Supplement to

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ACUTE PULMONARY EMBOLISM

New insights to enhance our understanding and improve our response

PERT CONSORTIUM®

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On behalf of the members of the PERT Consortium® and in conjunction with our corporate partners, we are delighted to publish this supplement to *Endovascular Today* focusing on pulmonary embolism (PE). PE is a significant public health risk; it is the third leading cause of cardiovascular mortality behind stroke and myocardial infarction, yet awareness, prevention, and treatment lag behind. According to the Centers for Disease Control and Prevention, PE may cause 60,000 to 100,000 deaths in the United States annually.[1] The PERT Consortium® was formed in 2013 with the aim of bringing together multiple disciplines to improve the care of patients with PE. What began as a true "coalition of the willing" has grown into a global phenomenon, with hospitals in countries such as China, Brazil, and Kuwait having embraced multidisciplinary care of patients with acute PE.

The recent COVID-19 pandemic has brought the care of patients with PE to the forefront of medical science, and the PERT Consortium® is leading the charge. Data are emerging that clearly link the virus to thrombosis and PE. Challenges in the diagnosis and treatment of patients with COVID-19 and PE abound, and the PERT Consortium® has taken a leadership role in addressing this issue. Our recently created COVID-19 PE database will undoubtedly contribute to a better understanding of PE in conjunction with the novel coronavirus.

Given that the PERT Consortium® is a multispecialty organization, the articles contained within this supplement span multiple interests and reflect the breadth of experience and knowledge of the members of the PERT Consortium®. From an in-depth examination of the basic science of thrombosis and platelet function to a thorough review of current interventional techniques and results for PE, the PERT Consortium® represents all aspects of PE care. Our commitment to improving understanding and care of PE is perhaps best demonstrated by our PERT registry, an ongoing initiative with both research and quality improvement capabilities. The PERT registry currently contains discrete data points for more than 3,400 patients who experienced PE, representing the contribution of nearly 30 centers.

Finally, our yearly educational meeting on PE, held each October and attended by over 500 people, will be a virtual meeting this year due to the pandemic. We are very excited by the potential of a virtual platform to expand and enhance the educational value of this one-of-a-kind meeting. Visit pertconsortium.org for upcoming details.

We at the PERT Consortium® are passionate about the science, prevention, and treatment of PE, and we hope this passion is reflected in this supplement. Thank you for your interest.

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Board of Directors

Richard Channick, MD
President, PERT Consortium®

1. Centers for Disease Control and Prevention. Data and statistics on venous thromboembolism. Accessed June 9, 2020. https://www.cdc.gov/ncbddd/dvt/data.html

COVID-19 and VTE: What We Know and What We Don't Know

A review of what is currently known about the role of inflammation, markers of disease in coagulation studies, pathologic and clinical evidence of thrombosis, and the approach to anticoagulation of COVID-positive hospitalized patients.

BY OREN A. FRIEDMAN, MD; EUGENE YURIDITSKY, MD; AND JAMES HOROWITZ, MD, FACC

In December 2019, an outbreak of novel coronavirus SARS-CoV-2, subsequently termed COVID-19, led to a global pandemic. At the time of this writing, more than 7.2 million cases and 411,000 deaths have been reported worldwide, with nearly 2 million cases and over 110,000 deaths in the United States.[1] Reports in the United States suggest a high intensive care unit (ICU) mortality and a stressed health care system.[2,3] It was soon recognized that the virus can manifest with high levels of inflammation, abnormal coagulation studies, pathologic evidence of microvascular thrombosis, and clinical evidence of large vessel thrombosis.

ROLE OF INFLAMMATION

SARS-CoV-2 infection is characterized by a high inflammatory state associated with elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, and interleukin (IL)-6 levels.[4] The inflammation plays an integral role in the pathology of the virus, and many anti-inflammatory and immunomodulatory treatments including IL-6 inhibitors, hydroxychloroquine, and JAK inhibitors have been used. In fact, higher levels of proinflammatory cytokines have been associated with worse disease.[5] Inflammation and coagulation are intricately linked at an evolutionary level, and disseminated intravascular coagulation, sepsis-induced coagulopathy, and deep vein thrombosis (DVT) are common in the highly inflamed states of severe infection.[6] Inflammation and its subsequent effects on coagulation are therefore not unique to COVID-19, but there is evidence that the degree of hypercoagulability in COVID-19 may warrant a different therapeutic approach. It is likely that the unique phenotype of inflammatory storm with COVID-19 will lead to a similarly unique coagulation profile.

LABORATORY CLOTTING STUDIES

The coagulation profile in COVID-19 typically reveals a normal prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), platelet count, and elevated fibrinogen and D-dimer levels. A classic disseminated intravascular coagulopathy pattern is rare. There is a link between elevated D-dimer and mortality. In a large study of 1,099 COVID-19 patients from > 550 hospitals in China, D-dimer was found to predict severe illness and mortality.[7] In response, many have advocated for serially trending D-dimer as a marker of disease and even to guide clinical decisions about anticoagulation or anti-inflammatory treatment.

Thrombocytopenia is less common with COVID-19, although one large meta-analysis of nine studies found that it was more common in patients with severe disease.[8] Elevated von Willebrand factor and factor VIII levels have also been described. The presence of antiphospholipid (APL) antibodies may be common, with one multicenter trial finding positive results in 50 of 57 patients who were tested.[9] However, the clinical implications of APL antibodies are not clear, as their presence can be seen in active infections, and the diagnosis of APL syndrome requires repeated positive results over time.

Thromboelastography (TEG) has been increasingly used in various clinical scenarios and may be a better tool to characterize clotting activity than traditional laboratory assays. TEG also allows separation of heparin effect with the use of heparinase assays. In a small cohort study of 20 critically ill COVID-19 patients, 19 of 20 had hypercoagulable TEG results, and elevated maximal amplitude (MA) on TEG conferred 100% sensitivity for thrombotic results. The MA on TEG was a better predictor of thrombosis than PT, INR, PTT, or platelet levels.[10] In a study of critically ill patients with COVID-19, Yuriditsky et al found a large proportion to have hypercoagulable TEG profiles. Parameters related both to coagulation factors, as well as fibrinogen and platelet function (MA) were commonly deranged.[11]

PATHOLOGIC EVIDENCE OF CLOT

Despite the high worldwide death rate with COVID-19, there are relatively few autopsy studies. Examining the

TABLE 1. ANTICOAGULATION RECOMMENDATIONS FOR PATIENTS WITH COVID-19

Anticoagulation Forum[25]	ISTH[26]	NIH[27]
▪ Recommend use of anti-Xa rather than aPTT to monitor UFH dosing ▪ Recommend standard dose of prophylaxis for noncritically ill patients ▪ For critically ill patients, increase dose of enoxaparin to 40 mg or 0.5 mg/kg subcutaneously twice daily or heparin to 7,500 units three times a day based on expert opinion ▪ Recommend against using biomarker thresholds (ie, D-dimer) as the sole reason to trigger escalations in anticoagulant dosing outside the setting of a clinical trial ▪ Recommend against extended routine VTE prophylaxis to discharged patients ▪ Recommend an evaluation at discharge for ongoing VTE risk factors balanced with bleeding risks to identify a population of patients similar to those in the rivaroxaban and betrixaban trials who may benefit from extended prophylaxis	▪ Recommend trending platelet count, PT, D-dimer, and fibrinogen, and if these parameters worsen, consider more aggressive critical care support and/or "experimental therapies" ▪ Use prophylactic "low-dose" LMWH in all patients in the absence of contraindications (bleeding and platelet count < 25 X 10^9/L) ▪ Note that bleeding is rare in the setting of COVID-19	▪ Insufficient data to suggest continuous monitoring of clotting parameters to guide management decisions ▪ Hospitalized patients should receive VTE prophylaxis per the standard of other hospitalized patients with VTE ▪ Limited data exist to recommend for or against increasing anticoagulant dosing for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial ▪ Evaluate for thromboembolic disease in patients with rapid deterioration of pulmonary cardiac or neurologic function or loss of peripheral perfusion

Abbreviations: aPTT, activated partial thromboplastin time; ISTH, International Society of Thrombosis and Haemostasis; LMWH, low-molecular-weight heparin; NIH, National Institutes of Health; PT, prothrombin time; UFH, unfractionated heparin; VTE, venous thromboembolism.

limited COVID-19 autopsy case series, several found microvascular thrombosis, including fibrinous thrombi in small pulmonary arterioles and an increased amount of megakaryocytes on pulmonary pathology.[12,13] Similarly, a series from Italy found fibrin thrombi in small arterial vessels in 87% of autopsies.[14] Another small series from New York found microvascular thrombosis as well as endothelial injury and complement deposition in lung and skin biopsies.[15] This series was notable in that it demonstrated a vascular tropism of the virus in more than one organ and also raised the possibility that complement deposition may contribute to the vascular injury pattern.

CLINICAL EVIDENCE OF THROMBOSIS

In addition to pathologic evidence of small vessel thrombosis, an even larger number of studies have identified clinically relevant large vessel thrombosis. A single center in Lille, France, noted a higher than expected number of patients with pulmonary embolism (PE) in their first consecutive 107 patients. They compared the COVID-19 patients to a matched cohort of influenza patients from 2019 and found PE was more frequent (20.6% vs 7.5%).[16] A small study of 26 critically ill COVID-19 patients on either prophylactic or therapeutic anticoagulation found a very high rate of thromboembolic events (69%; 18 DVT and 6 PE). They performed systematic screening with ultrasound and CTA for unexplained respiratory failure, which may have impacted the high percentages.[17] A single French center reviewed 34 ICU patients on mechanical ventilation due to COVID-19. They similarly screened all patients for DVT and found 65% had DVT on admission and 79% after 48 hours.[18]

A multicenter cohort study of 184 patients in the Netherlands found a 31% cumulative incidence of thrombosis, including 25 PEs and three arterial thromboses. All patients were receiving prophylaxis. The authors recommended higher doses of anticoagulation prophylaxis based on their findings.[19] Another multicenter prospective study from four French ICUs analyzed 150 COVID-19 patients with acute respiratory distress syndrome, finding 64 clinically relevant thrombotic complications. PE predominated, but ischemic strokes and clotting of renal replacement therapy were also common.[9]

The totality of these aforementioned findings suggests COVID-19 is associated with a high percentage of venous thromboembolism (VTE), but it is important to recognize that VTE is common in critically ill patients in general. Indeed, one study found a 29% rate of PE in critically ill patients sent for CTA.[20] Noncritically ill patients hospitalized with pneumonia also have an elevated risk for VTE related to active infection, immobility, and an elevated inflammatory state. Additional risk factors including age, obesity, cancer, heart failure, and prior history of VTE. Obesity is of interest, as it has been linked to severe disease with COVID-19.[2,21] Irrespective of

AUTHORS' PROPOSED VTE THROMBOPROPHYLAXIS RECOMMENDATIONS FOR HOSPITALIZED COVID-19 PATIENTS

- All hospitalized COVID-19–positive patients should receive standard VTE thromboprophylaxis
- Enoxaparin 40 mg twice daily should be used for obese patients
- Accelerated thromboprophylaxis (enoxaparin 40 mg subcutaneously twice daily or 0.5 mg/kg subcutaneously twice daily) should be used in critically ill patients
- Empiric therapeutic anticoagulation for a short duration should be considered on an individual patient basis
  - High-risk features include critically ill, highly elevated (two- to threefold higher) D-dimer levels, acute kidney injury, elevated dead space fraction on mechanical ventilation, rising inflammatory markers
- Follow anti-Xa levels for unfractionated heparin dosing as the prevalence of antiphospholipid antibodies may render the partial thromboplastin time unreliable
- Consider extended postdischarge prophylaxis with either rivaroxaban or betrixaban in selected patients after weighing risks of clotting versus thrombosis. Patients should be considered based on the populations who benefited in the MAGELLAN and APEX trials, respectively[28,29]
- Ongoing review of the literature is a must. Randomized controlled trials for anticoagulation are enrolling and have the potential to be practice-changing

COVID-19, a dose of enoxaparin 40 mg subcutaneously twice daily has been shown to be superior to standard dosing in morbidly obese patients.[22] Whether COVID-19 infection is truly associated with a greater occurrence of thrombosis than other severe viral illnesses is an area of active investigation.

TREATMENT

Unless there are contraindications, all hospitalized COVID-19 patients should receive VTE prophylaxis. However, there is debate as to whether COVID-19 patients should receive accelerated prophylaxis or therapeutic anticoagulation in the absence of diagnosed thrombosis. Some suggest full-dose anticoagulation not only to prevent large vessel clot but to mitigate microvascular thrombosis and capillary injury. However, prior trials of anticoagulation in sepsis have not shown a benefit. It is also unclear whether clinicians should follow D-dimer and other markers to guide decisions over anticoagulant intensity. Although there are ongoing randomized trials to help answer these questions, all data are currently retrospective. A retrospective analysis of 449 patients with severe COVID-19 (respiratory rate > 30 breaths/min; PaO_2/FiO_2 < 300 mm Hg) found that those with an elevated sepsis-induced coagulopathy score and those with elevated D-dimer (> 3 µg/mL) had lower mortality when treated with heparin prophylaxis.[23] Another larger retrospective study of 2,773 patients from a single center in New York City found an in-hospital mortality rate of 22.5% in patients receiving therapeutic anticoagulation and 22.8% in those who did not receive anticoagulation. In a subset of 395 mechanically ventilated patients, 29% who received anticoagulation and 62.7% who did not receive anticoagulation died.[24]

Societies including the International Society on Thrombosis and Haemostasis (ISTH), American Society of Hematology, National Institutes of Health (NIH), and the Anticoagulation Forum have published guidelines about anticoagulation for COVID-19–positive patients (Table 1),[25-27] and the authors' proposed recommendations are noted in the Sidebar.[28,29] The ISTH and NIH recommend standard prophylactic doses of low-molecular-weight heparin only.[26,27] The Anticoagulation Forum recommends a standard dose for noncritically ill patients and an accelerated dose of enoxaparin 0.5 mg/kg subcutaneously twice daily or heparin 7,500 units three times a day for critically ill patients.[25]

SUMMARY

COVID-19 infection appears to be associated with a high rate of venous thromboembolic disease. There is pathologic evidence of small vessel thrombosis, and observational clinical studies have shown high rates of DVT and PE. Many clinicians have begun to employ higher doses of thrombosis prophylaxis and even therapeutic anticoagulation for more severe cases of COVID-19, although data regarding benefit are sparse. The community is eagerly awaiting more data, especially results of randomized trials of full versus prophylactic doses of anticoagulation. Until then, several societies have published recommended anticoagulation guidelines for COVID-positive patients, and we have provided our recommendations. ■

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The PERT Consortium® COVID-19 PE Registry: Introduction and Implementation

A discussion of the goals of the registry and what types of data are being collected and reported.

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The novel coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China, in December 2019 and is currently spreading around the world, with over 9.2 million cases and more than 476,000 deaths as of June 24, 2020.[1,2] Although patients often present with respiratory insufficiency, those with the most severe form of the disease develop multiorgan failure. In those patients, one of the most significant poor prognostic features is the development of coagulopathy.[3] Early studies out of China have demonstrated that individuals who have elevated circulating D-dimer levels are at significantly increased risk of mortality compared with individuals who do not.[3,4] This finding has been confirmed in several other studies around the world.[5-8] Research has also shown that, similar to the SARS-CoV virus, pathologic fibrin thrombi are found within the pulmonary vasculature of affected patients. The coagulopathic state associated with COVID-19 and the resultant increased thrombin generation can increase the risk of venous thromboembolism (VTE), including pulmonary embolism (PE). Prior to the COVID pandemic, the incidence of PE was estimated at 1 to 2 per 1,000 individuals in the United States per year, accounting for at least 100,000 deaths per year.[9] Although the exact incidence of VTE associated with COVID-19 is currently unknown, reports range from as low as 1% in general wards to as high as 31% in intensive care units.[5,10-19] Given the prothrombotic state conferred by COVID-19 infection and the resultant higher incidence of PE and its associated morbidity and mortality in affected patients, there is an urgent need to study this unique population. Understanding the characteristics, prevention and treatment modalities, and outcomes of patients with COVID-19 who develop PE and how they compare to PE patients without COVID-19 is crucial as this pandemic continues. By characterizing the findings in COVID-19 patients with PE through the Pulmonary Embolism Response Team (PERT) Consortium® COVID-19 PE registry, future diagnostic and treatment algorithms can be optimized to improve outcomes and reduce related morbidity and mortality.

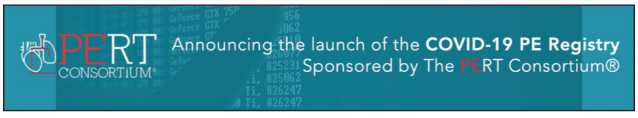

Figure 1. Announcement of the COVID-19 PE registry on the PERT Consortium® website (pertconsortium.org).

THE PERT CONSORTIUM®

The PERT Consortium® is a 501(c)(3) nonprofit organization founded in 2016 for the purpose of promoting the multidisciplinary care of patients with PE. The PERT Consortium® is ideally positioned to implement this essential project (Figure 1). Its membership represents > 150 institutions and > 1,500 clinicians in the United States and globally, and it is focused on improving outcomes for patients with PE by advancing its recognition, diagnosis, and treatment. PERT teams are on the front lines of managing patients with PE at their institutions and therefore are in the essential position to treat COVID-positive patients with PE. Moreover, the PERT Consortium®, in conjunction with the Boston Clinical Research Institute, manages an already established and mature database that is the largest prospective United States registry of PE patients to date. The PERT Consortium® is leveraging the infrastructure of this existing registry, which utilizes the user-friendly and rapidly scalable REDCap Cloud platform, to collect the necessary information for the COVID-19 PE registry and quickly scale it up to obtain data and address the impact of this rapidly growing disease.

THE COVID-19 PE REGISTRY

Goals and Participation

The goal of the COVID-19 PE registry is to utilize the existing infrastructure of a robust multicenter PE database to (1) identify the clinical characteristics, diagnostic strategies, treatment approach, and short- and long-term outcomes of all patients diagnosed with both COVID-19 and PE; and (2) compare the mechanisms of triage and systems of care and delivery between patients with

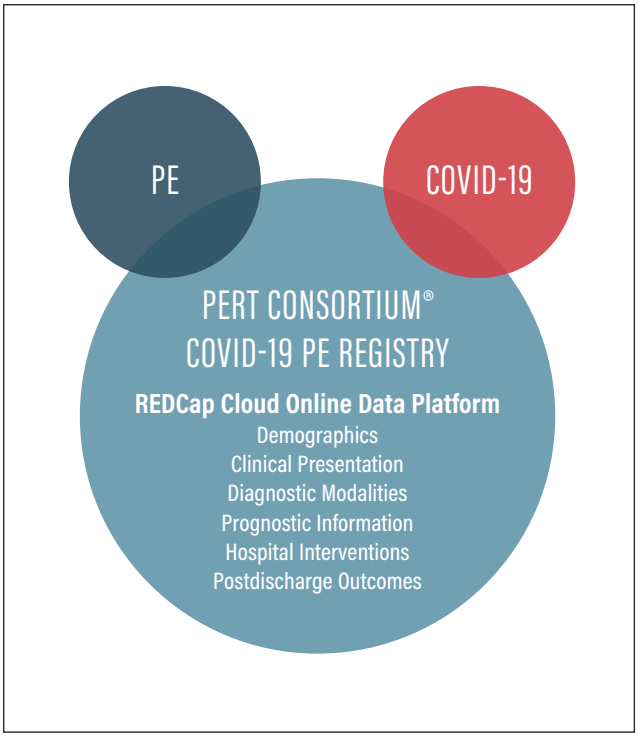

Figure 2. Embedding the COVID-19 PE registry into the existing PERT Consortium® database.

both COVID-19 and PE to historical PE controls from the existing PERT registry. This is being accomplished by collecting data from established participating sites by nesting a distinct COVID-19 PE registry within the existing data collection tool and inviting any other institution (regardless of membership status in the PERT Consortium® or participation to date in the registry) to join the COVID-19 PE registry and submit data for every PE occurring in COVID-19 patients at their institution (Figure 2). Participation is being offered without any cost centrally. Central institutional review board approval (IRB) is being orchestrated and achieved by the PERT Consortium® or local IRB approval at individual sites if preferred.

PERT Consortium® has created a deidentified observational registry within an existing large multi-institutional database dedicated to the study of patients with PE to capture the clinical characteristics and outcomes of patients with confirmed COVID-19 and PE. A major benefit of this registry is the ability to utilize historical data from the existing PE registry as a control group.

The PERT Consortium® contributing member institutions exist throughout the United States as well as in Europe, China, Asia, and Africa. Several of the participating United States institutions are located within current

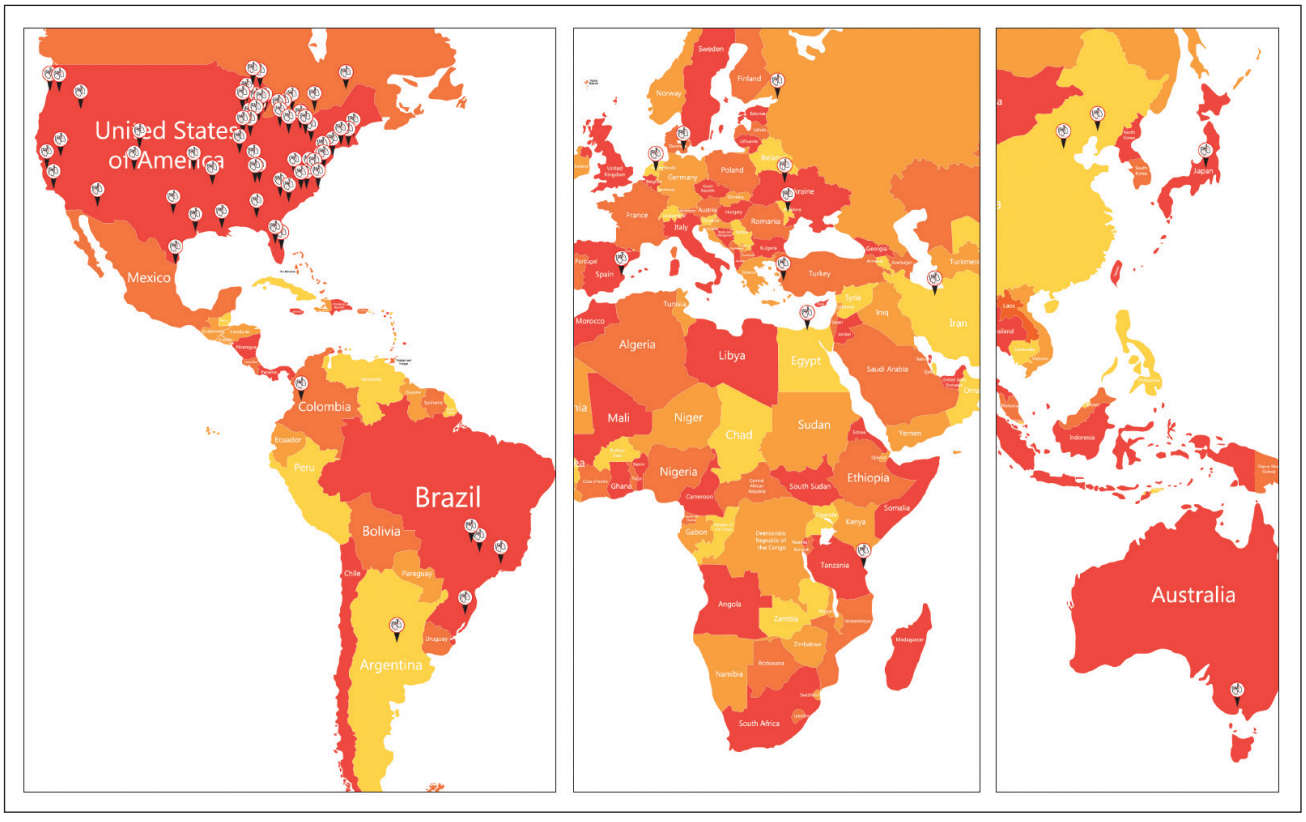

Figure 3. Map of PERT Consortium® sites around the world.

CURRENT PARTICIPATING SITES IN THE PERT CONSORTIUM® COVID-19 PE REGISTRY

- Abbott Northwestern
- Advent Health Orlando
- Allegheny Health
- AtlantiCare
- Augusta University
- Aurora Health
- Baptist Health System
- Baptist Health South Florida
- Beaumont Health
- Beth Israel Deaconess
- Cancer Treatment Centers of America
- Carle Foundation
- Catholic Health/Mercy Hospital of Buffalo
- Cedars-Sinai
- Christiana Care
- Cleveland Clinic
- Columbia University
- Community Foundation of Eastern CT
- Detroit Medical Center
- Duke University
- East Carolina University
- Edward-Elmhurst Heart Hospital
- Ellis Hospital
- Emory University
- Englewood Hospital
- Essentia Health St. Mary's Medical Center
- Gates Vascular/Kaleida Health
- Geisinger
- Grady Memorial
- Grandview Medical Center
- Gundersen Lutheran
- Henry Ford Hospital
- Infirmary Health
- Inova
- Jacobi Medical Center
- Jamaica Hospital
- Jefferson
- Jefferson Township
- Kobe University
- Lahey Medical Center
- Lancaster General
- Lenox Hill Hospital
- Loyola
- MacNeal Hospital
- Marshfield Clinic
- Massachusetts General Hospital
- Mayo Clinic
- Medical University of South Carolina
- MedStar
- Memorial Hermann
- Methodist Hospital
- Mission Hospital
- Mount Sinai Health System
- Newton-Wellesley Hospital
- Northeast Georgia Medical Center
- Northwestern Memorial/Bluhm
- NYU Langone
- Ohio Heart & Vascular
- Ohio State University
- Oklahoma State University
- Palos Community Hospital
- Penn Medicine Piedmont
- Providence Hospital
- Rhode Island Hospital
- Riverside Medical Center
- SSM Health
- Saint Vincent Hospital
- Southern Illinois Healthcare
- Spectrum Health
- St. Joseph Mercy
- Temple University Hospital
- Thomas Jefferson University Hospital
- Trinity Health
- UC Davis
- UC Health
- UW Health
- University of California
- University of Chicago
- University of Kentucky
- University of Michigan
- University of Minnesota
- University of Pittsburgh
- University of Rochester
- University of Tennessee
- University of Virginia
- University of Wisconsin
- Vanderbilt
- Weill Cornell
- Yale University

COVID-19 hot spots, which ensures that a cohort enriched with affected patients will be entered into the COVID-19 PE registry. Current participating sites are listed in the Sidebar, and a map of participating worldwide sites is shown in Figure 3.

Data Collection

The PERT Consortium® database, created in April 2018, is a robust clinical research and quality improvement database with > 200 discrete data elements per patient. Currently, data from > 3,500 patients with PE from the pre-COVID-19 era are included. Over 25 studies on PERTs have been published to date.[20-28] Prior American Heart Association and other societal position statements were spearheaded by PERT members.[29] More recent algorithms for management of acute PE have been published by the PERT Consortium® itself; these are living documents that are constantly being reviewed and updated by the Consortium. In October 2019, the PERT Consortium® hosted its 5th annual scientific session on management of acute PE with nearly 600 international attendees. More recently, PERT Consortium® has hosted several COVID-19 specific webinars, each with more than 600 attendees. In the PE world, PERT Consortium® is currently looked upon as the organization that provides the most current multidisciplinary guidance for PE management, as well as direction for quality assurance and scientific exploration that is focused on filling evidence gaps.

The COVID-19 PE registry allows physicians and other health care providers to enter data into a web-based data collection form (REDCap Cloud). Relevant COVID-19 PE elements have been identified and defined and are embedded in the new registry. This COVID-19 PE registry is open for participation to any institutional site, free of charge and regardless of current membership in the PERT Consortium®. The new COVID-19–related elements are also now nested in the existing multicenter registry of patient-level data. Data points collected include details on demographics, clinical presentation, diagnostic modalities, prognostic information, interventions, and

in-hospital and postdischarge outcomes. Reported outcomes include death, recurrent PE, bleeding, length of stay, readmission, and lab values when available. The existing multicenter registry will continue to be managed by the PERT Consortium®, in collaboration with Boston Clinical Research Institute serving as the host and data coordinating center. Importantly, both the existing and new focused registry operate with central IRB approval and waiver of consent.

Institutional Review Board

The COVID-19 PE registry is submitted as human subjects research exempt. Obtaining a non–human subjects research determination has facilitated the speed and efficiency of implementation and subsequent data collection. Data are completely deidentified and the registry complies with HIPAA (Health Insurance Portability and Accountability Act) safe harbor deidentification requirements. All steps necessary to comply with General Data Protection Regulation requirements for collecting and anonymizing personal data are being followed. Once entered, data are analyzed and observations are reported regarding clinical practice and patient outcomes in aggregate form to provide near-real-time insights to guide clinicians as they care for COVID-19 patients with PE.

Patient Population

The COVID-19 PE registry is enrolling patients with confirmed COVID-19 and confirmed or highly presumptive PE. A confirmed COVID-19 diagnosis is defined as a positive result on high-throughput sequencing or real-time reverse transcription polymerase chain reaction assay of nasal and pharyngeal swab specimens. For this registry, a PE diagnosis must be confirmed by CT, echocardiography, or MRI; although in the COVID era, a presumptive diagnosis of PE without absolute confirmation of thrombus in the pulmonary arteries by CT or MRI is possible. It is not the goal or intent of this COVID-19 PE registry to collect data indiscriminately on all COVID-19 patients; thus, patients with a known diagnosis of COVID-19 but without a confirmed or presumptive diagnosis of PE are excluded. Likewise, patients with known chronic PE but not acute PE and those with PE but without documented COVID-19 infection are excluded. However, interested sites are encouraged to join the existing main PERT PE registry and enter non-COVID PE patients into that registry. Importantly, the existing PERT PE database will provide a group of "controls" against which the COVID-positive PE patients can be compared. All central fees have been waived, and thus participation is free of charge for both the main PERT PE registry and the focused COVID-19 PE registry.

Results

The COVID-19 PE registry will enable the research committee of the PERT Consortium® to rapidly obtain information on the diagnosis, treatment, and outcomes of patients with concurrent COVID-19 and PE. To date, similar information—such as that from China, Italy, the United States, and elsewhere—are being reported from single centers.[5,10-19] The PERT Consortium® will examine this invaluable information in detail. The availability of data from a comparative cohort may provide insights into the unique aspects of PE in COVID-19. Importantly, the existing broad-based participation of the PERT Consortium®, with its large membership and infrastructure, will enable collection, analysis, and dissemination of information in a timely manner.

DISCUSSION

The PERT Consortium® recently published a consensus practice document on the care of patients with PE, which included detailed algorithms on diagnosis, treatment, and follow-up.[30] Important outcomes from the COVID-19 PE registry will include modification of those algorithms specifically targeted to COVID-19 and PE patients, as well as recommendations on how to best care for these critically ill patients. Currently, in some areas, the mortality rate of COVID-19 patients who are admitted to critical or intensive care units approaches 50%.[31] The ultimate goal of the COVID-19 PE registry is to influence prevention and treatment in concrete ways that can decrease the morbidity and mortality associated with this disease.

A potential limitation of this registry is that we are including both confirmed PE and some presumed PE patients. Use of imaging modalities can be challenging due to concerns of viral transmission; however, this limitation may also be a strength. As we learn about "real-world" management of documented and presumed PE in this challenging environment, we will also learn about the characteristics of COVID-19 and PE, including the precursors, signs, symptoms, and responses to treatment. This information will be useful to identify patients who may be at risk of developing PE and, in turn, how best to modify prevention and treatment strategies. Given that this pandemic will not be eradicated in the near future, this information is critical to the medical world.

CONCLUSION

The COVID-19 PE registry will provide expedient public reporting of aggregate data on the clinical characteristics and outcomes of patients with COVID-19 and PE in order to facilitate clinical decision-making and allocate resources. The PERT Consortium® already has successful mechanisms to quickly disseminate updates on the science of PE, including those that might emanate from analysis of COVID-19 PE registry data. These include the annual PERT scientific meeting, as well as regular national/international

webinars and other educational events that reach thousands of health care providers. The PERT Consortium® also has a robust website and provides monthly emails (entitled "PERTinent Updates"), relied upon by thousands of providers to stay current with the most important scientific discoveries in PE, as well as research and practical advice regarding optimal management of acute PE. Periodic dissemination of aggregate data from the COVID-19 PE registy to contributing centers and the clinical community at large will shape real-time decision-making and patient-level care as the pandemic evolves. Moreover, expedited publication of these data in high-impact journals will reach clinicians around the globe and positively impact patient care going forward. By leveraging existing resources to create the COVID-19 PE registry, it will be efficient, cost-effective, and scientifically powerful. ■

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The Search for the Holy Grail of New PE Devices

A review of interventional thrombolytic and catheter-based therapies for PE treatment.

BY MAHIR ELDER, MD, FACC, FSCAI, AND TERRY BOWERS, MD, FACC, FSCAI

Pulmonary embolism (PE) is a growing field in endovascular intervention, with a robust ongoing search for the endovascular "holy grail" to treat this life-threatening disease. Patients presenting with PE are now routinely risk-stratified with PE response team (PERT) algorithms to identify those with hemodynamic instability and right ventricular (RV) dysfunction. For patients with intermediate-high and high-risk features characterized by European Society of Cardiology criteria, care is escalated with systemic thrombolysis or endovascular approaches.

The endovascular holy grail is a device that can be used by one operator in a stand-alone procedure, with minimal bleeding and periprocedural risk, effective clot resolution, and minimal blood loss. Numerous devices have emerged throughout the past 10 years, but they have failed to meet all of these criteria. Many of the existing thrombectomy devices commonly used to treat venous thromboembolism have been repurposed from other medical devices and have undergone new iterations. There is no guideline-directed endovascular approach at this point, but the field is quickly moving forward with innovative devices and clinical trials to establish benefit. To date, no device has been shown in randomized trials to improve survival. This article outlines the currently available devices and discusses their supporting data.

Endovascular initiatives have progressed in two directions to allow for expeditious therapy and significant reduction of bleeding risk: (1) by reducing the dose of thrombolytic therapy required to achieve therapeutic benefit (EkoSonic endovascular system [EKOS; Boston Scientific Corporation], Bashir endovascular catheter [Thrombolex, Inc.]), or (2) with thrombectomy approaches (FlowTriever [Inari Medical], Indigo aspiration system [Penumbra, Inc.]).

Our current strategy at Beaumont Health is to discuss each escalation patient on a multidisciplinary PERT call and tease out clinical and CTA criteria to guide escalation. Recent device trials have focused on rapid improvements in RV/left ventricular (LV) ratios as assessed by CTA as proof of benefit (Table 1).[1-4] Clinical improvement, as determined by improvements in heart rate and oxygen requirements, and subjective improvements in dyspnea serve as our point-of-care endpoints. Length of stay has been shortened with the PERT risk stratification algorithm and the current escalation strategies.

REDUCED-DOSE THROMBOLYTIC THERAPY

The tissue plasminogen activator (tPA)–based approaches that have gained momentum are EKOS ultrasound-assisted thrombolysis (USAT) infusion and the Bashir endovascular catheter. Both have demonstrated effective clot lysis, achieving clinical endpoints with doses of tPA reduced to < 24 mg. Ongoing research is being pursued to understand the

TABLE 1. A COMPARISON OF TRIALS FOR PE TREATMENT

	EXTRACT PE[1] (N = 119)	SEATTLE II[2] (N = 150)	FLARE[3] (N = 106)	PEITHO[4] (tenecteplase arm, n = 506)
Treatment method	Indigo aspiration system	EkoSonic endovascular system	FlowTriever system	Fibrinolytic therapy
Primary efficacy (reduction in RV/LV ratio at 48 h)	0.43; *P* < .0001	0.42; *P* < .0001	0.38; *P* < .0001	NA
Primary safety	Major adverse events within 48 h, 1.7%	Major bleeding within 72 h, 10%	Major adverse events within 48 h, 3.8%	Death or hemodynamic decompensation within 7 d, 2.6%
Major bleeding	1.7% within 48 h	10% within 72 h	1% within 48 h	11.5% within 7 d
All-cause mortality (30 d)	2.5%	2.7%	1%	2.4%
Device time	37 min	12-24 h	57 min	NA

Abbreviations: NA, not available; LV, left ventricular; RV, right ventricular.

microvascular benefits of thrombolytic infusion that may occur beyond simple extraction of large visible clots via thrombectomy. Three-dimensional CTA is being used to characterize the blush score and evaluate microvascular perfusion before and after USAT.[5] These devices have been compared with anticoagulation-alone strategies in patients with submassive PE. As we move forward, identifying specific patient types for different strategies will help optimize outcomes. At Beaumont, we have evolved into a thrombectomy-first approach for proximal clot and a catheter-directed tPA approach for more diffuse and distal clot. Since January 2019, we have escalated therapy in 125 intermediate-high–risk PE patients using FlowTriever thrombectomy in 84 patients and EKOS in 41 patients, with favorable outcomes.

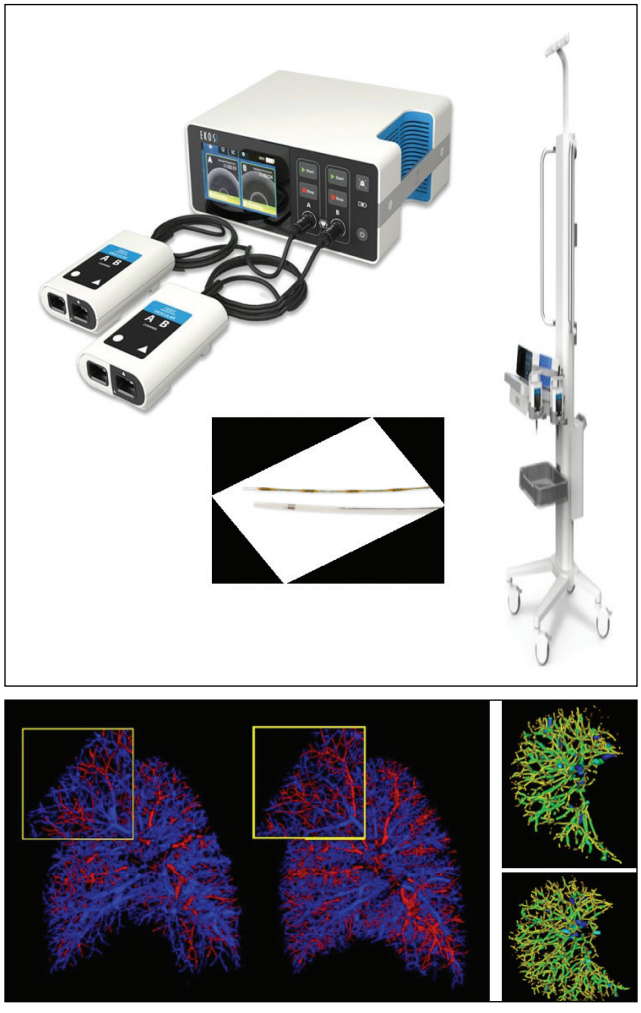
EKOS Control Unit PT3B With Acoustic Pulse Thrombolysis

EKOS therapy uses ultrasonic waves in combination with clot-dissolving drugs to treat PE. With a sophisticated catheter and an ultrasonic core, the system effectively targets the entire clot (Figure 1). The new generation of the device (EKOS Control Unit 4.0) simplifies bilateral PE treatment with the following features: the ability to manage two EKOS devices at once with A/B channels and easy-to-read screens for bilateral PE acoustic pulse thrombolysis treatment; a portable size to easily integrate into the hospital workflow; faster setup time due to on-screen step-by-step prompts; on-screen troubleshooting that identifies where an issue is and how to correct it; and a built-in battery to transport patients from the lab without interrupting therapy.

The safety and efficacy of EKOS have been evaluated in several trials. ULTIMA was a prospective randomized controlled trial of 59 patients that showed superiority of EKOS over anticoagulation alone in RV/LV ratio reduction without an increase in bleeding.[6] The prospective SEATTLE II trial (N = 150) confirmed that EKOS improved RV function, pulmonary hypertension, and clot burden without an increase in bleeding.[2] The prospective, randomized controlled OPTALYSE trial (N = 101) used lower doses and infusion times for the treatment of acute PE without an increase in bleeding.[7] The RV/LV ratio was reduced by 23% at 24 hours in ULTIMA, 25% at 48 hours in SEATTLE II, and 23% to 26% at 48 hours in OPTALYSE. All three trials demonstrated a low risk of bleeding and intracerebral hemorrhage (0% in ULTIMA, 10% in SEATTLE II, 3% in OPTALYSE). Results were achieved with 76% less thrombolytic drug dosage than standard treatment (total dose, 20 mg in ULTIMA, 24 mg in SEATTLE II, and 4/8 mg to 12/24 mg in OPTALYSE). The KNOCOUT PE retrospective and prospective registry (N = 1,500) is currently recruiting and aims to understand acoustic pulse thrombolysis treatment protocols and effects on long-term outcomes.[8]

Bashir Endovascular Catheter

The Bashir endovascular catheter is an interventional tool that puts the control of the procedure directly in the hands of the physician, who can control the expansion and contraction of the infusion basket from about 3 mm when closed and up to 45 mm in diameter when fully deployed (Figure 2). The device has a low-profile, 7-F design. It pulse sprays or infuses via 48 laser-drilled holes through the six limbs of the expandable infusion basket, and the Bashir endovascular catheter line also provides the ability to infuse along multiple lengths of catheter shaft together with the infusion basket. A unique aspect of this catheter-



Courtesy of Boston Scientific Corporation.

Figure 1. EKOS control unit PT3B with acoustic pulse thrombolysis.

Courtesy of Thrombolex, Inc.

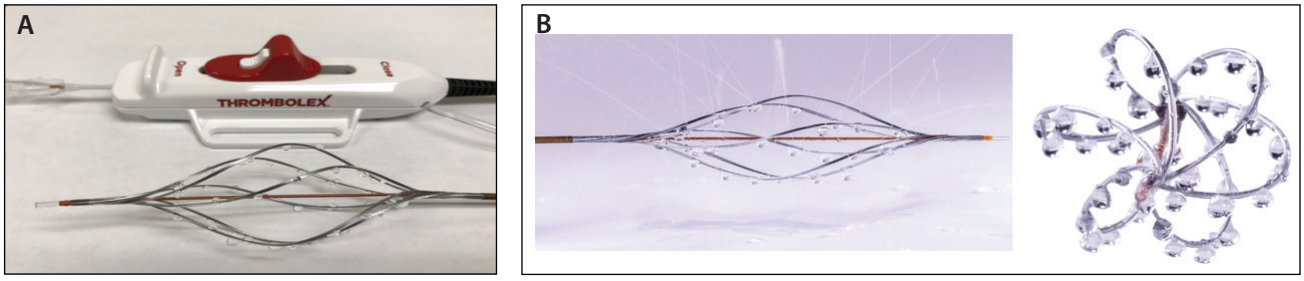


Figure 2. The Bashir endovascular catheter (A). The infusion basket has 48 laser-drilled holes through the six limbs and expands and contracts from 3 mm when closed and up to 45 mm when fully deployed (B).

directed thrombolysis (CDT) device is the ability to create immediate blood flow through the culprit clot once the infusion basket is deployed, promoting rapid reperfusion and accelerated thrombolysis of the clot burden, saving time, and using a smaller lytics dose.

A first-in-human (FIH) clinical trial to treat patients with acute submassive PE was completed in December 2019. The FIH trial met its primary endpoints with no major bleed events and no major adverse events. In addition, the trial demonstrated a significant mean reduction in the RV/LV ratio to 36.7% in 48 hours. There was a mean clot burden decrease of 37.1%, as measured with the Miller Index, after a mean dose of 13.6 mg of recombinant tPA over 8 hours. Patients treated with Bashir endovascular catheters had shorter intensive care unit (ICU) stays and overall stays compared with previously published studies in which CDT or mechanical thrombectomy devices were used to treat PE.[9]

The success of this FIH trial led to FDA approval of the pivotal RESCUE trial. This single-arm study will treat patients with acute submassive PEs and is targeting 125 patients at 20 institutions. The protocol of RESCUE has been modified to reduce infusion time from 8 hours in the FIH to 5 hours in the RESCUE trial. The recombinant tPA dose will be limited to up to 14 mg for bilateral PEs.

THROMBECTOMY APPROACHES

PE cases are treated with thrombolytic therapy as a front-line standard of care. However, more aggressive catheter-based strategies may be useful when there is excessive clot burden, in hemodynamically unstable patients, and when thrombolytics are contraindicated or standard therapy fails. There are five catheter-directed techniques: USAT, rheolytic embolectomy, rotational embolectomy, aspiration thrombectomy, and thrombus fragmentation. Interventional thrombectomy is increasingly being used, and PE intervention is one of the fasting growing fields in endovascular intervention. Recent advances specific to PE have pushed the field forward, and the FDA is involved with study design to help promote product approval and allow quicker clinical access to new technology. There is no current standard of care for endovascular PE intervention, but the devices that are available are a dramatic improvement over previous technology.

Indigo Aspiration System

The Indigo aspiration system provides aspiration thrombectomy for acute PE (Figure 3). The EXTRACT PE trial revealed a 27.3% reduction in RV/LV ratio at 48 hours and a 1.7% major adverse event rate. There was a low procedure time (37 minutes) and on-table

Courtesy of Penumbra, Inc.

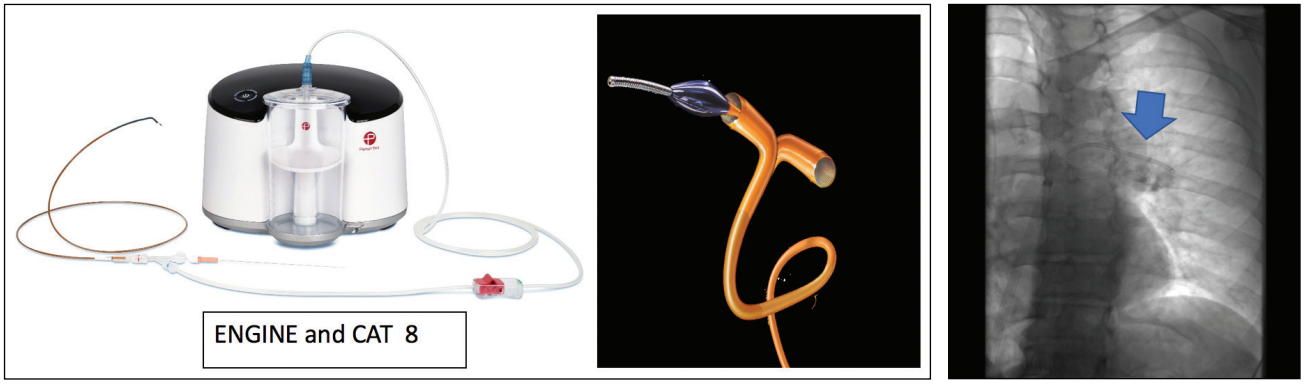


Figure 3. Indigo aspiration system.

Courtesy of Inari Medical.

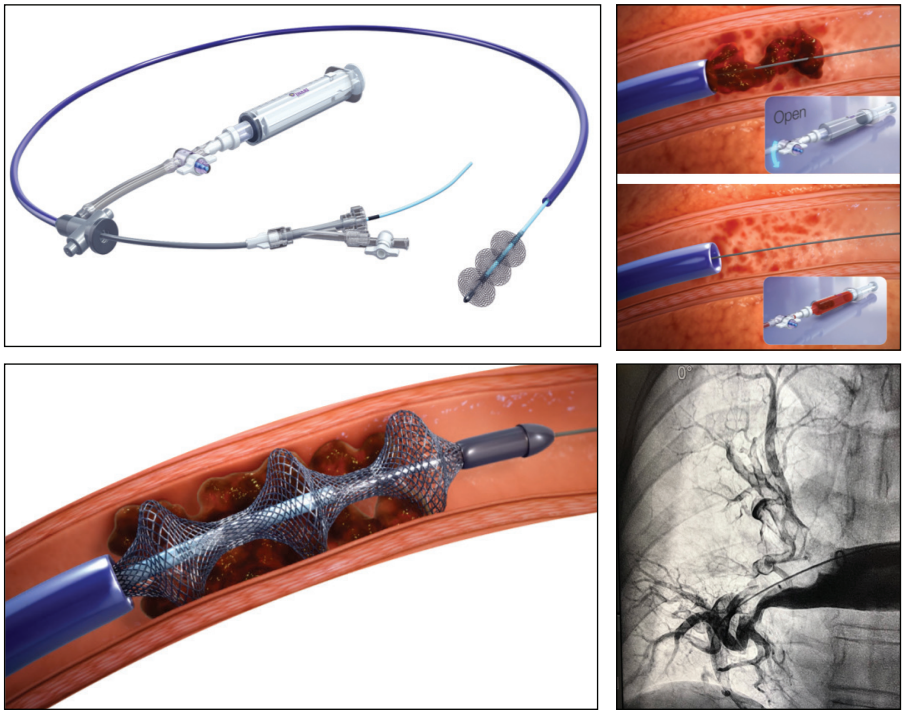
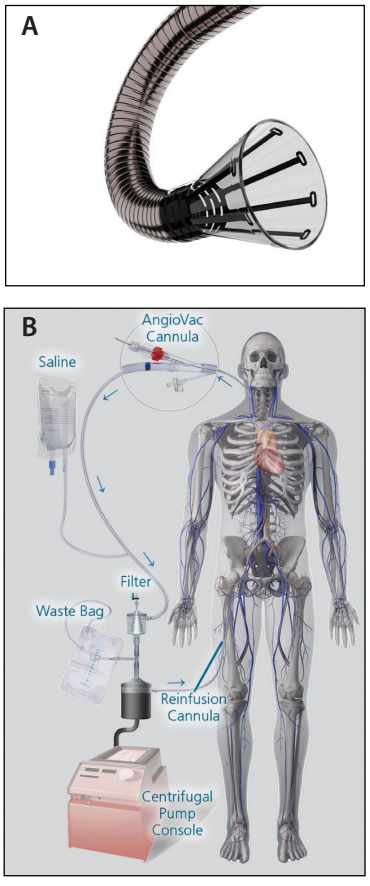


Figure 4. The FlowTriever system.



Courtesy of AngioDynamics, Inc. and its affiliates.

Figure 5. Third-generation AngioVac (A, B). Clot extracted using the AngioVac (C).

pulmonary artery pressure reduction. No thrombolytic drugs were used in 98.3% cases.[1] CAT8, the newest iteration, allows for greater clot extraction and improved suction minimizing.

FlowTriever System

The FlowTriever thrombectomy system is designed for the removal of clot from the pulmonary arteries through both large-bore aspiration and mechanical retraction, without the need for thrombolytics (Figure 4). The FLARE trial was a prospective, multicenter, single-arm study that earned the FlowTriever system a PE-specific indication.[3] The study met both of its primary safety and effectiveness endpoints, showing large and rapid reduction in right heart strain with no device-related major adverse events. The study also showed shorter ICU stay and overall length of stay for patients treated with FlowTriever compared to previous studies in which thrombolytic drugs were used.

AngioVac System

The third-generation AngioVac system (AngioDynamics) includes a cannula with either a 20°- or 180°- angled tip (Figure 5), which potentially facilitates easier navigation through the pulmonary vasculature. It features a self-expanding, nitinol, funnel-shaped tip to enhance drainage flow when actuated using a sliding sheath and prevent clogging of the cannula with undesirable intravascular material (eg, thrombi, emboli, vegetation). Data from the second-generation AngioVac device showed the device to be safe and effective in removing caval thrombus, right atrial thrombus, cardiac lead vegetation, and tricuspid valve vegetations. The device is used off label for PE.[10-13]

SUMMARY

Interventional treatment for PE has entered a rapid phase of evolution, with new devices becoming available on top of the transformational modification of first-generation devices. The data are inspiring but still lagging, and interventional guidelines need a universal standard. We need to continue to push for large data

sets driven by consortiums/collaborations (such as the FLASH registry promoted by Inari Medical) to allow for the development of guideline-directed approaches. We have made great strides in endovascular PE therapy but have not quite found the holy grail. Several new devices are in the pipeline for PE treatment. Start-up companies such as Truvic are getting closer to "grail" status in peripheral vascular thrombus management by enabling single-session thrombus removal without the use of thrombolytics and with minimal blood loss by allowing access to proximal and distal clot with advanced catheter technology.

Time will tell, but we are hopeful that these technologic advances will allow for dramatic clinical improvement and low periprocedural complications, thus broadening their use to all intermediate-risk PE patients. At this point, the decision to use CDT is based on the individual patient and their clinical scenario. Published literature supporting the effectiveness of CDT by clinical endpoints is still in development. ■

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New Insights Into the Mechanisms of Thrombosis Formation: A Focus on Inflammation

A discussion of the genetic mechanisms, role of intermediary metabolism, complex relationship between inflammation and thrombosis, and future targets for thrombus resolution.

BY SCOTT J. CAMERON, MD, PhD, AND VICTOR F. TAPSON, MD

Venous thromboembolism (VTE) represents a leading cause of global mortality. Most recent clinical studies have focused on improving patient mortality using advanced hemodynamic parameters as risk stratification tools and then advanced interventions beyond the use of systemic anticoagulation, with mixed results.[1,2] It is now clear that the long-term consequences of residual pulmonary thrombosis and thrombus burden in patients with acute pulmonary embolism (PE) should be evaluated. The determinants of thrombus development and thrombus resolution are incompletely understood. In vascular beds such as the infrarenal aorta, thrombus formation is hypothesized to stabilize a weakened aneurysmal wall, which may have sustained a dissection event.[3,4] However, the pulmonary vascular bed appears to respond only adversely to the presence of residual thrombosis.[5,6] An exaggerated hemostatic response leads to the formation of venous thrombi, obstructing blood flow and potentially causing acute and chronic symptoms as well as acute PE, which may be fatal.

A tremendous amount has been learned about VTE since Rudolf Virchow published his insightful treatise in 1856.[7] Known for his early insights into mechanisms of VTE, including coining the terms *embolism* and *thrombosis*, Virchow recognized that pulmonary artery thrombosis originated mostly from venous thrombotic events in the lower extremities, stating in 1859 that "the detachment of larger or smaller fragments from the end of the softening thrombus, which are carried along by the current of blood and driven into remote vessels, gives rise to the very frequent process on which I have bestowed the name of 'embolia.'"[2] This work refuted the work of the French pathologist Jean Cruveilhier, who claimed that "venous phlebitis causes the formation of thrombus so that coagulation is the main consequence of venous inflammation."[8] His theory did not explain the disease in its entirety, but time and research have demonstrated that Professor Cruveilhier was more correct than he was given credit for.

Neither René Laennec nor Cruveilhier considered that PE originates in the veins of the lower extremities or pelvis, as both believed that the thrombi arose primarily in the pulmonary arteries, a view long held by many before Virchow's work. Related to this research, Virchow described the factors contributing to venous thrombosis. More theories and discoveries evolved subsequently.

What do we know about mechanisms of clot formation in 2020 and their implications for clinical management? Clinical risk factors such as surgery, trauma, acute medical illness, cancer, age, and obesity translate into VTE risk factors based on one or more of Virchow's triad. Awareness of these risks enables evidence-based decision-making about VTE prevention. This article focuses on the hypercoagulability and venous injury/inflammation features that make these clinical risk factors important. A number of genetic and acquired risk factors have been identified for VTE that alter blood flow, activate the endothelium, and alter the activity of coagulation factors.[9]

GENETIC MECHANISMS

Heritability plays an obvious role in the susceptibility to acute VTE. The most impactful genetic risk factors for VTE are deficiencies of protein C, protein S, and antithrombin.[10,11] These phenomena are rare in the general population but increase VTE risk by as much as 10-fold in affected individuals. A less thrombogenic group of genetic abnormalities, including non-O blood group (increased factor VIII levels), factor V Leiden mutation, prothrombin gene 20210A mutation, and fibrinogen gamma variant 10034T, increase the risk of VTE by two- to fivefold. These genetic variants are present in a small percentage of the population as "gain of function mutations" that increase the risk of venous thrombosis.[11] Single nucleotide polymorphisms (SNPs), which are typically one-base variants in coding and noncoding DNA sequences, ultimately cause functional differences in protein that regulate hemostasis and thrombosis.[12] Examples include SNPs in genes encoding platelet glycoprotein 6,

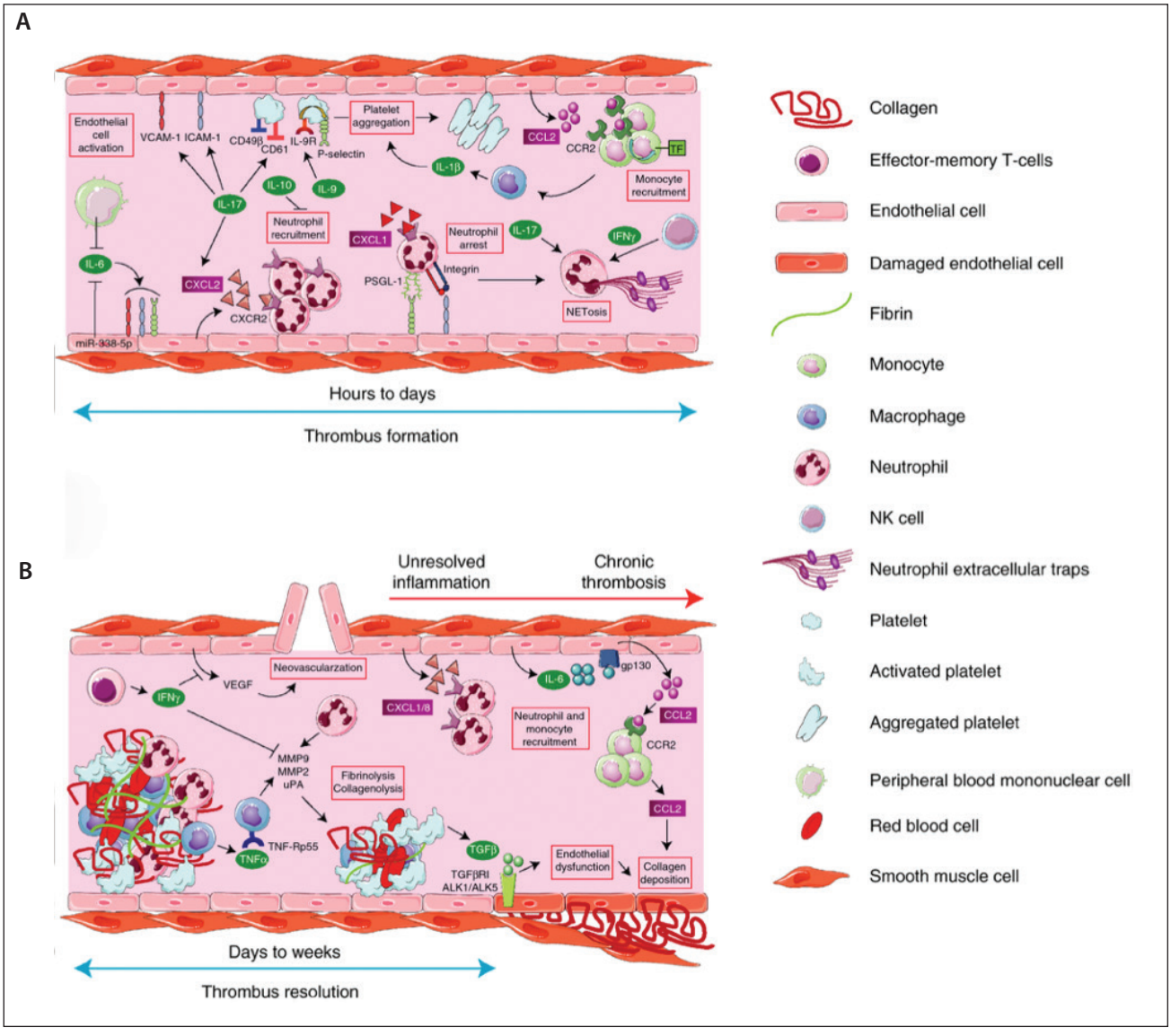


Figure 1. Cytokine and chemokine regulation of VTE. Panel A: Thrombus formation results from the interactions between endothelial cells, leukocytes, and platelets regulated by cytokines and chemokines. First, IL-6 and IL-17 induce endothelial cell activation by increasing the expression of adhesion molecules (VCAM-1, ICAM-1, and P-selectin). In addition, endothelial cells secrete CXCL2 and CCL2, promoting neutrophil and monocyte recruitment. IL-10 was found to inhibit neutrophil recruitment. P-selectin/PSGL-1 interaction and CXCR2/CXCL1 engagement cooperate to generate β2 integrin-dependent arrest in neutrophils and NETosis. Then, interferon (IFN)-γ, secreted by natural killer (NK) cells, and IL-17 promote NET formation and induce venous thrombosis. In parallel, IL-17 and IL-9 regulate platelet activation and aggregation through the expression of CD61 and P-selectin. CCL2-recruited monocytes/macrophages secrete IL-1β, also contributing to platelet aggregation. Panel B: Thrombus resolution, characterized by fibrinolysis, collagenolysis, and neovascularization, is regulated by tumor necrosis factor (TNF)-α and IFN-γ. TNF-α increases MMP-2/MMP-9 and urokinase plasminogen activator (uPA) expression, leading to collagenolysis and fibrinolysis, respectively. In contrast, IFN-γ produced by effector-memory T cells has detrimental roles in thrombus resolution by suppressing collagenolysis and neovascularization. Ultimately, uncontrolled inflammation leads to VTE chronicity in part through TGF-β and IL-6. TGF-β secreted by platelets signals via TGF-β RI to promote endothelial dysfunction and subsequently collagen deposition. IL-6 released by activated endothelial cells is proposed to exert profibrotic effects after deep vein thrombosis through CCL2 upregulation. The latter generates monocyte recruitment and CCL2 secretion leading to collagen deposition. Reproduced with permission from Najem MY, Couturaud F, Lemarie CA. Cytokine and chemokine regulation of venous thromboembolism. J Thromb Haemost. 2020;18:1009-1019. doi: 10.1111/jth.14759

antithrombin III (*SERPINC1*), and coagulation factor XI.[12] The clinical implications of determining the presence of such mutations in the general population is unclear and controversial. In certain settings, in the presence of acquired and heritable gain of function aberrations in thrombosis such as the presence of antiphospholipid antibodies, testing is an important step in guiding appropriate anticoagulation therapy.[13,14]

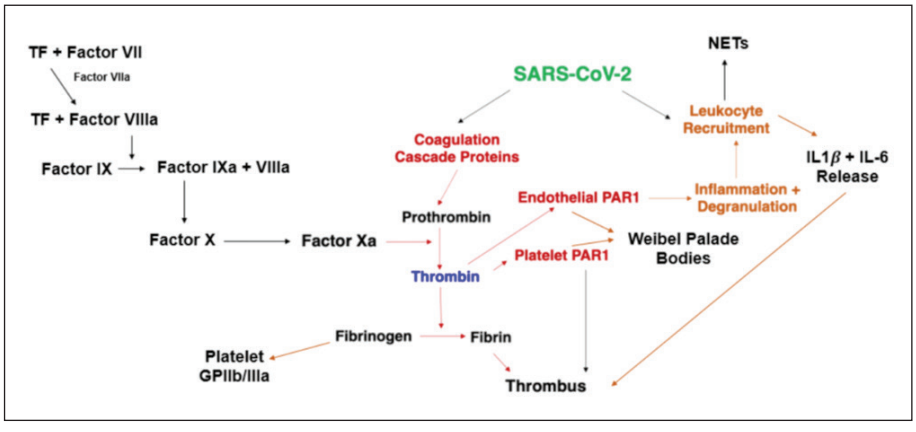
INTERMEDIARY METABOLISM

Metabolic syndrome (abdominal obesity, impaired glucose metabolism, dyslipidemia, and hypertension) is associated with a procoagulant and hypofibrinolytic milieu and thus an increased risk of vascular disease and venous thrombotic events.[15] Adipocytes secrete inflammatory cytokines (adipokines). Recently, Stewart et al demonstrated an association between metabolic syndrome and pulmonary artery pressure in patients with submassive PE at the time of diagnosis and after catheter-directed therapy.[16] This investigation is a cautionary note that the job of the physician is far from complete at the time of treatment. Careful attention to biochemical and clinical variables involved in thrombus formation and resolution may affect long-term patient outcomes. Lipoprotein(a) [Lp(a)] has Kringle domains that resemble those in plasminogen required for fibrin binding, although it is clear that we know less about the role of Lp(a) in VTE.[17,18] Meta-analyses suggest that Lp(a) is associated with an increased risk of VTE,[19] but other studies have been less conclusive; perhaps the risk of VTE increases in the presence of additional risk factors.[20] Larger cohort studies would be useful to resolve this question. Because antisense oligonucleotide therapy has demonstrated effectiveness in decreasing the blood concentration of Lp(a),[21] greater attention will likely be directed to understanding molecular and biochemical events caused by this inflammatory, thrombogenic, and vasoactive lipoprotein.

INFLAMMATION AND THROMBOSIS

The interaction between the innate immune system and thrombosis is important for thrombus formation and resolution (Figure 1).[22] Although hypothesis-driven research using randomized controlled trials is the benchmark for proving the effectiveness of new therapeutic agents, this is the final step in investigative research that cannot be reached without the efforts of our colleagues performing basic science research. Using animal models of thrombotic disease has allowed for observations in the research laboratory to be translated into humans. Physicians are reminded of the dynamic role between inflammation and thrombosis when managing conditions including diabetes, sepsis, obesity, bowel disease, acute respiratory distress syndrome, and cancer, as well as during surgical procedures. Three important cells that are potential targets for mediating "immunothrombosis" are leukocytes, platelets, and the vascular endothelium.[23-28] When endothelial cells are inflamed and tight junctions are disengaged by intracellular phosphorylation events, subendothelial tissue factor (TF) is released, activating the extrinsic coagulation cascade (Figure 2). Activated endothelial cells and platelets also release Weibel-Palade bodies containing von Willebrand factor and CD62 (P-selectin), which promote platelet and leukocyte recruitment, respectively.[29,30] Leukocytes also release cytokines including interleukin-1β (IL-1β) and IL-6, for which animal models have provided mechanistic insight.[31-33] Thus, there is a clear association between VTE and inflammation.[34-37]

Although a more detailed discussion is beyond the scope of this article, it deserves mention that the recent COVID-19 pandemic has clearly demonstrated the presence of in situ thrombosis (ie, thrombosis without the requirement for an embolic event), making the case clear for the immunothrombotic phenomenon and the IL-6 receptor a rational therapeutic target for the humanized antibody tocilizumab.[38] Another fascinating observation in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the presence of neutrophil extracellular traps (NETs).[39] NETs are extracellular DNA fibers extruded from neutrophils produced in response to infection, allowing the neutrophils to "trap" and eliminate



Courtesy of Scott J. Cameron, MD, PhD.

Figure 2. The interface and interconnection between coagulation and inflammation, a process exemplified by SARS-CoV-2 infection—"immunothrombosis."

invading microorganisms. However, NETs are a prominent feature of patients testing positive for the COVID-19 amplicon and in patients infected with another single-stranded RNA influenza B.[40-48] NETs appear to be involved in the activation of platelets, activation of the extrinsic and intrinsic coagulation cascades, and inhibition of antithrombin III.[49,50]

CANCER-ASSOCIATED THROMBOSIS

The principal fibrin-forming mechanism underlying cancer-associated thrombosis is considered to be upregulation of TF expression in cancer cells and cancer cell–derived membrane vesicles.[51] Although a detailed discussion is outside the scope of this article, it seems likely that the TF/factor VIIa pathway is a principal initiator of fibrin formation in cancer patients.[52,53] Cancer cells express TF on their plasma membrane and release TF-bearing procoagulant microparticles into the circulation. Furthermore, polyphosphate/factor XII–triggered coagulation has been demonstrated in prostate cancer–associated thrombosis.[54] Tumors have been shown to release molecules, including adenosine triphospate, that activate the platelet P2Y12 receptor, and platelet-derived mediators have also been shown to regulate tumor growth.[55,56]

FUTURE THERAPEUTIC TARGETS FOR THROMBUS RESOLUTION

It is clear that many patients with residual PE remain symptomatic, and it is the authors' belief that clot extraction and/or augmenting early thrombus resolution in carefully selected patients are tantamount to avoiding thrombus-mediated pulmonary artery remodeling and vascular dysfunction. Clinicians and basic scientists must make a concerted effort to delineate signal transduction pathways in cells that regulate thrombus formation and resolution. The composition of a thrombus includes fibrin, red blood cells (erythrocytes), platelets, and leukocytes. Long-term and current aspirin use was shown not to alter right ventricular strain or pulmonary thrombus burden using the Qanadli score for pulmonary artery thrombus burden in a small study,[57] yet targeting other pathways in the platelet may improve thrombus resolution in certain conditions. In a murine model of VTE, endothelial but not platelet transforming growth factor–β1 signaling was proposed as a critical determinant of thrombus resolution.[58] Venous thrombus was shown to secrete matrix metalloproteinases (MMPs) that can remodel veins, and activated platelet-derived MMPs are found in extracted thrombus and in the circulating blood in patients with acute thrombotic events.[59,60] Erythrocytes, like platelets and the vascular endothelium, produce nitric oxide (NO), which has anti-inflammatory, antithrombotic, and antiproliferative properties.[61] Erythrocyte-derived NO can alter vascular tone and regulate thrombosis in various vascular beds.[62] As the hematocrit rises, bleeding time shortens.[63] Therefore, erythrocytes can also tip the balance toward thrombosis in certain conditions such as polycythemia vera and perhaps even prolonged intravascular depletion.

CONCLUSION

Although there is a critical relationship between inflammation and thrombosis, the complex interactions, time course, and specific origin of various cytokines and chemokines involved in the development of VTE remain obscure. It is becoming clearer, as with the arterial side of cardiovascular disease, that unresolved inflammation in acute thrombosis could be critical in the evolution of acute and chronic venous thrombosis. The future is exciting, but many questions remain. ■

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