients whose dysfunction was resolved.⁴

I believe submassive PE patients who are hemodynamically stable can benefit from interventional therapy using ultrasound-assisted thrombolysis. In my experience using this device to date, I have been able to reverse right heart strain within 48 hours in most cases. However, it will not be easy for everyone to accept the concept of treating submassive PE with an interventional device because the prevailing thinking is that these patients are not dying, so they do not need a more aggressive treatment than systemic anticoagulation; they are stable, and they can tolerate the anticoagulation. Looking down the road, we know that a significant number of these patients could have a problem if that right heart strain is not reversed.

Which PE patients do you feel should not undergo treatment?

Minor PEs, which account for approximately 55% of the overall incidence, should not be subjected to the risk of any interventional treatment. Even though the risk is low, I do not think it is warranted in patients with minor PE.

What has your own experience been with the use of ultrasound-accelerated thrombolytic therapy in patients with acute massive PE? What have you learned from your early results?

I have performed this procedure in 32 PE patients. In my initial experience, I was not confining myself to 20 mg

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of rt-PA, and I encountered a few bleeding problems at the groin insertion site. These complications did not require surgery, although the patients were given transfusions. I subsequently cut my maximum rt-PA dose to 20 mg over 12 hours, and since that time, I have had zero bleeding complications while still achieving the same favorable results of reversing right heart dysfunction and a significant reduction in pulmonary artery clot burden.

What additional measures and aftercare do you employ for these patients?

All of my patients are anticoagulated. From the time they hit the emergency department, they are given 1 mg per kg of enoxaparin every 12 hours. We do not interrupt the anticoagulation during the course of the procedure. The patients remain on this course until they are adequately converted to warfarin, which they remain on for 6 months. As part of the treatment protocol, patients are evaluated by hematologists to determine whether they meet the criteria for being hypercoagulable. If they are hypercoagulable, they will likely remain on warfarin for life. If they are not, I usually run the anticoagulation for 6 months and stop warfarin at that time.

The question of inferior vena cava filter use in these procedures has not yet been definitively addressed, although we have made the individualized decision to use these in some patients, such as elderly patients with cancer or risk factors for additional PE.

What is the process by which PE patients are referred to you?

Most of the time, PE patients are referred to me upon presentation to the emergency department in our hospital. This is a question I am frequently asked by other interventional physicians who are interested in starting a similar program. One of the most significant barriers physicians face is that the patients are not being referred out of the emergency department. I tell them that if they can successfully administer a life-saving therapy in one dramatic, massive PE case in which the patient is otherwise likely to die, that can be a big first step to establishing a referral. Based on our experiences, our emergency department physicians call me for consultation on nearly all PE patients. Our protocol for treating these patients is still being developed, but

currently patients with a right ventricular/left ventricular volume ratio of one or greater are treated.

Education of hospital staff is of paramount importance. It is incumbent upon me to continue to educate our staff on the nuances of massive versus submassive versus minor PE, as well as our progress in this arena. Much of this can be seen in a computed tomography scan of the chest, which shows heart size very well. We also have cardiologists and pulmonologists who are aware of our practice and are on board with it.

But a change in referral is a change in the standard of care in the local setting, and people often understandably feel more comfortable with the status quo, especially if the alternative treatment can introduce new questions or complications and the new option is still an off-label device use with limited clinical experience reported.

What types of formal study are currently underway regarding this therapy?

There is currently a randomized, controlled trial underway in Europe called the ULTIMA trial. The ULTIMA trial will look at traditional anticoagulation versus the use of the Ekos catheter for submassive PE. The Ekos device has received CE Mark approval for treating PE in Europe, and the ULTIMA study will provide evidence of its clinical utility.

The EkoSonic system has been cleared by the US Food and Drug Administration for the infusion of solutions into the pulmonary artery, but use of the device to treat PE in the United States is off-label. A single-arm study is expected to begin in the United States, hopefully by mid-year, also evaluating the device in submassive PE treatment. The data from this study will be used to support further indications for use for the device.

Our center's results have been encouraging, but we stand to learn much more about the optimal use of this technology when data become available. ■

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