# The Progression of Decision-Making for PE Treatment: A Pulmonologist's Evidence-Based Perspective

From thrombolytics hesitancy to the development of catheter-based thrombolysis and embolectomy, a pulmonologist shares her perspective on the history of PE care decisions and its supportive evidence over the years.

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"Are you going to push the tPA?" the cardiology fellow asked of me after completing a STAT echocardiogram 10 years ago. At the time, I was a pulmonary and critical care medicine fellow on an overnight shift in the medical intensive care unit (ICU). My patient, a man in his mid 60s without significant past medical history, recently returned from a transatlantic flight and presented with acute-onset shortness of breath and syncope at home. He was intubated in the emergency department for respiratory distress and was started on vasopressors for postintubation hypotension. Cross-sectional imaging revealed bilateral pulmonary embolism (PE) that was nearly obstructive in the right main pulmonary artery (PA), as well as a distal main left PA embolus extending to all segmental and subsegmental branches. The STAT bedside echocardiogram showed severe right ventricular (RV) enlargement with decreased function, McConnell's sign, and bowing of the intraventricular septum with an underfilled, hyperdynamic left ventricle. I stood frozen in the hallway, not knowing how to answer the question. My thoughts turned to the multiple physicians across three specialties who evaluated the patient and had not recommended systemic thrombolysis despite published societal practice guidelines.

Five years earlier was the release of "The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism."[1] Although effective strategies for minimizing venous thromboembolism (VTE) existed, it was suggested that lack of awareness and inconsistent adherence to evidence-based practices were contributing the burden of disease. The vision for the future included (1) increased public awareness of the disease; (2) the routine application of evidence-based practice for screening, prevention, and diagnosis; and (3) new scientific discovery to fill gaps in knowledge and quickly distribute findings to the public and medical professionals to be incorporated into practice. Although this call to action focused on prevention, I had witnessed firsthand how evidence-based practices were not followed in the care of a patient with massive PE. In the same year as the Surgeon General's charge, Dr. Victor Tapson, a pulmonologist with expertise in pulmonary hypertension and PE, called for a more aggressive therapeutic approach to VTE.[2] He recommended a multidisciplinary response to improve patient outcomes through research, education, and well-defined goals.

The concept of PE response teams (PERTs) was introduced around the time my patient presented, with the aim to rapidly evaluate and triage patients with PE, formulate a treatment plan, and mobilize necessary resources. The team consists of multiple specialists with an interest in PE. A group at Massachusetts General Hospital introduced this model with aspirations of developing a clinical, educational, and research infrastructure to promote advancements in the field through the creation of the PERT Consortium.[3] PERTs promote a collaborative decision-making model that prevents physicians from carrying the burden of mak-

## THE PULMONOLOGIST'S APPROACH TO PE

- Mortality exists on a spectrum in the intermediate-high–risk PE classification group. Some high-risk features include elevated heart rates, lactate, extent of clot burden, reflux of contrast into the hepatic veins, and echo-derived estimates of cardiac output.
- Elevated PA systolic pressure and prolonged symptoms may suggest subacute or chronic thrombus that may be more difficult to treat with endovascular therapies.
- The ACCP recommends systemically administered thrombolytic therapy (over CDT) for patients with acute PE without hypotension who have an acceptable bleeding risk.
- When expertise and resources are available, the ACCP recommends catheter-assisted thrombus removal for patients with acute PE with hypotension who are at a high bleeding risk, have failed thrombolysis, or are in shock at high risk of death before systemic thrombolytics could take effect.
- Patients with PE should be followed long term after the sentinel event and screened for post-PE impairment syndrome.

ing individual decisions to administer medications with a high risk of adverse events.

### HESITANCY TO ADMINISTER THROMBOLYTICS

That night as a fellow in the ICU, I reviewed my specialty's VTE practice guidelines that were published just months earlier, which recommended systemically administered thrombolytic therapy for patients with acute PE associated with hypotension who do not have a high bleeding risk.[4]

So, why the hesitancy in administering systemic thrombolytic therapy? Registries show that only 30% of patients classified as having massive PE received thrombolytic therapy.[5,6] In a survey of practicing pulmonologists, only 54% had reported experience using thrombolytic therapy for acute PE, although all surveyed pulmonologists responded that they would favor treating massive PE associated with hypotension with thrombolytics.[7] Thankfully, massive PE is a rare event, representing approximately 5% of patients presenting with acute PE, which may also explain pulmonologists' inexperience with using thombolytic therapy.[8]

The evidence base for thrombolytics in high-risk PE is also lacking. There is only one randomized trial of thrombolysis versus anticoagulation conducted in patients with massive PE.[9] Patients were randomized to receive either streptokinase and heparin or heparin alone. Of the first eight patients randomized, four patients who received thrombolytic therapy with streptokinase experienced improvement of hemodynamic disturbances within 1 hour of therapy and survived without minor or major bleeding complications; the four patients who received heparin experienced further decompensation and died despite maximum supportive care. The trial was terminated early and another of its kind was never attempted.

Given the paucity of data in high-risk PE, pulmonologists extrapolate data regarding bleeding risk from PEITHO, the largest trial of thrombolytics, which randomized 1,006 intermediate-risk PE (intermediate-high–risk by today's criteria) patients to receive tenectaplase plus unfractionated heparin versus heparin alone.[10] Although the primary endpoint of death or clinical decompensation (driven by clinical decompensation) was met in the thrombolytic group, this came at the expense of increased major extracranial bleeding (6.3% vs 1.2%) and hemorrhagic stroke (2% vs 0.2%) in the thrombolytic versus placebo arms, respectively. It is reasonable to hypothesize that the hesitancy to administering thrombolytics stems from this 10-fold increase in intracranial hemorrhage with systemic thrombolytics as compared to anticoagulation with heparin. Additionally, if a physician's decision to administer thrombolytics resulted in an adverse outcome, there is a predictable postevent trajectory that includes questioning one's abilities and could influence the decision to offer another patient the same therapy.[11]

Perhaps a lower dose of peripherally administered thrombolytic agent could obtain a high enough systemic concentration to be efficacious, with a reduced risk of bleeding and no need for an invasive procedure? The MOPETT trial investigated a total dose of 50 mg of alteplase (half the current FDA-recommended dosage) in patients with intermediate-risk PE.[12] The primary endpoint of pulmonary hypertension and the combined endpoint of pulmonary hypertension and recurrent PE occurred in 16% versus 57% and 16% versus 63% for the alteplase group compared to the standard anticoagulation group, respectively, at an average follow-up of 28 months. Although limited by the small study size, there was no difference in mortality and no bleeding events reported in either cohort. This study demonstrated that a reduced dose of alteplase was safe and effective in reducing PA pressure (PAP) in this intermediate PE population; however, the study was criticized for the unusually elevated incidence of pulmonary hypertension in the cohorts.[13] In a large PE registry, there is a trend toward increased mortality and decreased bleeding with standard versus moderate dose thrombolysis, but the difference did not reach statistical significance.[14]

## ADOPTION OF CATHETER-DIRECTED THROMBOLYSIS

In 2016, the American College of Chest Physicians (ACCP) guidelines recommended against systemically administered thrombolytic therapy for most patients with acute PE that is not associated with hypotension.[15] In select patients who deteriorate on anticoagulation and have a low bleeding risk, systemically administered thrombolytic therapy was suggested over no therapy. The ACCP also recommended thrombolytic therapy via a peripheral vein rather than catheter-directed thrombolysis (CDT), except in patients with active bleeding or at high risk of bleeding and those who have failed thrombolytics and might benefit from CDT.

As the PEITHO study taught us, traditional doses of thrombolytic therapy, although efficacious, have an unacceptably high risk of major bleeding in the intermediate-risk PE population, including hemorrhagic stroke.[10] The practice of waiting for clinical deterioration to administer a high-risk therapy was common, and yet, a search for an alternative therapy with a superior safety profile to prevent clinical deterioration was underway.

Until this time, the benefit of administering thrombolytics directly into the thrombus was theoretical. In a series of in vivo experiments in six dogs, PE was simulated by introducing preformed thrombus into the pulmonary arterial system.[16] Contrast was injected via a pigtail catheter immediately adjacent to the leading edge of the occluding embolus in the PA. The migration time, defined as the migration of > 50% of the contrast spot, was in the range of 0.40 to 0.64 seconds for all trials, indicating that the contrast cloud had only brief contact with the proximal surface of the thrombus. The experiment was reproduced in an in vitro model using a glass cast of a human PA with an occluding balloon to simulate a PE. Circulatory flow was simulated by a continuous infusion of saline at a rate of 5 L/min. A vortex flow pattern was visualized using illumination of suspended microspheres. The authors concluded that locally administered thrombolytic therapy in the PA likely provides no benefit over the peripherally administered route due to this vortex flow observation. They suggested that interventionalists might advance the catheter directly into the clot or combine intrapulmonary injection of thrombolytic agents with mechanical catheter fragmentation, with the latter therapy being largely abandoned due to concerns related to patient deterioration.

Initially, there were only three studies of 310 patients with acute intermediate- and high-risk PE that evaluated the efficacy of CDT with ultrasound-assisted catheter-directed thrombolysis (USAT) or standard infusion catheters, with only 59 patients randomized to either USAT or heparin alone.[17-19] These studies demonstrated the efficacy of CDT, with improvements in RV/left ventricular (RV/LV) ratio and PA systolic pressure at a short-term follow-up of 24 to 48 hours. Among these initial three studies, there was one major extracranial bleeding event and no reports of intracranial hemorrhage. Interestingly, this method of intrathrombus delivery of thrombolytics allowed for much lower doses of alteplase, ranging on average from 20 to 28 mg infused over an extended period of time. Efforts were made to determine the shortest dwell time and dose of thombolytic therapy to achieve an optimal result while mitigating risk to the patient. Finally, at 90-day follow-up in Kucher et al, there was no difference in RV/LV ratio in the patients treated with USAT versus heparin, raising a question regarding the benefit of patients receiving this therapy in the long term.[17]

A recent large meta-analysis of 9,789 patients from mostly observational studies supports the safety and efficacy of CDT compared to heparin in patients with intermediate-risk PE.[20] Findings included a significantly lower in-hospital mortality (risk ratio [RR], 0.41; 95% CI, 0.30-0.56; $P < .00001$), 30-day mortality (RR, 0.37), 90-day mortality (RR, 0.36), and a trend toward lower 1-year mortality that neared but did not achieve statistical significance—all favoring CDT. There was no difference between the two strategies in the risks of major and minor bleeding or in the rates of blood transfusion. Certainly, there is clinical support for investigating these therapies in a randomized comparator study that looks at short- and long-term intervals, including quality-of-life indicators and functional outcomes.

## DEVELOPMENT OF CATHETER EMBOLECTOMY

The most recent guidelines in the pulmonary literature recommend that catheter-assisted thrombus removal should be reserved, if expertise and resources are available, for patients with acute PE and hypotension at high bleeding risk, have failed thrombolysis, or are in shock and at high risk of death before systemic thrombolytics could take effect.[21]

The development of small- and large-bore catheters has allowed for thrombus removal to provide immediate resolution of PA occlusion by thrombus, without the need for a thrombolytic agent. Understandably, this strategy is an attractive alternative to current management strategies for patients with high-risk PE and elevated bleeding risk. Two small, single-arm, prospective studies have shown short-term improvements in RV/LV ratio, with acceptable safety profiles and rare administration of thrombolytics.[22,23] A large single-arm registry of 800 patients with intermediate- or high-risk PE underwent embolectomy with a large-bore catheter showed efficacy in several clinical endpoints and a favorable risk profile.[24] Patients experienced immediate improvements in mean PAP, pulmonary vascular resistance, cardiac index, and heart rate, with a 1.8% major adverse

event rate (11 major bleeding events, three procedure-related events) and 30-day mortality of 0.8%.

A nonrandomized comparison study of high-risk PE compared 53 patients treated with large-bore catheter thrombectomy versus 61 patients treated with either systemic thrombolysis, CDT, or anticoagulation (context arm).[25] The primary endpoint was an in-hospital composite of all-cause mortality, bailout to an alternate thrombus removal strategy, clinical deterioration, and major bleeding. The study was terminated early, with a planned interim analysis revealing that the primary endpoint was reached in 63% patients who received standard therapy compared to 17% who underwent mechanical embolectomy. There was only one death in the embolectomy arm (mortality rate, 1.9%). The mortality in the context arm was 29.5%, which is comparable to the 28.5% mortality rate in historical controls.

## FUTURE DIRECTIONS

With societies such as the PERT Consortium that are committed to advancing the science of VTE, we are beginning to see the fruits of labor ignited by the Surgeon General's "Call to Action." Data are on the horizon, as several clinical trials are underway to close data gaps, with many studies focused on the intermediate-risk PE population. We hope to learn which patients are at highest risk of decompensation to refine current risk stratification methods. We hope to learn more about the long-term symptoms as well as the functional and psychologic impact on patients with PE.

Pulmonologists are becoming more aware of post-PE impairment syndrome, which exists beyond the development of chronic thromboembolic pulmonary hypertension.[26] Recommendations exist for a holistic approach to caring for PE patients in both the short and long term.[27] The next several years will be enlightening for the multidisciplinary specialties that care for patients with VTE. I am hopeful that the data produced will help inform the next generation of multidisciplinary guidelines for chest physicians. ■

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