

It's Alive! The Evolution of Thrombus and Why Fast, Effective Removal Is Key

Dr. Scott J. Cameron shares insights in venous thrombus biology, and Drs. Labib Haddad and Octavio Cosme present case reports using the FlowTrier and ClotTrier systems after unsuccessful thrombolysis.

WITH SCOTT J. CAMERON, MD, PhD, FACC, FSVM; LABIB HADDAD, MD; AND OCTAVIO COSME, MD, FACC, FSCAI

Reshaping the Way We Think About Thrombus—A Discussion With Dr. Scott J. Cameron



Scott J. Cameron, MD, PhD, FACC, FSVM

Associate Section Head in Research
Section of Vascular Medicine
Department of Cardiovascular Medicine
Cleveland Clinic Foundation
Cleveland, Ohio
cameros3@ccf.org

Disclosures: None.

Given your scientific research in thrombosis, your training in vascular medicine and cardiology, and your role in pulmonary embolism (PE) patient care as a noninterventionalist, you are uniquely positioned to discuss the role of clot in venous thromboembolism (VTE). How should we be thinking about venous clot and its consequences?

At the highest possible level, I think we all agree that thrombus is bad. In PE, we know thrombus acutely affects patient mortality. We also need to focus on longer-term adverse events: post-PE syndrome, heart failure, pulmonary hypertension, recurrence, and overall quality of life. A meta-analysis by Sista et al suggests that roughly one-third of patients with acute PE experience post-PE syndrome or chronic thromboembolic disease.¹ This is an overwhelming amount.

In deep vein thrombosis (DVT), residual thrombus has been linked to higher mortality, postthrombotic syndrome

(PTS), and recurrence.²⁻⁶ The pulmonary vascular system likely responds in a similar manner. We know “what” happens (venous thrombosis can change the function of a blood vessel), but we need to ask “why” this happens.

Now that we have discussed what happens to patients with residual venous clot, let's dig into the why. What have you learned about thrombus formation and evolution in VTE that would cause these clinical sequelae?

The response of different vascular beds to thrombosis is not the same. For example, for thrombus found in aneurysmal segments of the infrarenal aorta, there is both a beneficial role (ie, containing a dissection and preventing rupture) and an ongoing deleterious process (ie, accelerating vascular injury and aneurysmal growth).^{7,8} The venous system does not respond as favorably. No good comes from having thrombus present in a vein. Venous thrombus is also not an inert entity; rather, thrombus is composed of many cells, including leukocytes and platelets, that are very much alive and secreting molecules that damage blood vessels. We previously reported a change in the circulating platelet phenotype in patients with coronary artery disease. Platelets and thrombus extracted from patients continued to secrete enzymes, including matrix metalloproteinases (MMPs), to distant sites.^{9,10} MMPs are well known for remodeling blood vessels. When blood vessels remodel, the intricate physiology (the local endothelial cell production of dilator and constrictor molecules) is altered. When thrombus stays in a blood vessel for a length of time, the thrombus composition changes, making it more adherent to the blood vessel wall. These aberrant events change the anatomy and physiology of the blood vessel.

THE FLOWTRIEVER AND CLOTTTRIEVER SYSTEMS

Sponsored by Inari Medical

In addition, proteins from which a thrombus is comprised undergo conformational changes as the thrombus ages; this alters the intricate chemistry required in the substrate binding site of enzymes, especially tissue plasminogen activator (tPA). Thus, as an investigator and a clinician who treats patients with PE, I am not surprised that some patients with PE are resistant to tPA.

Lastly, let's discuss one commonly used metric in PE: right ventricular (RV) dysfunction. We often find ourselves focusing on the RV/LV ratio but don't always consider the cause of RV dysfunction. I encourage all physicians to ask "why" in addition to "what." RV dysfunction comes from prolonged and/or persistent perfusion defects in the upstream pulmonary vasculature. The heart is an innocent bystander. We need to focus on the thrombus because that will help us understand why RV function changes.

The literature suggests that close to one-third of patients fail to clear thrombus up to 1 year after index PE when receiving anticoagulation with or without thrombolytics agents added.¹¹⁻¹³ Why do some patients clear thrombi on their own or with the aid of a thrombolytic agent, while others seem resistant to a pharmacologic approach?

There are lessons to learn from our work in platelet biology. The fundamental biology of a platelet can change based on the vascular disease it is exposed to (eg, coronary artery disease, peripheral artery disease, abdominal aortic aneurysms).^{9,14,15} This means that some patients may not respond as predicted to medications. The same concept likely applies to the coagulation cascade and thrombolysis. To me, the best analogy is a lock and key. Every patient's thrombus is structured with locks (fibrin attachments) in areas easily accessed by the key (plasminogen). If the lock and key concept (which is a simple way to visualize the activity of tPA) stops working—likely in aged, fibrotic thrombus—thrombolysis and thrombus resolution will be less likely. Therefore, patients with VTE frequently fail to completely resolve their thrombus.^{11,16} Unfortunately, we cannot predict who will and will not respond to tPA. This is an important area of basic research to explore.

In addition to the limitations of thrombolytic drugs, other approaches such as thrombus maceration have been attempted but did not resolve the problem. I personally feel that thrombus maceration is not in a patient's best interest because solving the hemodynamic problem (RV failure) often comes at the consequence of the secondary problem of oxygenation. Thrombus is a biologically active entity, and thrombus maceration may release inflammatory cytokines and toxic enzymes into the bloodstream. I believe that early thrombus extraction offers the best possible solution for patients with VTE, but we need more data.

Understanding there is much research still needed in the VTE field, how should the field approach VTE given what you outlined?

Although I spend a lot of time as a scientist thinking about and studying the process of thrombus, I deeply care about my time spent with patients in the clinic, where I have witnessed firsthand the suffering endured due to residual venous thrombus.

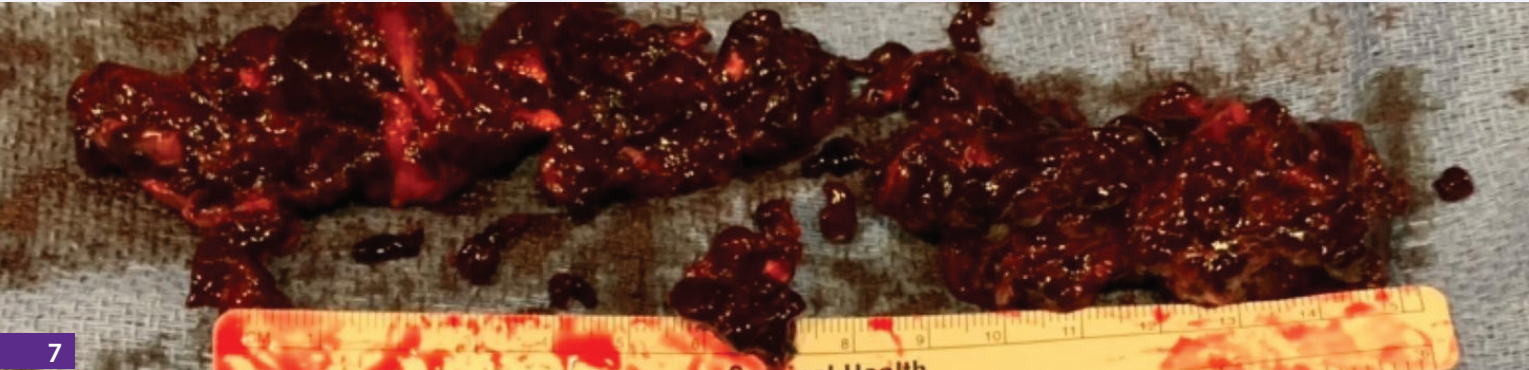
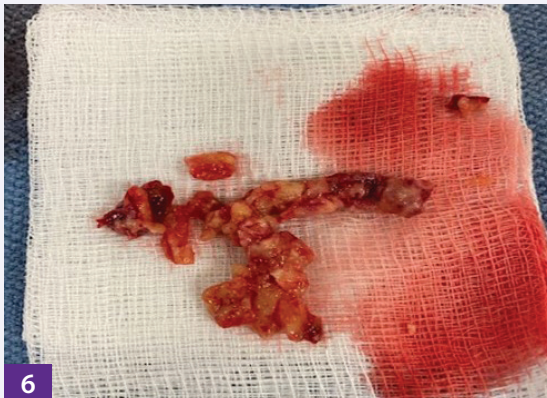
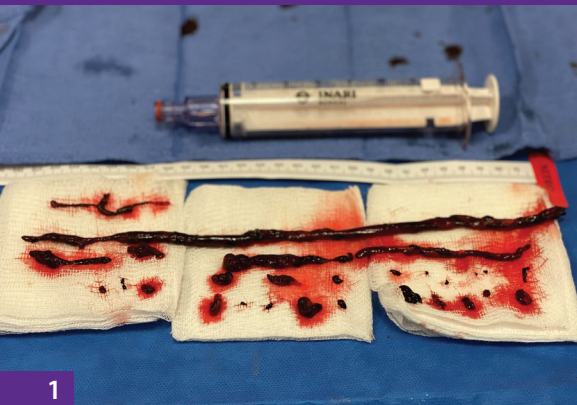
To this end, I think about venous thrombosis in very simple terms. Let's be more aggressive: remove the clot as soon as it is diagnosed and don't give blood vessels time to remodel. Our current risk stratification models for PE, such as the Pulmonary Embolism Severity Index (PESI) score, focus only on who might die acutely without considering the longer-term implications. It is important to recognize why patients with PE do not do well (ie, have residual thrombus) and consider this downstream consequence at the time of acute PE diagnosis.

In PE, I think this treatment effect may be even more pronounced. There is something special about the pulmonary vascular circulation that makes it behave differently from any other vascular bed (eg, responsiveness to oxygen tension, difference in expression of ion channels that control blood vessel tone and blood flow). If thrombus remodels pulmonary arteries (PAs), the delivery of oxygen is affected—and the vascular bed of the lung is very sensitive to changes in oxygen. The PA has completely different physiology compared with other blood vessels. The bottom line is that with new tools available to extract clot, the field will shift to this treatment approach. I am optimistic about future research results because I believe this approach will be game-changing for patients with VTE.

1. Sista AK, Miller LE, Kahn SR, Kline JA. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: systematic review with meta-analysis. *Vasc Med*. 2017;22:37-43.
2. Carrier M, Rodger MA, Wells PS, et al. Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis. *J Thromb Haemost*. 2011;9:1119-1125.
3. Donadini MP, Ageno W, Antonucci E, et al. Prognostic significance of residual venous obstruction in patients with treated unprovoked deep vein thrombosis: a patient-level meta-analysis. *Thromb Haemost*. 2014;111:172-179.
4. Dronkers CE, Mol GC, Maraziti G, et al. Predicting post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: a systematic review and meta-analysis. *Thromb Haemost*. 2018;118:1428-1438.
5. Tan M, Mos ICM, Klok FA, Huisman MV. Residual venous thrombosis as predictive factor for recurrent venous thromboembolism in patients with proximal deep vein thrombosis: a systematic review. *Br J Haematol*. 2011;153:168-178.
6. Young L, Ockelford P, Milne D, et al. Post-treatment residual thrombus increases the risk of recurrent deep vein thrombosis and mortality. *J Thromb Haemost*. 2006;4:1919-1924.
7. Cameron SJ, Russell HM, Owens AP 3rd. Antithrombotic therapy in abdominal aortic aneurysms: beneficial or detrimental? *Blood*. 2018;132:2619-2628.
8. Behr-Rasmussen C, Grøndal N, Bramsen MB, et al. Mural thrombus and the progression of abdominal aortic aneurysms: a large population-based prospective cohort study. *Eur J Vasc Endovasc Surg*. 2014;48:301-307.
9. Schmidt RA, Morrell CN, Ling FS, et al. The platelet phenotype in patients with ST-segment elevation myocardial infarction is different from non-ST-segment elevation myocardial infarction. *Transl Res*. 2018;195:1-12.
10. Cameron SJ, Ture SK, Mickelsen D, et al. Platelet extracellular regulated protein kinase 5 is a redox switch and triggers maladaptive platelet responses and myocardial infarct expansion. *Circulation*. 2015;132:47-58.
11. Bonnefoy PB, Margelidon-Cozzolino V, Catella-Chatron J, et al. What's next after the dot? Residual pulmonary vascular obstruction after pulmonary embolism: from imaging finding to clinical consequences. *Thromb Res*. 2019;184:67-76.
12. Keaton C. Natural history of venous thromboembolism. *Circulation*. 2003;107(suppl 1):I22-30.
13. Mukhopadhyay S, Johnson TA, Duru N, et al. Fibrinolysis and inflammation in venous thrombus resolution. *Front Immunol*. 2019;10:1348.
14. Cameron SJ, Mix DS, Ture SK, et al. Hypoxia and ischemia promote a maladaptive platelet phenotype. *Arterioscler Thromb Vasc Biol*. 2018;38:1594-1606.
15. Elbadawi A, Omer M, Ogunbayo G, et al. Antiplatelet medications protect against aortic dissection and rupture in patients with abdominal aortic aneurysms. *J Am Coll Cardiol*. 2020;75:1609-1610.
16. Fernandes T, Planquette B, Sanchez O, Morris T. From acute to chronic thromboembolic disease. *Ann Am Thorac Soc*. 2016;13(suppl 3):S207-214.

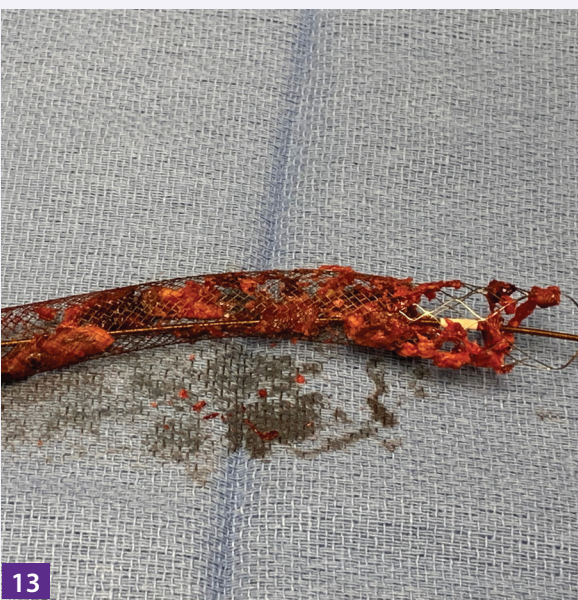
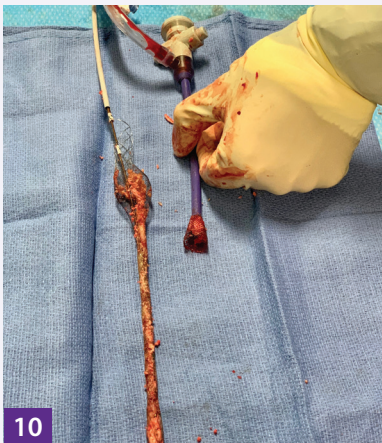
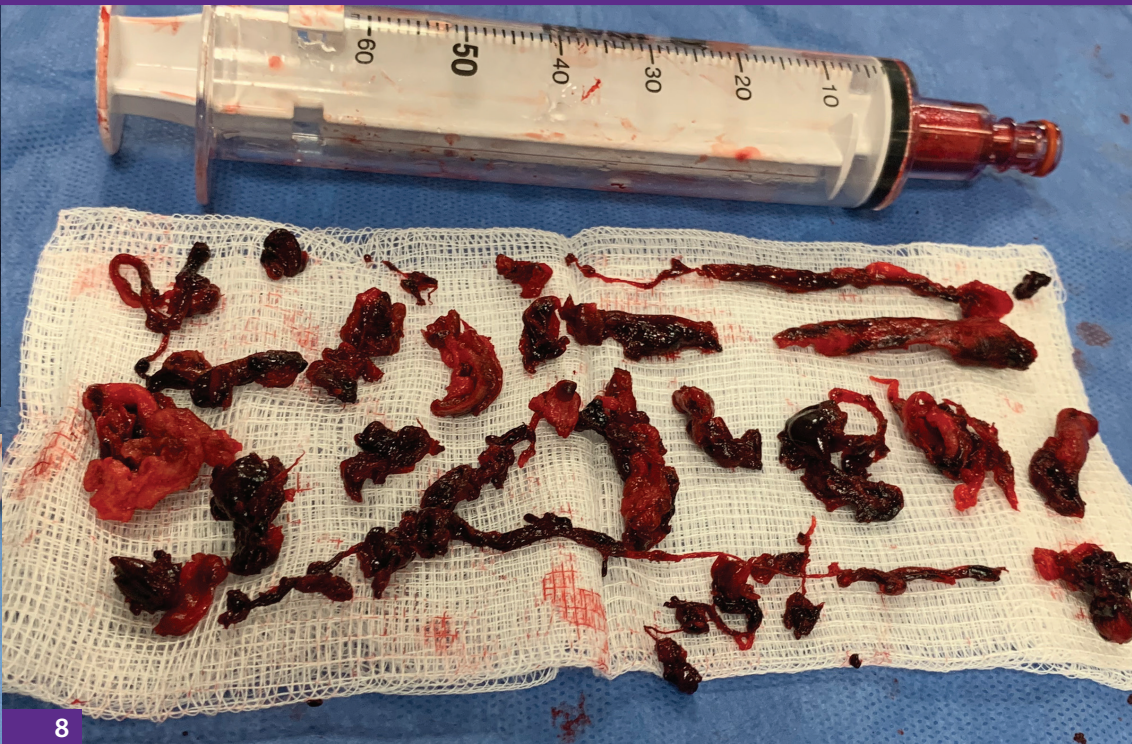
FlowTrieve

Clot extracted from the pulmonary arteries



ClotTrieve

Clot extracted from the lower extremity deep veins



1. Dr. Arash Saemi, University Hospital-University of Missouri, Columbia, Missouri; 2. Dr. Scott Cheney, Covenant HealthCare, Saginaw, Michigan; 3. Dr. Douglas Yim, Avera McKennan Hospital & University Health Center, Sioux Falls, South Dakota; 4. Dr. Haiying Yu, Sparrow Hospital, Lansing, Michigan; 5. Dr. Mehdi Shishehbor, University Hospitals Health System, Cleveland, Ohio; 6. Dr. Naveed Saqib, Memorial Hermann Southeast Hospital, Houston, Texas; 7. Dr. Steven Abramowitz, MedStar Washington Hospital Center, Washington, DC.

8. Dr. Andy Baadh, Regions Hospital, Saint Paul, Minnesota; 9. Dr. Clark Schumacher, Allina Health-Abbott Northwestern Hospital, Minneapolis, Minnesota; 10. Dr. Rahul Patel, Mount Sinai Medical Center, New York, New York; 11. Dr. Ian McLoughlin, Seton Williamson County, Round Rock, Texas; 12. Dr. Kristofer Schramm, UCHealth, Denver, Colorado; 13. Dr. Matthias Albin, Essentia Health, Fargo, North Dakota.

Successful FlowTrierer Thrombectomy After Failed Thrombolysis in a Patient With Massive PE Postcardiac Arrest



Labib Haddad, MD

Interventional and Vascular Radiology
West County Radiological Group
Mercy Hospitals
St. Louis, Missouri
haddadlf@yahoo.com

*Disclosures: Consultant and faculty for
Bard/BD, Medtronic, and Penumbra, Inc.*

A 75-year-old male smoker presented with dyspnea to the emergency department via emergency medical services (EMS). EMS noted that his initial oxygen saturation was 86% on room air and improved to the low 90% range on therapy with a nonrebreather mask. On arrival, he was in respiratory distress and did not indicate a history of VTE. He quickly deteriorated and eventually stopped breathing, experiencing cardiac arrest. Two rounds of cardiopulmonary resuscitation were performed, and one dose of epinephrine was administered. Spontaneous circulation was achieved, with a heart rate of 70 bpm and sinus rhythm. The

patient was then intubated and sedated. However, even with the endotracheal tube checked for correct placement and bilateral breathing sounds, his oxygen saturation remained at approximately 70%. After consulting with the intensive care unit (ICU) team, the patient was admitted to the ICU, and diagnostic imaging was ordered to evaluate for a potential PE. Chest CTA revealed a large saddle PE and RV strain (Figure 1A), leading to activation of the resident PE response team and the decision to initiate thrombolytic therapy. Despite receiving a full dose of tPA (100 mg), the patient's condition continued to deteriorate over the next few hours, with oxygen saturation remaining at approximately 70%. This prompted the decision to intervene with FlowTrierer (Inari Medical) mechanical thrombectomy approximately 4 hours after thrombolytic therapy initiation.

PROCEDURAL OVERVIEW

The patient was transferred to the interventional radiology suite and prepared in a sterile fashion. Access was achieved via a right transfemoral approach, and a 22-F DrySeal sheath (Gore & Associates) was placed and advanced into the inferior vena cava. Subsequently, a selective pulmonary catheter was advanced into the main PA, and bilateral selective pulmonary angiograms were obtained, which demonstrated extensive thrombus within the right lower lobe PA. The Trierer20 (T20) aspiration guide catheter (Inari Medical) was then advanced into the PA to target the right interlobar artery and basal trunk (Figure 1B). The T20 was positioned adjacent to the thrombus, and a vacuum was manually created by pulling back a 60-mL custom syringe connected to a side port tubing connector. When released, this vacuum created a powerful suction, allowing for thrombus retrieval through the catheter and into the syringe. Two aspirations were performed in this manner, which resulted in significant thrombus removal (Figure 1C). Repeat angiography demonstrated restored perfusion and almost no residual thrombus. The patient tolerated the procedure well without any complications. He was extubated less than 24 hours later, with oxygen saturation > 97% on room air. A follow-up CT scan 6 weeks later showed complete resolution of the PE (Figure 1D).

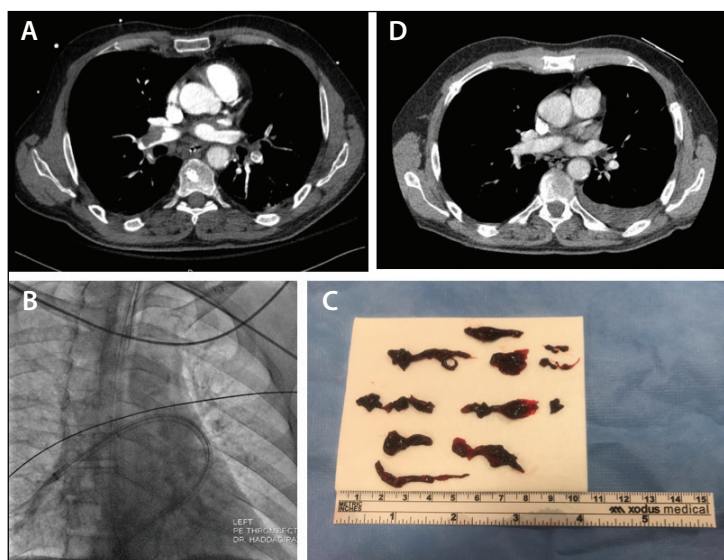


Figure 1. Preintervention CTA (A). PA angiography during thrombectomy showing the advanced T20 aspiration guide catheter (B). Extracted organized thrombus (C). Follow-up CTA (D).

DISCUSSION

We were able to extract large amounts of organized thrombus (Figure 1C) in a critically

THE FLOWTRIEVER AND CLOTTTRIEVER SYSTEMS

Sponsored by Inari Medical

ill patient with PE who was initially treated with thrombolysis. Older, more organized thrombus can present a challenge for lytic approaches because an initially fibrin-dominant state remodels over time to a fibrotic collagenous framework that is resistant to thrombolysis.¹⁻³ A failure to respond to thrombolysis is not uncommon in PE. A 2006 study by Meneveau et al showed that 40 (8.2%) massive PE patients did not respond to thrombolysis after 36 hours and continued to severely deteriorate. Importantly, in those who failed thrombolytic treatment, rescue surgical embolectomy led to a better in-hospital course compared with repeat thrombolysis.⁴

In our case, we had the opportunity to effectively treat the patient with a nonsurgical option: the Inari FlowTriever System. Because the patient continued to deteriorate, it was not an option to allow more time for thrombolysis to possibly take effect. In our experi-

ence, FlowTriever provided a valuable rescue option, allowing us to quickly treat a patient who continued to deteriorate after thrombolysis. Not only were we able to remove his emboli rapidly, but we also saw immediate stabilization of hemodynamics and fast improvement in the patient's oxygenation status. Finally, the 6-week follow-up confirmed the PE had fully resolved, highlighting how an initially complex case presentation was quickly and successfully treated with FlowTriever thrombectomy.

1. Beythien C, Terres W, Gutensohn K, Meinertz T. Thrombus age as a determinant of lysis efficacy of in vitro produced platelet-fibrin thrombi. *Z Kardiol*. 1996;85:661-667.

2. Czaplicki C, Albadawi H, Partovi S, et al. Can thrombus age guide thrombolytic therapy? *Cardiovasc Diagn Ther*. 2017;7(suppl 3):S186-S196.

3. Vedantham S, Piazza G, Sista AK, Goldenberg NA. Guidance for the use of thrombolytic therapy for the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:68-80.

4. Meneveau N, S  ronde MF, Blonde MC, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. *Chest*. 2006;129:1043-1050.

Extensive Thrombolysis-Resistant DVT Successfully Treated With ClotTriever Thrombectomy



Octavio Cosme, MD, FACC, FSCAI

Tampa Cardiovascular Associates
Pepin Heart Institute
Advent Health Hospital
Tampa, Florida

ocosme@tampabay.rr.com

Disclosures: None.

A 67-year-old smoker with history of hypertension and diabetes mellitus was transferred to our department for DVT management due to bilateral leg swelling. He had a history of diverticulitis and a recent but resolved gastrointestinal bleed that prompted prolonged hospitalization. During his hospital stay, a comprehensive workup uncovered meningioma, and he was furthermore diagnosed with extensive bilateral DVT. The meningioma surgery was postponed to a future date, but his symptomatic DVT warranted immediate intervention. Ultrasound-assisted catheter-directed thrombolysis (CDT) was initiated with the EkoSonic endovascular system (Boston Scientific Corporation) after the patient was cleared to receive the treatment by both his gastrointestinal and neurosurgery teams. After 24 hours of thrombolysis, the patient was

brought back to the catheterization laboratory for removal of the catheter and follow-up venography via right popliteal access. Post-CDT venography revealed persistent extensive thrombosis of the right femoral vein, right common femoral vein, and right iliac vein (Figure 1A and 1B). To address this thrombolysis-resistant occlusion, the decision was made to perform mechanical thrombectomy with the ClotTriever System (Inari Medical).

PROCEDURAL OVERVIEW

The 6-F sheath that was in place for venography was exchanged with the dedicated 13-F ClotTriever specialty sheath. The ClotTriever sheath has an attached funnel to maximize thrombus capture and allow insertion of the ClotTriever catheter over a 0.035-inch guidewire. After advancing and positioning the ClotTriever tip beyond the thrombosed vessel segments, the catheter was unsheathed, deploying the laser-cut coring element with its attached woven nitinol collection bag. Thrombectomy was performed by slowly pulling the ClotTriever catheter back toward the sheath, coring thrombus from the vessel wall. Once the initial pull-back was completed, the ClotTriever catheter was collapsed and removed from its sheath. Outside the body, collected thrombus was cleaned off the device to prepare it for reinsertion. The process was repeated two additional times for a total of three passes, and a significant amount of organized thrombus was collected. Due to further persistent stenoses in the right iliac and mid saphenous veins, balloon angioplasty of both segments was performed, followed by intravascular

THE FLOWTRIEVER AND CLOTTRIEVER SYSTEMS

Sponsored by Inari Medical

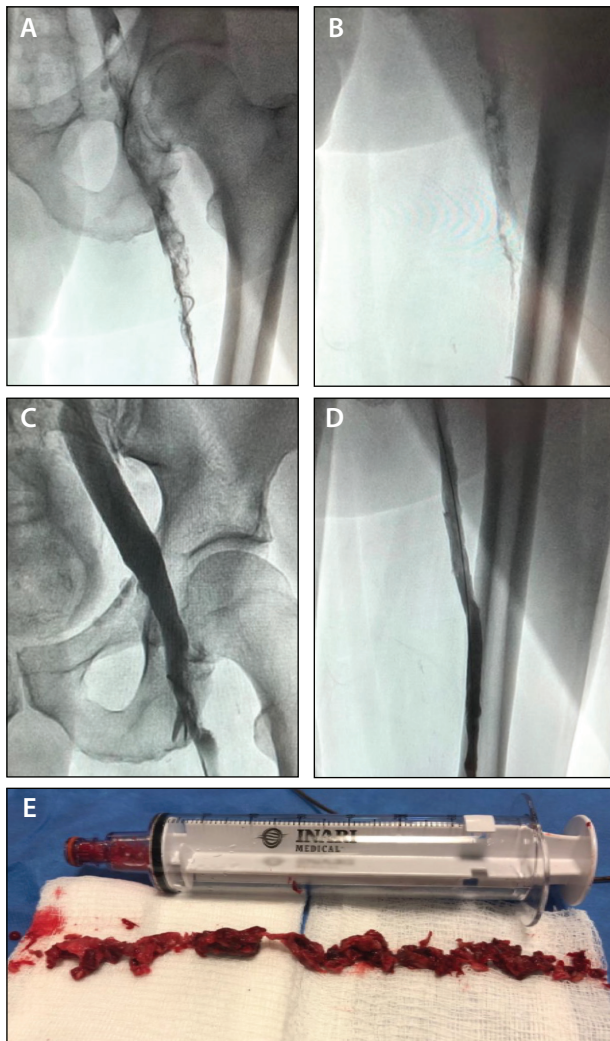


Figure 1. Venography of the iliac and common femoral vein (A) and femoral vein (B) after 24 hours of CDT and before ClotTriever thrombectomy. Venography of the iliac and common femoral vein (C) and superficial femoral vein (D) after ClotTriever thrombectomy. Removed organized and thrombolysis-resistant thrombus (E).

ultrasound and fluoroscopy-guided stenting of an iliac compression (consistent with May-Thurner syndrome) using a 16- X 60-mm Wallstent (Boston Scientific Corporation). Follow-up venography confirmed an excellent result, with a patent Wallstent and no residual thrombus in the treated segments (Figure 1C and 1D). After removing all catheters and the sheath, hemostasis was achieved via mattress suture. The patient toler-

ated the procedure well with no complications. His treatment plan included anticoagulation for the next 6 months, after which neurosurgery was planned to address the meningioma.

DISCUSSION

We successfully treated an extensive thrombolysis-resistant DVT with ClotTriever thrombectomy and subsequent iliac vein stenting. The removal of large amounts of organized thrombus highlights the potential to successfully address DVT with ClotTriever thrombectomy, independent of thrombus age (Figure 1E). Thrombus can remodel to a state that is resistant to anticoagulation and thrombolytic therapy as soon as 15 days after formation,¹ which can cause long-term adverse consequences for patients. In a study of various combinations of CDT and pharmacomechanical thrombolysis, Avgerinos et al reported an immediate treatment failure in 12% of patients.^{2,3} Importantly, both the Avgerinos et al study and comparable work by Haig et al showed that primary patency loss was significantly associated with incomplete thrombolysis and patency was linked to PTS risk.^{2,3} Leaving a patient with residual vascular obstruction after DVT treatment not only influences PTS risk⁴ but has also been linked to a higher risk for DVT recurrence.⁵⁻⁷ Based on these data, a strategy of acutely removing as much thrombus burden as possible seems desirable.

In this case, the ClotTriever mechanical thrombectomy device was highly effective in removing organized thrombus, allowing us to achieve an excellent result with no residual vascular obstruction. The novel device adds a valuable option for treatment of both acute and thrombolysis-resistant DVT. Future studies are needed to determine the potential of the ClotTriever to improve longer-term clinical outcomes. ■

1. Fernandes T, Planquette B, Sanchez O, Morris T. From acute to chronic thromboembolic disease. *Ann Am Thorac Soc*. 2016;13(suppl 3):S207-214.
2. Avgerinos ED, Hager ES, Naddaf A, et al. Outcomes and predictors of failure of thrombolysis for iliofemoral deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2015;3:35-41.
3. Haig Y, Enden T, Slagvold CE, et al. Determinants of early and long-term efficacy of catheter-directed thrombolysis in proximal deep vein thrombosis. *J Vasc Interv Radiol*. 2013;24:17-24; quiz 26.
4. Dronkers CEA, Mol GC, Maraziti G, et al. Predicting post-thrombotic syndrome with ultrasonographic follow-up after deep vein thrombosis: a systematic review and meta-analysis. *Thromb Haemost*. 2018;118:1428-1438.
5. Carrier M, Rodger MA, Wells PS, et al. Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis. *J Thromb Haemost*. 2011;9:1119-1125.
6. Donadini MP, Ageno W, Antonucci E, et al. Prognostic significance of residual venous obstruction in patients with treated unprovoked deep vein thrombosis: a patient-level meta-analysis. *Thromb Haemost*. 2014;111:172-179.
7. Tan M, Mos ICM, Klok FA, Huisman MV. Residual venous thrombosis as predictive factor for recurrent venous thromboembolism in patients with proximal deep vein thrombosis: a systematic review. 2011;153:168-178.