

The Next Era of Pulmonary Embolism Treatment

Burgeoning options for treating this serious disease process using catheter-based techniques.

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Pulmonary embolism (PE) is a disease process that is both common and associated with high morbidity and mortality. In fact, the mortality rate for PE is underappreciated and is in excess of 15% in the first 3 months after diagnosis, with nearly 25% of patients presenting with sudden death.^{1,2} Interventional cardiology is once again upon the era of evaluating pharmacologic versus mechanical treatment for acute PE. Previously, acute myocardial infarction was treated pharmacologically with thrombolytics followed by the advent of primary coronary intervention (mechanical), which was initially met with controversy and debate. By way of analogy, the concept of approaching acute PE with mechanical treatment is now upon us, and not surprisingly, similar debates are following. In general, patients with massive PE (ie, those in shock) are usually offered more aggressive treatment without much controversy (usually in the form of systemic thrombolytics).

However, where the real area of growth and potential for improvement lies is in the patients with submassive PE. These patients are hemodynamically stable but show evidence of right ventricular (RV) strain (ie, abnormal RV/left ventricular [LV] ratio, elevated troponin, brain natriuretic peptide, etc.). Studies have shown that patients with persistent RV dysfunction at discharge are eight times more likely to have recurrent PE and have four times the mortality rate of patients with normal RV function on discharge.³ Moreover, at 1 year after PE, 44% of submassive PE patients with RV dysfunction at hospital discharge will have chronic pulmonary hypertension.⁴

NEW TRIALS ON INTERVENTIONAL TREATMENTS FOR ACUTE PE

In the current era, evidence-based medicine is the driving force for new treatments (both pharmaco-

logic and mechanical). However, unlike the arena of coronary disease, the available data have been mainly small, single-center, retrospective studies until recently. Two pivotal studies have launched interventional acute PE treatment onto the main stage and have led to the recent (May 23, 2014) US Food and Drug Administration (FDA) clearance of the EkoSonic endovascular system (Ekos Corporation, a BTG international group) as the first approved treatment for acute PE.

In November 2013, Kucher et al published the results of the ULTIMA trial (NCT01166997), which was a multicenter, randomized controlled trial investigating whether ultrasound-assisted catheter-directed thrombolysis (USAT) using the EkoSonic device was superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk (or submassive PE) patients.⁵ Fifty-nine patients were studied who had acute main or lower lobe PE with echocardiographic evidence of RV dysfunction (RV/LV ratio ≥ 1) and randomized to unfractionated heparin or USAT. The primary outcome was the difference in RV/LV ratio from baseline to 24 hours; other safety outcomes included death, major/minor bleeding, and recurrent venous thromboembolism at 90 days. In the USAT group, the mean RV/LV ratio was reduced from 1.28 ± 0.19 at baseline to 0.99 ± 0.17 at 24 hours ($P < .001$); in the heparin group, mean RV/LV ratios were 1.2 ± 0.14 and 1.17 ± 0.2 , respectively ($P = .31$).

Safety outcomes showed no difference in major bleedings, and in fact, there were no patients who had major bleeding with USAT. There were only three patients with mild bleeding who did not require medical intervention in the EkoSonic-treated group. In addition, the USAT group showed a statistically significant

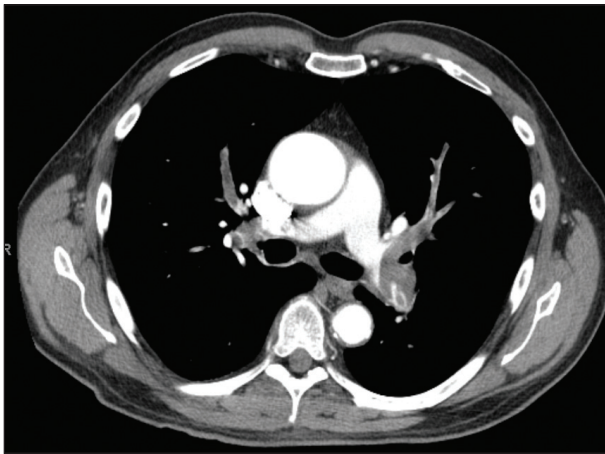


Figure 1. CT pulmonary angiogram revealing bilateral PE involving the right and left pulmonary arteries.

improvement in hemodynamic parameters upon early follow-up, including a reduction in pulmonary artery (PA) pressures and an improvement in cardiac index. Interestingly, one point that is often argued against the use of USAT for acute PE is the evidence of “catch up” at 90-day follow-up, with improvement in RV/LV ratio (ie, RV function) in the heparin arm. Although this phenomenon needs to be better understood, it is clear that in those with significant PE, the main goal in interventional treatment is acute because by dealing with the problem in an acute manner, you decrease the risk of chronic changes such as chronic pulmonary hypertension. Hence, several studies have shown an increased risk of chronic pulmonary hypertension and mortality if RV dysfunction remains at the time of discharge.

In March 2014, the results of the SEATTLE II trial (NCT01513759) were presented at the American College of Cardiology’s annual meeting. SEATTLE II was a prospective, single-arm, multicenter trial evaluating the safety and efficacy of ultrasound-guided, catheter-directed thrombolysis using the EkoSonic device. There were 150 patients evaluated: 31 with acute massive PE and 119 with acute submassive PE. Chest CTs had to demonstrate proximal PE and an abnormal RV/LV ratio ≥ 0.9 . The mean RV/LV ratio in the study decreased from 1.55 before the procedure to 1.13 at 48 hours after the procedure, a difference of 0.42 ($P < .0001$). From a safety standpoint, there were no intracranial hemorrhages, which is often the most feared complication with thrombolytic treatment; there was only one severe bleed noted in this study. The overall conclusion was that the use of EkoSonic treatment for acute PE improved RV function and

decreased pulmonary hypertension with a minimal risk of significant bleeding.

TREATMENT OPTIONS

There has been a multitude of aggressive strategies to treat significant PE described in the literature, with a wide variety of risk and success. From a surgical standpoint, there is surgical embolectomy, which remains an option for patients with a large thrombus burden who are not candidates for thrombolysis. Historically, this technique is associated with both high morbidity and mortality rates (up to 27%).⁶ More recently, a contemporary series was published showing much-improved survival rates (89%) due to improved surgical techniques, rapid diagnosis and triage, and careful patient selection.⁷

Catheter-based techniques, not surprisingly, have taken over the arena of invasive management for PE. One early method described the use of a rotating pig-tail catheter, which basically functioned to mechanically fragment the thrombus. In one study, this technique was successful in seven of 10 patients, with a recanalization rate of $29.2\% \pm 14\%$, therefore providing only partial flow restoration with a mortality rate of 20%.⁸



Figure 2. Abnormal RV/LV ratio = 1.69, indicative of RV strain.

Rheolytic thrombectomy is a technique that relies on aspiration of the thrombus locally via the Bernoulli principle, which creates a vacuum behind high-pressure saline jets. This has been shown to be very effective at removing clot burden, particularly in the acute setting. It has been successfully used in both the arterial and venous beds. However, when used in the pulmonary vessels, the release of adenosine from disrupted platelets can lead to bradycardia, pulmonary vasospasm, and worsening hypoxia, as well as increased mortality. Therefore, the FDA has issued a “black box” warning for AngioJet (Bayer) rheolytic thrombectomy for PE treatment.⁹

Another device shown to be effective at removing large clot burden without requiring thrombolytic exposure is the Vortex Angiovac catheter (AngioDynamics). This device requires large-vessel access (26 F), a perfusionist, and general anesthesia. The basic concept is aspiration of blood at high flow rates using a perfusion circuit (similar to bypass surgery but with venous-venous flow). The blood aspirated is then filtered to facilitate removal of clot and then returned to the patient via a return cannula. This device is not a simple undertaking and, hence, has a

niche role in treating patients with very large thrombus burden in the PA who have contraindications to thrombolysis.

The last technology to be described is EkoSonic ultrasound-assisted thrombolysis for catheter-directed treatment for PE. As previously described, the EkoSonic device was recently cleared by the FDA for treatment of PE and has a growing body of evidence supporting its use. The EkoSonic device uses ultrasound energy, which thins the thrombus, allowing more permeation of the locally delivered thrombolytic. In turn, this decreases the time of infusion and amount of thrombolytic required.

TECHNIQUE

I have found that ultrasound-guided thrombolysis with the EkoSonic system is very easy to learn and can be done so fairly quickly. Most PEs that are significant and warrant treatment are bilateral; therefore, the options for access include placement of two 6-F sheaths into the common femoral vein (this allows contralateral limb freedom of movement, which aids in patient comfort). There are several approaches to negotiate and access the PA, including the use of



Figure 3. Placement of a 12-cm EkoSonic catheter into treatment zones in the bilateral PAs.

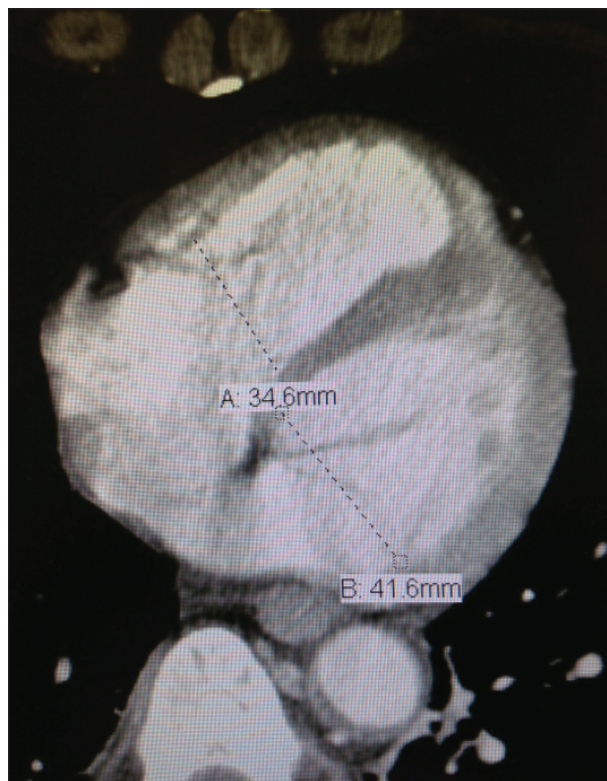


Figure 4. CT pulmonary angiography after EkoSonic treatment showing complete normalization of the RV/LV ratio (RV/LV = 0.83).

a swan catheter, the pigtail method, etc. By way of experience, the simplest and quickest method is to negotiate a 5-F JR 4 catheter over an exchange-length J-wire into the right atrium, clocking the tip toward the RV, followed by advancing the wire into the RV. After advancing the JR 4 into the RV, rotate the catheter to point cephalad followed by once again advancing the JR 4 into the main PA. At this point, the wire is removed, and a PA pressure should be obtained. The J-wire should then be advanced into the distal right or left PA. The location of the distal EkoSonic catheter should be directed by knowledge of the thrombus burden as seen on the CT pulmonary angiography, which is what led to the diagnosis the vast majority of times. Of note, most PE cases require a 12-cm treatment zone EkoSonic catheter for each side.

Once the initial catheter is placed and secured, the sequence of events is repeated with placement of the EkoSonic catheter into the contralateral side. The right PA angulation occasionally makes advancing a J-wire very difficult; typically, if this is the case, an angled glide stiff wire is the most effective in making this transition and allowing the JR 4 catheter to follow. Drug administration should be undertaken after both catheters are secured and the sheaths are sutured in the groin. Normal saline is administered through the coolant port at 35 mL/hr, and tissue plasminogen activator is administered through the drug port at 1 mg/hr for 24 hours if the procedure is unilateral or 1 mg/hr for 12 hours if bilateral. Heparin is given through each sheath at a fixed dose of 250 to 300 units per hour without partial thromboplastin time monitoring. This is mainly done to maintain patency in the sheath and to prevent thrombus formation. Of note, this technique is done entirely dyeless, with no contrast injected during the entire procedure.

CASE EXAMPLE

A 51-year-old man with no significant medical history presented with a 2- to 3-day history of worsening shortness of breath and left-sided chest pain. In the emergency department, his vital signs were measured (blood pressure, 118/83 mm Hg; pulse, 120 bpm). The results of an electrocardiogram showed sinus tachycardia with right-sided precordial T-wave abnormalities. His lab results showed an elevated brain natriuretic peptide of 2,804 pg/mL and a borderline troponin T level of 0.04 ng/mL. He was hypoxic and required high-flow oxygen using bilevel positive airway pressure.

The patient underwent urgent CT pulmonary angiography, which revealed bilateral PE with an abnormal

RV/LV ratio consistent with acute submassive PE (Figures 1 and 2).

The patient underwent ultrasound-guided thrombolysis, per the technique previously described, with one EkoSonic catheter placed into each PA (Figure 3), with a measured initial PA pressure of 50/22. After treatment, the patient had substantial clinical improvement within the first 24 hours, with a significant reduction of oxygen requirements to only 2 liters via nasal cannula. The patient's repeat PA pressure was normal at 26/15. Also, repeat CT pulmonary angiography within 72 hours revealed normalization of the RV dilation, with an RV/LV ratio of 0.83 (Figure 4).

CONCLUSION

The interventional community is once again faced with the decision to either remain stagnant regarding treatment options in a field that has a very large patient population with a high mortality rate or, as is customary in the field, to lead the charge on the footsteps of the growing body of evidence supporting more invasive/interventional approaches to this condition. The data seem to show immediate improvement in both RV function and hemodynamics, which is often what leads to both short- and long-term outcomes that are favorable. The next important steps in future trials are to evaluate salient outcomes such as mortality and also quality-of-life parameters (eg, the 6-minute walk test) to aid in the growing body of evidence to support more aggressive treatment in these patients. ■

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