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VIEWPOINT

Revisiting Systemic Thrombolysis in Acute Pulmonary Embolism

Zach Rozenbaum, MD

Systemic thrombolysis (ST) for acute pulmonary embolism (PE) has been studied in numerous trials, and evidence for its use remains debatable. Data are not lacking but rather failed to demonstrate an overall convincing risk-benefit ratio. The most robust study, representing today's practice, is the Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism trial, which showed no mortality benefit with ST for intermediate-high-risk PE.[1] Moreover, 1 of every 9 patients had major bleeding,[1] and there was even no long-term pulmonary hypertension reduction.[2] In unstable patients who have more to gain from ST, the bleeding risk is increased due to several mechanisms, such as venous congestion affecting the liver and gastrointestinal tract and increased right atrial pressure enabling small paradoxical emboli via patent foramen ovale that may undergo hemorrhagic conversion. Meta-analyses showed that ST is not beneficial for stable patients.[3] While ST reduces the mortality risk in unstable patients (number needed to treat = 59), it increases major bleeding (number needed to harm = 18), including intracranial bleeding (number needed to harm = 78).[4] Younger patients have a lower risk of major bleeding[4]; however, over half of patients with high-risk PE are not treated with ST because of a perceived increased risk of bleeding.[5] Consequently, the rate of ST use is only 2.5% overall and 11% in patients with high-risk PE.[6] Similar to intermediate-risk PE, there are no robust data supporting the use of ST in high-risk PE. Studies examining the mortality benefit of ST in high-risk PE have not been consistent, and the consensus for the practice is based on a trial that consisted of 4 patients in the treatment arm.[7] Of note, the agent that was given was streptokinase, which is less commonly used nowadays compared to Alteplase. Accordingly, mortality rates in patients with PE remain high, and over the course of 20 years, there has been no clear reduction in the trend of overall PE mortality.[8]

The probable reason ST is still recommended as first-line therapy in PE patients with high-risk features is the lack of randomized controlled trials (RCTs) of newer therapies. Catheter-based therapies, such as percutaneous aspiration devices (PASDs), became available in recent years and are being utilized more commonly in all spectrums of PE risk profiles.[9] There are over a 1,000 published cases of PASD use, and many more unpublished cases were likely performed. An example of the main part of a saddle PE removed as a single unit using a PASD is shown in **Figure 1**. Registry data show that the risk of major procedural complications with PASDs is <1%.[10] Similarly, the 30-day mortality rate with PASD is <1%. Moreover, results of the FLowTriever for Acute Massive Pulmonary Embolism study demonstrated an over 90% in-hospital mortality reduction compared to the 29.5% mortality rate seen in patients treated with other therapies.[11] Additional areas of potential benefit include long-term complications such as chronic thromboembolic pulmonary hypertension (CTEPH) and post-PE syndrome. CTEPH and post-PE syndrome may occur in up to 6% and almost 50% of patients with PE, respectively.[5] In the FlowTriever All-Comer Registry for Patient Safety and Hemodynamics study, CTEPH was found in only 1.2% of patients at follow-up.[10]

There are many therapies in medicine that are not supported by RCTs. For example, conducting a RCT of diuretic therapy vs placebo in patients with pulmonary edema is deemed unethical but remains standard of practice. Likewise, most surgical operations

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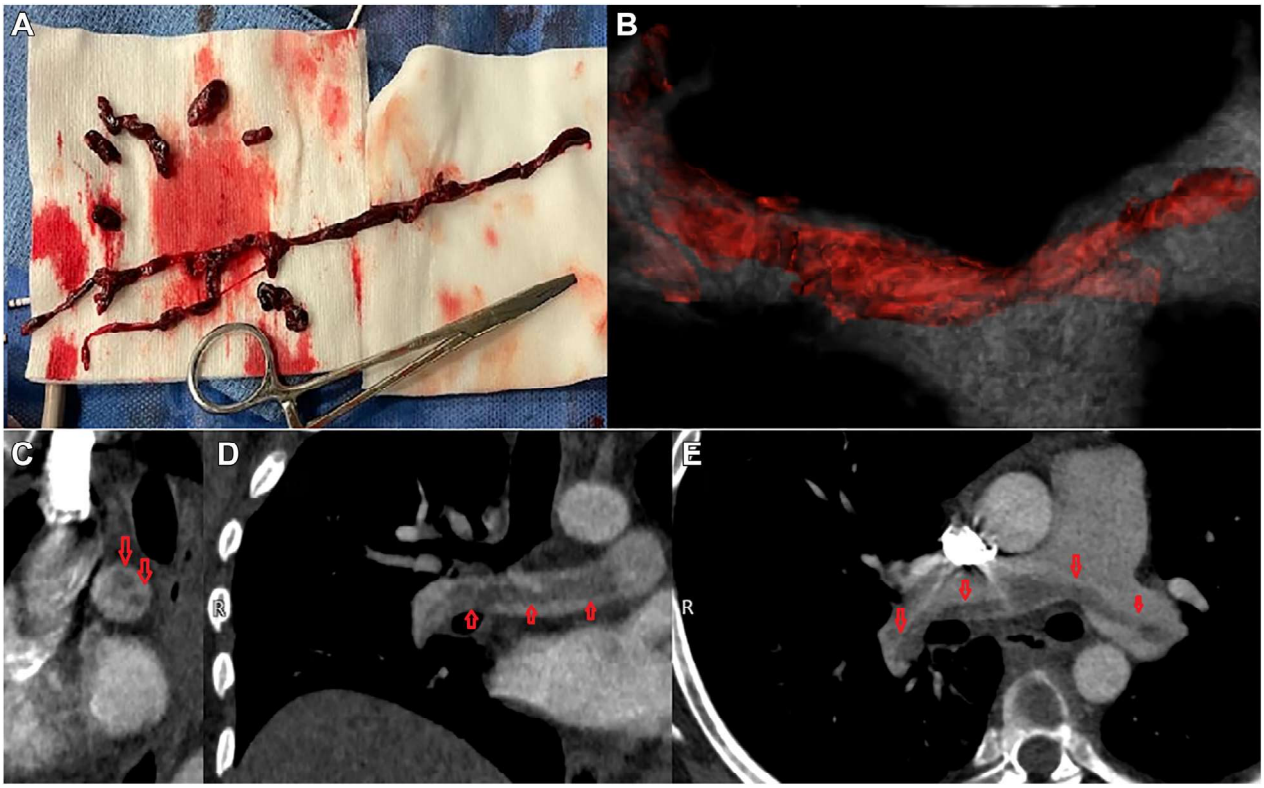
FIGURE 1 Saddle Pulmonary Embolism Before and After Aspiration



(A) The aspirated material. The main part of the thrombus was removed as a single unit, and additional small fragments are seen. (B) 3D reconstruction of the saddle pulmonary embolism. (C) Sagittal view of the pulmonary embolism. Red arrows mark the 2 ends. (D) Coronal view of the embolism in the right pulmonary artery, marked by red arrows. (E) Axial view of the pulmonary embolism extending bilaterally, marked by red arrows.

are not based on RCTs. RCTs of PASDs are anticipated, but it may be years until results are published. In the meantime, PASDs are becoming first-line therapy in many centers for the simple reason that we observe high efficacy and low rates of major complications. ST has been used for PE for over 50 years, despite a lack of convincing evidence. In the era of new effective technologies for PE treatment with low procedural risk, for many, the use of ST is becoming unethical.

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Letters

TO THE EDITOR

Systemic Thrombolysis is Still the First-Line Treatment for Unstable Pulmonary Embolism

We read Dr Rozenbaum's viewpoint on systemic thrombolysis (ST) for acute pulmonary embolism (PE) with interest.[1] We agree with Dr Rozenbaum that catheter-directed treatments have an expanding role in the treatment of PE. However, for unstable PE, ST is still the first-line treatment. Dr Rozenbaum cites a meta-analysis to question the efficacy of ST for unstable PE, citing a number needed to treat of 59. On a precise reading of Chatterjee's meta-analysis, the number needed to treat of 59 was calculated based on all patients with PE, both unstable and stable.[2] Of 2,115 patients, only 31 (1.5%) had unstable PE, and the meta-analysis did not perform a subgroup analysis on this small cohort, preventing any meaningful conclusions on patients with unstable PE.

Currently, the role of alternative treatments is limited for patients with unstable PE, and ST remains an integral part of management for these patients. The most recent randomized control trial on ST in patients with unstable PE is 29 years old. It was stopped after enrolling 8 patients with unstable PE. Four patients in the treatment arm survived, while the four patients who did not receive ST died.[3] Consensus guidelines still maintain that ST is the first-line treatment for unstable PE based on this randomized controlled trial and other studies. These same guidelines assert that the evidence supporting catheter-directed therapies has only low certainty and recommend using them only in specific scenarios. Additionally, an increasing trend of PE mortality cannot be attributed to the failure of ST, as only a minority of patients with unstable PE receive ST when indicated.[4] As such, Dr Rozenbaum's statement that "for many, the use of ST is becoming unethical" may be an overstatement, even in the minority of facilities able to rapidly institute procedural interventions in hemodynamically unstable patients. ST should be employed for patients with unstable PE who have no contraindications to ST.[5] This principle is especially true in centers with no access to catheter-directed therapies.

PE is a complicated, dynamic condition. Despite the potential benefits of ST, the inherent risks necessitate the development of other therapeutic strategies. As the field continues to explore catheter-directed therapies, ST should also be further studied with close attention to novel dosing regimens (eg, reduced-dose thrombolytics) that could maintain the therapeutic benefit of ST, limit the risk of hemorrhage, and prevent patients from undergoing surgery or catheter-directed therapies, which carry a separate set of risks.

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REPLY: Improving Outcomes of Unstable Patients With Acute Pulmonary Embolism

I thank Dr Rouleau and colleagues for their response to our paper,[1] and agree that the current recommendations and guidelines regard systemic thrombolysis (ST) as first-line therapy for unstable pulmonary embolism (PE) patients. Yet, the risk-benefit ratio is far from robust due to high bleeding rates.[1] Moreover, studies investigating high-risk PE did not consistently report efficacious results;[2] hence, the viewpoint aimed to challenge guidelines.[1] Furthermore, guidelines are not in line with real-world practice, as 88.7% of unstable PE patients do not receive ST,[1] thus reflecting the risky nature of ST therapy. Since ST has been available for many years, the extent of its use is unlikely to increase, and newer therapies should be pursued in order to attempt to improve the presently suboptimal outcomes of patients with PE.[3]

An important point made by Dr Rouleau and colleagues is that not all centers have access to catheter-directed therapies. This could be a result of the guidelines that mention catheter-directed therapies as one of the alternative options. A strong recommendation may encourage more widespread availability. Dr Rouleau and colleagues also mention the importance of further studies on novel dosing regimens. Notably, most ongoing or planned randomized studies do not use ST as the control group.[4]

When the standard of treatment has high complication rates, a replacement should be considered, leaving ST as the alternative and not vice versa. The discrepancy between the treatment workflow of centers with access to catheter-directed therapies and the guidelines highlights the need for widespread awareness of newer effective options for treating PE.

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