HHS Public Access

Author manuscript

Circ Cardiovasc Interv. Author manuscript; available in PMC 2024 October 17.

Published in final edited form as:

Circ Cardiovasc Interv. 2023 October ; 16(10): e013536. doi:10.1161/CIRCINTERVENTIONS.123.013536.

Massive Pulmonary Embolism: Optimizing Collaborative Care and Endovascular Therapy

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Keywords

pulmonary embolism; thrombosis; thrombectomy; thrombolysis; outcomes; endovascular; trial design

Editorial Text

The management of patients with massive pulmonary embolism (PE) has benefited from systematic efforts to ensure rapid achievement of therapeutic anticoagulation, advances in critical care medicine, and increased use of mechanical circulatory support tools. Nevertheless, mortality rates in this PE sub-population are high, prompting ongoing interest in therapies that enable rapid thrombus dissolution, reversal of right heart dysfunction, and patient stabilization. Systemic thrombolysis (ST) is widely available and can be uniformly delivered in the intensive care unit setting. Meta-analysis of randomized controlled trials (RCTs) suggest the presence of a small mortality benefit with ST, but also increased major bleeding and intracranial bleeding, compared with anticoagulation alone (1,2). Hence, while ST is recommended for patients with massive PE, its actual utilization and clinical impact are constrained by concerns about its safety profile.

Catheter-based strategies for PE treatment were introduced in the 1990s and have seen increasing utilization during the past decade. The ULTIMA study, a small RCT (n=50) that evaluated ultrasound-assisted catheter-directed thrombolysis (UA-CDT) for patients with massive or sub-massive PE, demonstrated a greater reduction in RV/LV ratio at 24 hours with UA-CDT compared with anticoagulation alone (3). However, that study was not designed to compare major clinical outcomes and there do not exist any other completed RCTs evaluating CDT. As with ST, challenges with utilizing CDT for massive PE include the relatively long time (often 12–24 hours) needed to achieve thrombus removal, and the potential for bleeding.

Large-bore mechanical thrombectomy (LBMT) offers an exciting new therapeutic option for patients with massive PE, with potential to enable rapid cardiopulmonary recovery without

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Conflict of Interest Disclosures

SV is national co-principal investigator of the PE-TRACT Trial that is evaluating catheter-directed therapy for intermediate-risk PE, and receives grant support from the National Heart Lung and Blood Institute / National Institutes of Health (1UG3HL155798-01A).

thrombolytic bleeding risks. In clinical practice and early studies, LBMT has shown an ability to rapidly aspirate pulmonary arterial thrombus without use of fibrinolytic drugs (4). Many patients have experienced clinical improvement with an immediacy that suggests a causal relationship with the LBMT procedure, prompting increasing utilization in some clinical centers. However, questions remain about how LBMT should be integrated into clinical management pathways.

In this respect, the recent FLAME study evaluating LBMT with the FlowTriever device (Inare Medical, Irvine, CA) reflects a serious effort to obtain quality data in the massive PE sub-population (4). Strengths include its prospective design and pre-specified analysis plan. As many patients with massive PE are at imminent risk of death, the LBMT results reported – particularly the 1.9% mortality rate - are impressive at first look. On the other hand, the FlowTriever Arm patients had more favorable baseline characteristics than patients in the other arms, including a lower likelihood of being intubated (15% FlowTriever vs 33% Context vs 47% Historical), of having had a cardiac arrest (21% FlowTriever vs 33% Context vs 43% Historical), and of having a high shock class (D or E: 21% FlowTriever vs 53% Context). Non-inclusion of patients treated by less experienced operators may have enhanced LBMT outcomes beyond what would be seen in some clinical practices. Rates of clinical deterioration were similar in all arms, but Context Arm patients were more often crossed over at physician choice to receive bailout procedures, thereby meeting a component of the primary outcome. The primary outcome comparison, which presumably influenced the DSMB's stopping guidelines, was based on a control arm estimate of the primary composite outcome that was arbitrarily inflated by 10%, lowering the bar for LBMT.

Nevertheless, the FLAME study suggests that under some conditions at least, the use of LBMT for massive PE may be associated with favorable outcomes. Therefore, it would be worthwhile for physicians at hospitals that manage PE patients to re-assess their processes for optimizing the outcomes of critically ill PE patients, keeping the following principles in mind.

First, multi-specialty collaboration is important in optimizing risk stratification, in weighing the advantages and disadvantages of endovascular therapy, and in delivering that care safely. Ideally this should involve physicians with specialized expertise in critical care (emergency medicine, pulmonary medicine, anesthesia), thrombosis (hematology), and image-guided procedures (interventional radiology, vascular surgery, interventional cardiology). Cardiothoracic surgery should be consulted early to prepare for establishment of extracorporeal membrane oxygenation (ECMO) or for conversion to open surgical embolectomy if needed. The anesthesiologist should be aware of the special considerations for managing patients with acute pulmonary hypertension; if possible, cardiac-specialized anesthesiologists may be utilized.

Second, the proliferation of PE Response Teams (PERTs) has been a welcome addition to PE patient care processes in many institutions. Since hospitals vary in the availability of specialist care in PE-relevant domains, the feasibility of extending PERT consultations to nearby centers should be explored. In addition to enabling more patients to benefit from multi-specialty input, such models might also help in reducing disparities. For example,

in FLAME, despite similar co-morbidities, 66% of patients in the Context Arm, but only 30% of patients selected for FlowTriever LBMT, were Black. The reasons for this apparent difference are unclear, but it is hoped that extension of collaborative care can reduce variability and promote equitable care.

Third, in pursuing PERT consultations and in considering endovascular therapy, it is important not to delay the achievement of fully therapeutic anticoagulation since the latter time interval correlates with PE mortality. In most patients, low molecular weight heparin (LMWH) will enable more rapid achievement of therapeutic anticoagulation than unfractionated heparin (UFH). With performance of endovascular procedures on LMWH, the likelihood of serious bleeding that would necessitate anticoagulation reversal is quite low and is unlikely to outweigh the negative effects of a delay in achieving therapeutic UFH levels. Similarly, consideration of a procedure should not be permitted to delay patient transitions to the intensive care unit.

Fourth, the local outcomes of PE care should be tracked and periodically reviewed from a quality improvement lens. Expertise with ST, CDT, LBMT, and surgical embolectomy varies across hospitals, as do the availability of anesthesia support, ECMO, and the ability to rapidly activate endovascular care pathways and monitor critically ill patients in procedure areas. As such, the FLAME study results may not accurately estimate the results that would be observed with use of LMBT in a given practice setting, and the optimal algorithm for use of aggressive thrombus removal treatments may differ across institutions. For these reasons, tracking local outcomes over time may be more useful than benchmarking against published reports. Having said that, the PE community should validate standard metrics of assessment that may be broadly applicable – it is important to learn what patient selection criteria, care processes, and resources should be in place for LBMT and other endovascular care options to consistently succeed. Many centers may want to offer LBMT but if robust supportive care resources are not available, it may be better to transfer patients to a center with specialized expertise. As for acute stroke therapy where “time = brain”, PE providers should view excellence in stabilizing a patient and executing timely transfer as no less important than advanced endovascular capabilities. These processes should be tracked, improved, and openly recognized as key elements of quality PE care.

Finally, centers must collaborate in obtaining data. With intermediate-risk PE, the PERT collaborations have provided a strong foundation for the pursuit of ongoing multicenter studies, including the randomized, NIH-sponsored PE-TRACT Trial (5). For massive PE, conducting a traditional RCT to evaluate endovascular therapy would pose substantial feasibility challenges. However, additional ways to answer key questions with a minimum of bias should be explored, such as cluster RCTs, preference cohorts, propensity matching, or RCTs that are embedded into electronic health record systems. Physicians should be excited about LBMT and other catheter-based therapies but should remain ambitious in their efforts to enhance the quality of evidence.

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