

# OPTALYSE PE Demonstrated Significant Improvement in Right Ventricular Size With Shorter Infusion Times and Lower Doses of tPA, Making Ultrasound-Accelerated Thrombolysis Even Safer

BY VICTOR F. TAPSON, MD



The hypothesis of the OPTALYSE PE trial is that less-intensive thrombolytic therapy—shorter infusions and lower doses of thrombolytics—is safer and more advantageous to patients with acute pulmonary embolism (PE) who receive ultrasound catheter-directed therapy. The lower the dose of tissue plasminogen activator (tPA), the lower the risk of major bleeding events, including catastrophic intracranial hemorrhage (ICH). The faster patients' clots are lysed, the less time they spend in the intensive care unit and in the hospital.

In the past, I've found that administering tPA in the range of 10 mg (or urokinase at low doses), pushed through a syringe instead of a drip, over approximately 10 minutes will often resolve a very fresh, large proximal embolus. However, tPA has a short half-life, and the too-short infusion time may be inadequate in many cases. My belief is that at least 2 hours of systemic or catheter-directed therapy should be considered, except in more emergent settings when a patient is deteriorating and may arrest (or has arrested).

My experience suggested that short infusions of low-dose tPA could work to improve right ventricular (RV) function and decrease pulmonary artery pressure. We needed a study to compare low-dose thrombolytic therapy to the "standard" (ULTIMA and SEATTLE II) regimen of approximately 24 mg of tPA over 12 to 24 hours with ultrasound-facilitated, catheter-directed thrombolysis (EKOS® device, BTG International) for intermediate-risk PE. This was the basis of the OPTALYSE PE trial.

OPTALYSE PE, which we presented at the American Thoracic Society International Conference in May 2017, demonstrated that shorter-duration infusions with lower doses of tPA utilizing EKOS® therapy were just as effective as the standard doses utilizing EKOS® therapy, but with a

much lower rate of bleeding. See Figures 1 through 5 for an illustrative case example.

## REDUCTION IN RV/LV RATIO IN HALF THE TIME AND DOSE

The OPTALYSE PE study included 101 participants at 17 centers with acute proximal PE in at least one main or proximal lobar pulmonary artery with a right ventricular to left ventricular (RV/LV) end-diastolic diameter ratio  $\geq 0.9$  on chest CTA.<sup>1</sup> Participants were randomly assigned to one of four ultrasound-facilitated, catheter-directed thrombolysis regimens, which varied in duration and total amount of

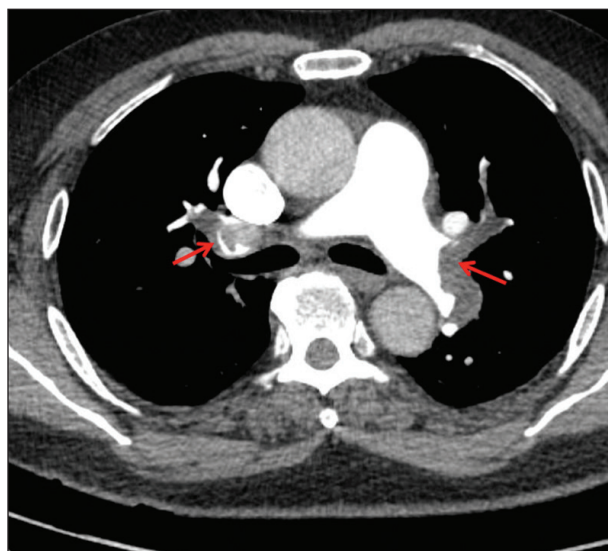


Figure 1. An extensive bilateral PE (arrows). The patient had dyspnea, a heart rate of 120 bpm, and blood pressure of 110/70 mm Hg. Oxygen saturation was 94% on room air. Troponin and BNP were elevated at 2.7 ng/mL and 146 pg/mL, respectively.

tPA. Cohort 1 received 4 mg of tPA (per lung) over 2 hours, cohort 2 received 4 mg of tPA (per lung) over 4 hours, cohort 3 received 6 mg of tPA (per lung) over 6 hours, and cohort 4 received 12 mg of tPA (per lung) over 6 hours. A few patients received therapy to one lung, but the majority received bilateral tPA via a catheter in each lung. All patients also received therapeutic anticoagulation, although the heparin dose was reduced between 300 and 500 U/h during the thrombolytic infusion.

The RV/LV ratio was significantly reduced in all cohorts 48 hours after the procedure, ranging from -0.46 in cohort 1 to -0.48 in cohort 4 (a reduction of 23%–26%). This is consistent with results achieved in SEATTLE II, a large, prospective, single-arm trial in which 24 mg of tPA was given over 12 hours with bilateral catheters.<sup>2</sup> The mean RV/LV ratio in SEATTLE II participants decreased from 1.55 before the procedure to 1.13 at 48 hours after the procedure (difference, -0.42). Patients in the OPTALYSE PE trial also saw statistically significant improvements in their modified Miller score (embolic burden on CTA), with increasing reductions from cohort 1 (mean change, -5%) to cohort 4 (mean change, -26%).

### A LOWER RATE OF BLEEDING EVENTS

The smaller doses of tPA used in OPTALYSE PE appeared to reduce the risk of major bleeding complications (overall major bleeding rate was 3%). In comparison, participants in SEATTLE II, which evaluated the standard regimen of 24 mg of tPA, had a 10% rate of major bleeding (but no fatal bleeding events or ICHs). In OPTALYSE PE, the few major bleeding events occurred only in cohorts 2 and 4. One patient with PE and residual deep vein thrombosis had an excellent response to the 8-mg OPTALYSE PE regimen but developed severe recurrent PE about 24 hours after the EKOS® procedure. She received intravenous (IV) tPA at a systemic dose and developed multifocal ICH but completely recovered. Based on the temporal relationships,

it was highly unlikely that the ICH was related to the very low-dose OPTALYSE PE regimen but rather was related to the IV tPA. A second patient who developed ICH had a prior history of abnormal platelet function and labile hypertension. This was the first reported ICH that may have been EKOS®-related in the 277 patients participating in the EKOS® PE trials. In contrast, systemic thrombolysis carries a 2% to 3% risk of ICH.<sup>3</sup> The ULTIMA, SEATTLE II, and OPTALYSE PE studies confirm that we can effectively lyse clots with EKOS® therapy, yet minimize the risk of ICH and other major bleeding.

We sometimes use ultrasound catheter-directed thrombolysis in patients with relative contraindications to higher-dose systemic thrombolysis, such as recent surgery, trauma, or recent bleeding. In such cases, the low-dose, shorter-infusion OPTALYSE PE regimens could be advantageous (patients deemed at high risk for bleeding were excluded from OPTALYSE PE). As patients become more compromised, there is a higher potential for bleeding, and thus more experience and caution are required. For example, a recent gastrointestinal bleed or surgery usually requires rapid and detailed consultation with a specialist (eg, endoscopic surgeon) prior to consideration of a thrombolysis-based plan, even if it is low dose and catheter-based.

More work is still needed in the setting of massive PE. Some high-risk patients were treated with catheter-based therapy in the SEATTLE II trial, but we do not have experience treating high-risk PE using these low-dose, shorter-infusion regimens. However, shorter infusions with less tPA may be effective in treating patients with high-risk PE, particularly those on the less severe end of the spectrum (ie, those who are hypotensive but who stabilize after fluid and low-dose single pressor therapy).

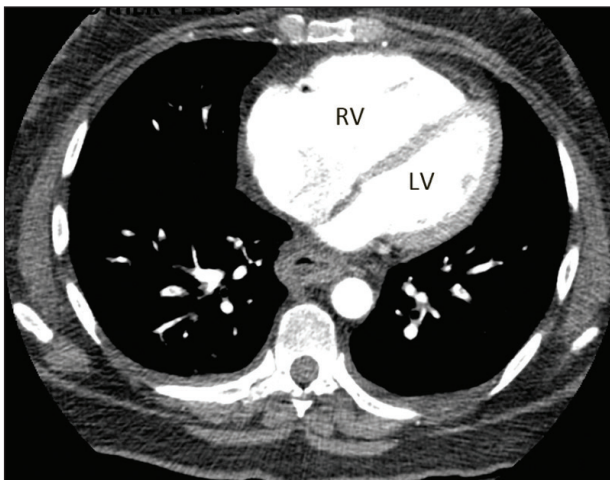


Figure 2. CT showing a dilated right ventricle.

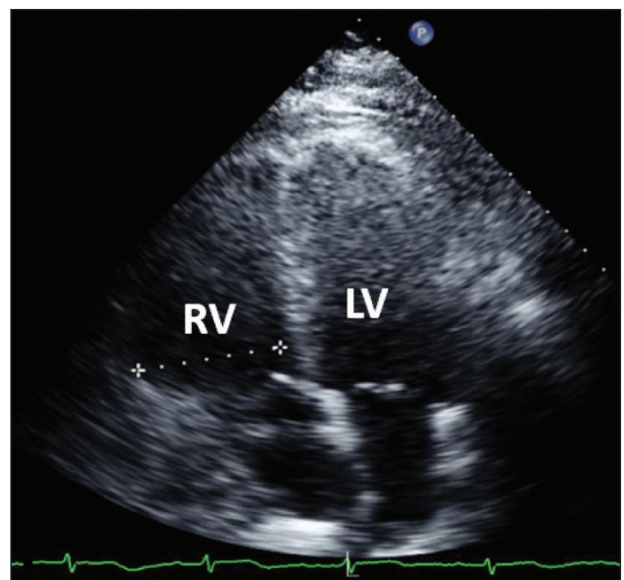
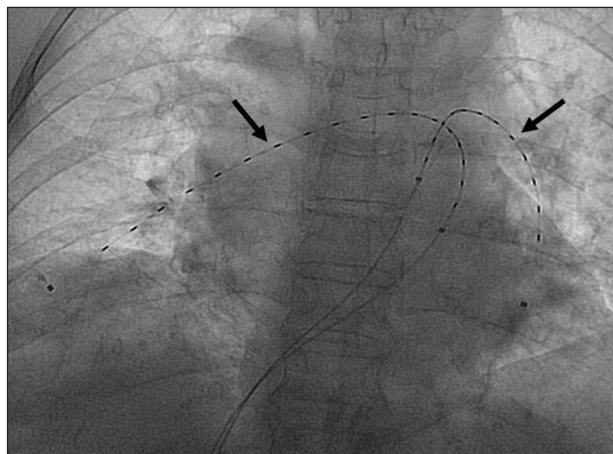


Figure 3. An echocardiogram showing that the right ventricle was dilated and markedly hypokinetic.



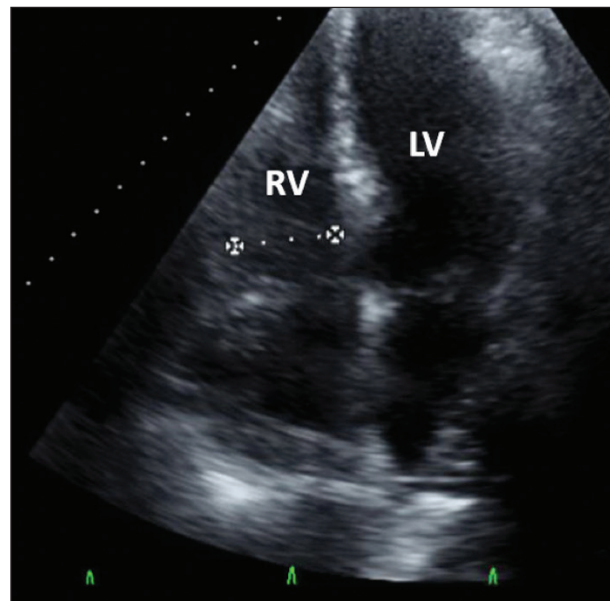
**Figure 4.** A bilateral ultrasound showing EKOS® catheters in place (arrows).

Based on preliminary OPTALYSE PE data, no single treatment regimen emerged as superior to the others. Although the two lowest doses of 8 mg of total tPA (cohorts 1 and 2) resulted in the smallest but still statistically significant improvement in modified Miller score, we saw a statistically and clinically significant improvement in RV/LV ratio in all four groups. Analyzing additional secondary endpoints of the study may give us a better idea of the most effective dosing regimen. My own clinical experience leads me to favor the cohort 3 regimen (ie, 6-hour infusion of a total of 12 mg of tPA or 6 mg to each lung) to treat intermediate-risk PE. Clinicians may still wish to individualize treatment for patients based on clinical parameters and perceived bleeding risk, but what is clear now is that the standard regimen of 24 mg of tPA over 12 to 24 hours is no longer necessary to achieve optimal results.

### WHICH PATIENTS TO TREAT?

All participants in our OPTALYSE PE study had intermediate-risk PE, but some had more concerning parameters, such as an abnormal RV and elevated troponin or brain natriuretic peptide, which can be classified as high-intermediate-risk PE or very severe RV hypokinesis. Other participants were on the other end of the spectrum with intermediate-low-risk PE, characterized by a more mildly abnormal RV or elevated troponin or brain natriuretic peptide. Some clinicians may choose to take all patients with intermediate-risk PE to the interventional radiology or cardiac cath lab, but OPTALYSE PE did not evaluate which intermediate-risk patients should be treated with low-dose, short-duration EKOS® therapy.

To date, most rigorous clinical trial data are derived from catheter-based thrombolysis with the EKOS® device, including the ULTIMA study, which randomized patients with acute PE to EKOS® and heparin or heparin alone.<sup>4</sup> However, more research is needed to define the optimal EKOS® dosing regimen. Our cohorts were small, and a larger study



**Figure 5.** An echocardiogram showing that the right ventricle had significantly improved in size and function by 12 hours after the infusion.

focusing on a few short, low-dose regimens would be valuable, as well as studies that evaluate whether catheter-based therapy improves mortality and in which populations and whether it improves long-term outcomes including chronic thromboembolic disease and pulmonary hypertension.

### CONCLUSION

Knowing that we can safely and effectively lyse clots in intermediate-risk PE patients with shorter-duration, lower-dose, ultrasound-accelerated thrombolysis is a major step in advancing PE treatment. We do not need as much tPA or duration of infusion as we once thought—and our patients will benefit from very good outcomes and a safer procedure. ■

1. Tapson VF, Piazza G, Goldhaber SZ, et al. Optimum duration and dose of r-tPA with the acoustic pulse thrombolysis procedure for submassive pulmonary embolism: OPTALYSE PE. Presented at: American Thoracic Society International Conference 2017; May 19–24, 2017; Washington, DC.
2. Piazza G, Hohlfelder B, Jaff MR, et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv.* 2015;8:1382–1392.
3. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet.* 1999;353:1386–1389.
4. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation.* 2014;129:479–486.

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