Pulmonary embolism (PE) is the third leading cause of cardiovascular death in the United States. There are between 300,000 and 600,000 PEs per year, and 10% are fatal in the first hour. All told, 100,000 to 180,000 people die every year from PE. Moreover, 25% to 40% present with right ventricular dysfunction, and one-third to one-half of patients will have residual thrombus 6 months after the PE in spite of anticoagulation. These statistics highlight the importance of improving PE outcomes; endovascular therapy has the potential to do precisely that in select PE patients.

Even though this opportunity exists, several facts need to be acknowledged. First, many deaths occur before patients present to the hospital. Second, most patients have low-risk PEs and are well treated by anticoagulation alone. Third, prospective randomized trials indicate that submassive PE carry only a 3% mortality. Fourth, endovascular therapies currently suffer from a dearth of level 1 data regarding their clinical effectiveness and safety. This brief article covers PE stratification, pathophysiology, and endovascular therapy for massive and submassive PE.

**DEFINITIONS AND STRATIFICATION**

Pulmonary embolism is stratified by short-term mortality. The 3 categories (massive, submassive, and low-risk) are based on systemic and right ventricular hemodynamics.¹,² Massive PE patients have hypotension (systolic blood pressure less than 90 mmHg for greater than 15 minutes or a 40 mmHg drop from baseline), require vasopressor support, or have profound bradycardia (less than 40 beats/minute associated with hypotension). Submassive PE patients have a blood pressure greater than 90 mmHg with right ventricular dysfunction by imaging (echocardiography, computed tomography), biomarkers (troponin, brain natriuretic peptide), and/or electrocardiography (S1Q3T3 pattern, new right bundle-branch block). Low-risk PE patients have neither hypotension nor right ventricular dysfunction. Massive PE carries a 25% to 65% mortality. Registry data from the 1990s for submassive PE showed a 19% 30-day mortality,³ whereas contemporary randomized trials demonstrate a 2% to 3% mortality with prompt initiation of anticoagulation and close monitoring.⁴,⁵ Low-risk PE carries a <1% mortality.

**SEVERE PATHOPHYSIOLOGY**

Patients with severe PE (submassive or massive) typically have central occlusive thrombus in pulmonary artery branches. The increased pulmonary vascular resistance dilates the right ventricle, which impinges on the septum and reduces LV chamber size. Concomitantly, less pulmonary artery blood flow leads to reduced LV filling. Reduced preload in turn causes lower cardiac output and hypotension, which reduces coronary perfusion. The combination of RV dilation and ischemia further compromises RV function. Massive physiology refers to decompensation of the RV and ensuing systemic hypotension, whereas submassive physiology implies preserved but compromised RV function, enough to maintain the systemic blood pressure.

**ENDOVASCULAR TREATMENT OF MASSIVE PE**

Systemic thrombolysis and surgical embolectomy are essential tools for a pulmonary embolism response team confronting a massive PE patient. Systemic lytic drugs can be administered more quickly than interventional or surgical teams can be mobilized. Surgical embolectomy has several strengths: (1) large clot volumes can be extracted, and (2) a team of cardiopulmonary specialists can provide advanced support such as extracorporeal membrane oxygenation (ECMO). There are, however, select patients that may be well suited to endovascular therapy. The more stable massive PE patients who are hypotensive but not arresting may tolerate a less invasive procedure. Others are poor surgical candidates or are unwilling to undergo major surgery.

The interventionalist should be prepared in the event the patient decompensates. Specifically, he or she may consider a hybrid operating room or the involvement of a cardiac anesthesiologist to monitor the patient during the intervention. Given the sobering mortality rate of massive PE, the goal should be to rescue the patient from the vicious cycle described above and downgrade him or her to a submassive PE. Thus, achieving 100% clot lysis is not necessary. Maceration, aspiration, thrombus disruption, and local fibrinolytic administration are standard techniques. Beyond these, novel devices such as the Cleaner (Argon Medical), the Indigo Aspiration system (Penumbra, Inc.), and the Flowtriever (Inari Medical) have been used off label in the pulmonary circulation.
Prospective trials are essential to determine the safety and efficacy of these devices in severe PE.

ENDOVASCULAR TREATMENT OF SUBMASSIVE PE

The optimal treatment for submassive PE is unknown. Registry data from the late 1990s implied a high mortality rate for submassive PE, but contemporary randomized trials show a much lower mortality. Systemic thrombolysis appears to reduce the rate of clinical deterioration and may have a small mortality benefit when combining all studies, but it still carries an alarmingly high bleeding rate.

Catheter-directed therapy (CDT) for submassive PE has promise because it delivers a focused, lower dose of thrombolytic drug. A multiple sidehole infusion catheter (either ultrasound-assisted or not) is placed within the thrombus and infuses a fibrinolytic drug such as recombinant tissue plasminogen activator (rtPA) at a rate of ~1 mg/hour, for a total of 20 mg to 24 mg (Figure 1). Thus, efficacy is theoretically preserved with less bleeding.

However, CDT has been insufficiently studied in submassive PE. The sole randomized trial, the Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial, only included 59 patients. SEATTLE II (a Prospective, Single-arm, Multi-center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism) studied 150 patients but had no control arm. The primary endpoint was radiological, not clinical. The PERFECT registry (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) showed a high clinical success rate but lacked a control arm. While no intracranial bleeding was seen in any of these studies, 17 of 150 patients in SEATTLE II had a bleed requiring a transfusion. These trials demonstrated efficacy, but lack the methodological rigor to conclude that we should routinely offer CDT to submassive PE patients.

Another glaring knowledge gap is whether acute thrombus resection with CDT will lead to better long-term outcomes. Survivors of PE are at higher risk of having exercise intolerance, and reduced exercise capacity correlates with residual pulmonary artery thrombus. Early thrombolytic therapy may improve long-term outcomes. However, a randomized trial of CDT and/or systemic thrombolysis with clinically relevant short and long-term endpoints is badly needed.

CONCLUSION

It is an exciting time for the endovascular management of PE. Novel devices and strategies, alone or in combination, have the potential to reduce morbidity and possibly mortality. However, the interventional community needs to insist on high quality studies of both devices and techniques such as CDT so that future patients can receive the optimal therapy for this vexing disease.

REFERENCES


