Reversing the Death Spiral: FlowTriever Thrombectomy for High-Risk PE

A panel of experts shares their high-risk PE treatment strategies and an update on the FLAME study, plus case reports of FlowTriever thrombectomy use in high-risk patients after cardiac arrest.

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Q&A: High-Risk PE, Current Treatment Options, and the FLAME Study

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Can you describe your experience managing high-risk (massive) pulmonary embolism (PE) patients and your perspective regarding unmet needs?

Dr. Silver: We have a long history of treating PE at our center and have developed a rigorous approach to triage and treat high-risk PE patients that we believe is critical to achieving excellent outcomes. Specifically, we have trained staff and implemented an ST-segment elevation myocardial infarction (STEMI)–like process for high-risk PE. Key stakeholders are educated to quickly recognize and confirm high-risk PE and activate our on-site 24/7 cath lab team. Our referring centers are educated regarding how to stabilize and transport patients, including via helicopter, akin to STEMI. Posttreatment, patients go to a cardiac critical care unit that is accustomed to taking care of higher-acuity patients with large-bore access and right heart failure–related hypotension.

In terms of unmet needs, we haven't meaningfully impacted mortality in the past 20 years, with rates hovering around 30% to 40%. It will take a true paradigm shift in treatment pathways and a movement to definitive catheter-based treatment to make progress. Systemic thrombolysis can be effective, but 40% to 50% of patients are contraindicated and the bleeding risks can be catastrophic. Furthermore, contraindicated patients typically have multiple comorbidities and are often the sickest patient subset. Mechanical thrombectomy offers a viable treatment path for these patients. We feel that the

safest and most rapid treatment path to unloading the right ventricle (RV) will be the nidus for a paradigm shift in PE care.

Dr. Toma: True high-risk PEs are relatively rare and represent about 10% of our PE response team (PERT) activations at UPMC Presbyterian. These patients are usually very sick and on multiple pressors, and they often present with out-of-hospital cardiac arrest. As such, mortality remains very high, with our rate exceeding 35% largely because we haven't had the right tools for the job. Historically, the only treatment options were systemic thrombolysis or surgical embolectomy, although there is an increasing array of percutaneous options emerging. With the multitude of treatment options now available, an unmet need in the field is a lack of comparative data in this patient population to guide therapy.

What are your high-risk PE treatment goals? Do you have any advice or "watch outs" for health care providers who are less experienced in PE patient management?

Dr. Silver: The most important treatment goal is fast access to definitive treatment to rapidly unload the RV, using a strategy such as thrombectomy with the FlowTriever System (Inari Medical). It takes too much time to order, prepare, and administer thrombolytics, let alone the additional time needed for thrombolytics to achieve a result. Efficient thrombus removal is the priority. We also have a low threshold for providing circulatory support in this sick patient population—whether it is preprocedural extracorporeal membrane oxygenation to help stabilize the patient or Impella RP (Abiomed, Inc.) postprocedure when additional hemodynamic support is warranted.

A key watch out is to ensure all members of the care team, from point of diagnosis to treatment, understand that sedation and intubation should not be performed. If a patient presents in extremis with respiratory distress, the first reaction is to manage the airway with intubation. This could be a catastrophic decision. Because these patients are preload dependent, intubation and sedation can worsen hypotension and cause a spiral to cardiogenic shock and heart failure. My advice is that caregivers should be trained to coach patients to remain calm and avoid both general and conscious sedation.

Dr. Horowitz: In terms of treatment goals, speed is of the essence. We are looking to stabilize the patient, reverse cardiogenic shock, and save their life. These patients can turn on a dime and decompensate, requiring swift action. We encourage PERT teams to focus on the fundamentals: Quickly get the diagnostic CTs and start anticoagulation, and call in the rest of the team to form a plan. Similarly, you don't necessarily need to wait for the "official" echocardiogram to get useful information. A point-of-care ultrasound can be completed by many types of providers, including staff from both the emergency department and intensive care unit, and can examine the RV size and function as well as look for a clot in transit.

In terms of watch outs, avoiding anesthesia is a big one, as Dr. Silver mentioned. Understanding how the hospital could kill a patient before you have a chance to help them is critical. For instance, if a patient presents with abnormal vitals that activate the sepsis pathway, they may end up receiving 2 to 3 L of fluids in the emergency department before the PERT is even activated, which could tip over an already tenuous RV and lead to the RV "spiral of death."

What is your experience with FlowTriever thrombectomy in high-risk PE patients, and is there an associated learning curve?

Dr. Silver: Since the FlowTriever Pulmonary Embolectomy Study (FLARE) investigational device exemption trial, we have been a high-volume frontline user of FlowTriever, with approximately 125 patients treated, including 14 high-risk PE patients.

For physicians new to FlowTriever, I recommend beginning with intermediate-risk patients. It takes about four to six cases to get through the learning curve and feel technically comfortable treating high-risk PE patients. In unstable patients, it is particularly important to have meticulous technique, including ultrasound guidance, micropuncture access, and rapid clot extraction to unload the RV. If a CTA was obtained within the last hour, I would proceed with proximal clot removal without performing formal pulmonary angiography given that efficiency is critical. My perspective is to target the low-hanging fruit—thus, any occlusive proximal clot. This rapid clot removal can restore hemodynamics immediately, without necessitating every segmental branch be cleared out.

Dr. Toma: Our cardiology team helps with PERT calls, and we are part of the discussion for most high-risk PE patients who present or are transferred to our institution. Importantly, we discuss candidacy for mechanical circulatory support as well as various reperfusion options. FlowTriever has become an attractive option, particularly given the number of patients who are at high risk of bleeding. As such, we have started taking

these patients to the cath lab for hemodynamic evaluation and percutaneous mechanical thrombectomy with FlowTriever, with the goal of safely and efficiently unloading the RV.

Before treating unstable PE, I also recommend gaining comfort with the device in intermediate-risk patients, where your ability to navigate the pulmonary arteries (PAs) and get used to the device components may be done in a less emergent manner and with time to deliberate. The learning curve has certainly been shortened from the first-generation FlowTriever System used in the FLARE trial. The current third-generation device has streamlined our procedure significantly compared to when we first started, decreasing our procedure time to under 1 hour in most cases, with some completed in as little as 20 minutes.

What data exist and what additional data are needed to further our understanding of this critically ill patient cohort?

Dr. Toma: Data in the high-risk PE population are limited. The most robust study in high-risk PE consists of only eight randomized patients. Additional data in the field are needed to determine if emerging PE-specific treatment tools such as FlowTriever can impact the mortality and overall complication rate seen in this sick cohort.

Preliminary data and experience certainly support this concept. At the Transcatheter Cardiovascular Therapeutics conference, we presented a multicenter retrospective study evaluating 27 patients who either met the strict definition of high-risk PE, were intubated, and/or had hemodynamic evidence of impending shock. Of this cohort, 22% of patients received cardiopulmonary resuscitation (CPR) and 11% failed systemic thrombolysis prior to FlowTriever thrombectomy; one patient (3.7%) died. The majority of patients experienced on-table improvements in hemodynamics, including PA pressure and cardiac output. There were no device- or procedure-related complications. Although this study represents a selected group of patients with experienced operators, the results are very encouraging and demonstrate initial safety and effectiveness of FlowTriever in high-risk PE.[1]

Dr. Horowitz: I agree that the data on high-risk PE are very limited, with most data comprising small case series. That said, the guidelines are clear in terms of recommending therapy beyond anticoagulation given the very high mortality rate.

It is quite difficult to study high-risk PE patients, similar to what you see in cardiac arrest studies. It can be difficult to enroll and consent patients given how critically ill they are, especially if they are also intubated. However, because of the high event rates in this cohort, it may be easier to achieve fairly clear-cut endpoints with a smaller number of patients. In contrast, we largely need to resort to softer surrogate endpoints for intermediate-risk PE patients. That said, a busy center may only see eight to 12 high-risk PE patients in 1 year compared to 100+ intermediate-risk patients, thus complicating the ability to study high-risk PE patients.

Can you describe the recent American Heart Association (AHA) guidance as well as the FLAME study considerations you are spearheading as Co-National Principal Investigators?

Dr. Horowitz: Last fall, AHA released a guidance about the need for obtaining additional data in PE.[2] This guidance also acknowledged that a randomized controlled trial would not be feasible in high-risk PE and, to that end, set forth a framework for conducting an acceptable study.

What is most appealing to me with regard to the FLAME study is that it is meant to be as "real world" and robust as one can get outside of a randomized controlled trial. It is relatively large in scale with a sound statistical approach, and it has been vetted by a great group of thought leaders in PE to optimize design and practical enrollment considerations.

In fact, if the FLAME study is successful, it might give us a glimpse into how we should think about PE treatment more broadly. If we can safely and successfully rescue unstable patients with a large-bore catheter crossing the right heart, maybe there will be a reassessment of when to intervene in intermediate-risk, especially intermediate-high–risk patients.

Dr. Silver: Because of the emergent nature and significant mortality associated with high-risk PE, AHA and other societal guidelines favor advanced therapeutic approaches. Now that the field is evolving to definitive catheter-based solutions and advancements in mechanical support are more readily available, AHA has acknowledged that additional approaches should be considered and warrant further study. As such, we are excited to be designing the FLAME study with Inari Medical. This study is positioned to be one of the largest dedicated high-risk PE studies ever conducted.

While a randomized controlled trial is always desirable, there are numerous obstacles inherent to randomization in high-risk PE, including small patient numbers, ethical considerations, the emergent nature

of the disease, and failure to recognize the disease state at presentation. Thus, randomization is not feasible. Furthermore, given small patient numbers and practical enrollment considerations, a performance goal > 30% is needed for sample size reasons. Literature meta-analysis and expert opinion suggest that a robust composite endpoint of meaningful metrics is thus required, as mortality alone would not constitute a sufficient event rate for a statistically sound study.

With these considerations in mind, the FLAME study will evaluate real-world, high-risk PE patients in a nonrandomized, prospective, observational study. The study will comprise two groups: One group will receive frontline FlowTriever thrombectomy and the context group will receive the standard of care. The primary endpoint will be a composite endpoint including in-hospital all-cause mortality, major bleeding, clinical deterioration, and bailout to a second thrombus removal rescue strategy.

Overall, we look forward to generating this important data set for the PE field, and Dr. Horowitz and I appreciate the dedication and thoughtful advice provided by steering committee members (including Drs. Jay Giri, Wissam Jaber, Sameer Khandhar, Ken Ouriel, and Catalin Toma) throughout the protocol design process.

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FlowTriever Thrombectomy Saves a High-Risk PE Patient After Two Cardiac Arrests

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A 52-year-old obese woman experienced sudden left-sided chest pain and palpitation, which progressed to diaphoresis and shortness of breath before syncope and collapse to the shower floor. She crawled from the shower to call her daughter, who called emergency medical services (EMS). EMS administered nitroglycerin for her chest pain and dyspnea, then transported her to the nearby county hospital.

Due to clinical suspicion of PE, an emergent chest CT was conducted and revealed extensive PA thrombus burden (Figure 1). The CT indicated bilateral PE extending from the left and right PAs (Figure 1A) into the subsegmental branches (Figure 1B). Right heart strain was also evident, with a RV/left ventricular (LV) ratio of 2.2 (Figure 1C). The patient went into shock, requiring vasopressors and inotropes. She subsequently experienced two cardiac arrests, each with pulseless electrical activity for about 2 minutes and return of spontaneous circulation after CPR. Systemic tissue plasminogen activator (tPA) was initiated but stopped due to hematemesis. The PERT at St. Joseph's Medical Center was activated, and the patient was transferred to our facility for emergency thrombectomy with the FlowTriever System. Due to hemodynamic instability, the patient was intubated and sedated prior to transfer to our facility.

PROCEDURAL OVERVIEW

On presentation to the interventional radiology angiography suite, the patient was cyanotic with a blood pressure of 70/59 mm Hg, heart rate of 131 bpm, and oxygen saturation of 72%. The right common femoral vein was accessed under ultrasound guidance. Right iliac venography was subsequently performed to rule out proximal deep vein thrombosis before any catheters were inserted. After serial dilatation of the vein, a 24-F DrySeal sheath (Gore & Associates) was introduced, through which an angled pigtail catheter

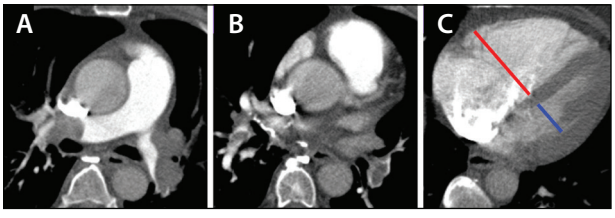

Figure 1. CT slices prior to thrombectomy. Extensive clot burden in the right and left PA (A). Clot extended into the subsegmental branches (B). RV (red)/LV (blue) ratio was 2.2, indicating extensive right heart strain (C).

was inserted into the main PA. Mean PA pressure was elevated at 42 mm Hg.

Initial pulmonary angiography showed minimal left lung perfusion and compromised right lower lobe perfusion (Figure 2A). With the guidewire positioned in the left PA, the 24-F Triever24 (T24; Inari Medical) aspiration guide catheter was advanced, with the Triever16 (Inari Medical) aspiration guide catheter telescoped through the T24 for extra support through tortuous anatomic turns. The T24 was placed close to the thrombus, and a vacuum was applied to the catheter side port via the 60-mL custom large-bore syringe. Opening the side port valve produced an abrupt high-flow suction that pulled thrombus through the T24 into the syringe.

A single aspiration in the left PA extracted large amounts of organized thrombus (Figure 2D), and subsequent angiography demonstrated significantly improved left lung perfusion (Figure 2C). The guidewire was then maneuvered to advance the T24 into the right PA. A single aspiration in the right PA removed organized thrombus (Figure 2D) and improved right lung perfusion (Figure 2B). Postthrombectomy, the patient's vital signs quickly improved: her heart rate decreased from 131 to 99 bpm, blood pressure increased from 70/59 to 100/74 mm Hg, oxygen saturation increased from 72% to 98%, and mean PA pressure decreased from 42 to 25 mm Hg. All devices were removed from the patient, and the access site was closed with a purse-string suture. The total procedure time was 90 minutes, with an estimated blood loss of 200 mL. The patient experienced no complications during the intervention and tolerated the procedure well. She was transferred back to the intensive care unit and extubated the next morning.

The day after thrombectomy, the patient was weaned off vasopressors and inotropes. Two days after thrombectomy, esophagogastroduodenoscopy revealed a large adherent clot in the lesser curvature in the fundus of the stomach, which was likely the underlying ulcer that bled secondary to thrombolysis and caused her initial hematemesis at the outside hospital. After an interventional radiology procedure to embolize the left gastric artery, she was off oxygen and could walk with no difficulty. She walked out of the hospital 5 days after thrombectomy.

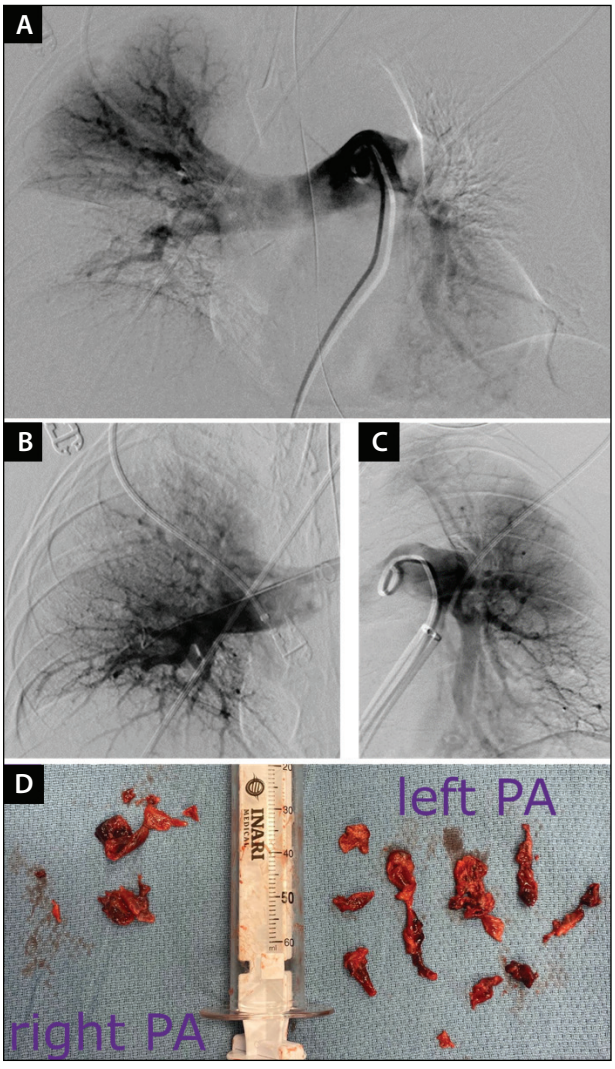

Figure 2. Angiography before thrombectomy showed poor lung perfusion (A). Right (B) and left (C) lung each showing improved perfusion after thrombectomy. Extracted thrombus from each PA (D).

DISCUSSION

High-risk PE constitutes only about 5% of patients with PE, but it represents the population with the highest mortality.[1,2] High-risk PE patients with cardiogenic shock have an in-hospital mortality rate of approximately 25%, which increases to 65% if the patient experiences cardiac arrest.[3] This case patient experienced cardiac shock and was then resuscitated from two cardiac arrests. She was cyanotic at the beginning of the procedure, with sustained hypotension and tachycardia. FlowTriever thrombectomy promptly restored lung perfusion and relieved right heart strain, which led to on-table improvements in her mean PA pressure, arterial blood pressure, heart rate, and oxygenation.

The primary treatment goal for acute high-risk PE is to rapidly reverse hemodynamic compromise and gas exchange abnormalities to reduce PE-related mortality,[4] and the Inari FlowTriever System is engineered to achieve this goal. Our hospital system's current PERT algorithm defaults to systemic tPA for high-risk PE, but

if the patient does not respond or has a contraindication to tPA (as with this patient), we can consider FlowTriever aspiration thrombectomy. Our preliminary outcomes treating high-risk PE with FlowTriever are very encouraging because we typically observe hemodynamic and oxygenation improvements within minutes of thrombus removal. However, we currently lack enough data to shift our response algorithm to FlowTriever thrombectomy as the primary treatment for high-risk PE. Data from the FLAME study could be instrumental in refining our high-risk PE treatment algorithm.

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Successful FlowTriever Thrombectomy in a High-Risk PE Patient Resuscitated From Cardiac Arrest

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Eight days after spinal surgery, a 67-year-old obese man experienced a cardiac arrest in his hospital room. He required intubation, vasopressor support, and therapeutic anticoagulation with unfractionated heparin after resuscitation. Chest CT scan revealed extensive saddle PE, extending from the main PA into all five lobar arteries, as well as the subsegmental branches of the bilateral lower lobes (Figure 1). His RV/LV ratio was 1.2, indicating right heart strain. Given his recent spinal surgery, thrombolytic therapy was absolutely contraindicated due to the risk of bleeding. Interventional cardiology was consulted, and the patient was brought to the catheterization laboratory for thrombectomy with the FlowTriever System.

PROCEDURAL OVERVIEW

The patient was admitted to the catheterization laboratory in critical condition, still intubated and on vasopressors. Right common femoral vein access was achieved with ultrasound guidance. A pigtail catheter was advanced into the PA, and selective angiography confirmed thrombus burden in the main PA extending to the bilateral segmental branches. Mean pressure in the main PA was elevated at 39 mm Hg. The access site was dilated to accommodate a 22-F DrySeal sheath. A Rosen guidewire was advanced to achieve distal purchase in the right PA. It was then exchanged for a 1-cm, short-tip, Amplatz Super Stiff guidewire (Boston Scientific Corporation), over which the 20-F Triever20 (T20) aspiration guide catheter was advanced into the right proximal interlobar artery. Vacuum was applied to the T20 by drawing back the plunger on the 60-mL FlowTriever large-bore syringe. A total of six aspirations were applied to the right interlobar artery, the truncus anterior, and the right main PA, extracting significant thrombus. The T20 was then maneuvered into the proximal left main PA, where two additional aspirations extracted small remnants of thrombus. Removing the large thrombi from the PAs (Figure 2A) restored lung perfusion (Figure 2B and 2C) and improved hemodynamics

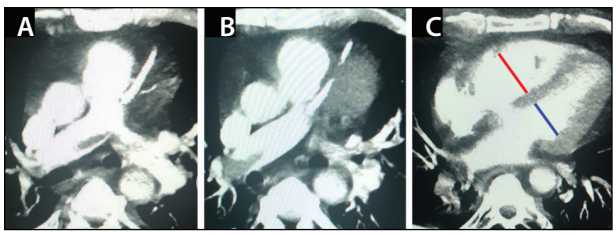

Figure 1. CT slices prior to thrombectomy. Thrombus at the main PA bifurcation, in the right PA, and in the segmental branches of the left PA (A, B). RV (red)/LV (blue) ratio was 1.2, indicating right heart strain (C).

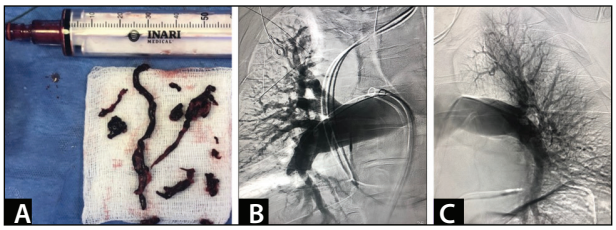

Figure 2. Total thrombus extracted (A). T20 in the right PA, showing restored right lung perfusion after thrombectomy (B). Left lung perfusion was also restored after thrombectomy (C).

TABLE 1. THE CASE PATIENT'S VITAL SIGNS AND HEMODYNAMIC PARAMETERS

Parameter	Beginning of Procedure	End of Procedure
Heart rate (bpm)	118	101
Blood pressure (mm Hg)	96/50	110/60
PA pressure (mm Hg)	64/26/39	42/27/33
Oxygen saturation (%)	92	100

(Table 1). The total procedure time was 55 minutes, the total device time was 35 minutes, and eight aspirations were applied, which resulted in only 300 mL of estimated blood loss. There were no complications, and the patient was discharged to the intensive care unit and extubated that evening. The next day, he had no chest pain or trouble breathing and was taken off vasopressors with a stable blood pressure of 115/58 mm Hg.

DISCUSSION

In a single short procedure, the FlowTriever System rapidly reversed hemodynamic compromise by extracting the large thrombus burden from a high-risk PE patient who had experienced cardiac arrest. The current guidelines advise physicians to consider advanced reperfusion therapy in high-risk PE to reduce mortality by improving hemodynamics and oxygenation.[1,2] Although this frequently translates to thrombolytic therapy in practice,[3,4] this patient's recent spine surgery represented an absolute contraindication to thrombolytic treatment.

We selected the Inari FlowTriever System for this critically ill postsurgery patient because it enables efficient thrombus extraction without the increased bleeding risk associated with systemic thrombolysis. Although the procedure requires large-bore venous access, we have found the risk of access-related complications to be negligible with the use of ultrasound-guided access and meticulous technique. Our health system and others continue to study and gain experience with the FlowTriever in patients with intermediate- and higher-risk PE who warrant aggressive, catheter-based therapeutic strategies. The FlowTriever's ability to rapidly enhance lung perfusion, decrease right heart strain, and improve hemodynamics without the bleeding risks associated with systemic thrombolysis continues to represent a major advance in PE therapeutics.[1] ■

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