Standard of care for pulmonary embolism (PE) includes anticoagulation, attempts at identifying the underlying etiology, and reduction of risk factors. The main goal of this therapy is to prevent further venous thromboembolism (VTE) and minimize the immediate morbidity and mortality risk of the event.

For a select subgroup of this patient population, medical therapy may not be sufficient to either reduce the immediate risk or prevent another VTE. Catheter-based treatments for PE are based on the premise that accelerated, local removal of clot (either with or without thrombolytic agents) may offer more rapid clinical improvement with a low risk of adverse events. This accelerated removal of thrombus from the pulmonary circulation may also translate to the prevention of intermediate and long-term morbidity/mortality. The following discussion of these treatments will be further divided into two categories: massive and submassive PE.

**MASSIVE PE**

Massive PE is a clinical diagnosis whereby the patient has a sustained blood pressure of < 90 mm Hg or is in shock secondary to a PE. The overall mortality rate of massive PE approaches 60%, with most deaths occurring in the first 2 hours of presentation. It is second only to cardiac arrest as the leading cause of sudden death, and in autopsy studies, it has accounted for up to 80% of sudden deaths in the hospital setting.

The American College of Chest Physician (ACCP) guidelines have recommended systemic thrombolytic therapy for treating patients with massive PE. The US Food and Drug Administration has approved a dosage of 100 mg of tissue plasminogen activator, usually infused over a 2-hour time course. Although studies have demonstrated the effectiveness of this approach, it is also associated with an approximate 20% risk of significant hemorrhage and a 3% to 5% risk of intracranial hemorrhage.

Catheter-directed therapy has evolved to more directly remove the clot burden and rapidly restore systemic blood pressure (Figure 1). Catheter-based techniques include fragmentation with a pigtail catheter...
(Figure 2), balloon maceration (Figure 3), or use of a rheolytic mechanism. Additional local, intraclot delivery of thrombolytics can be performed at a fraction of the systemic dose typically used for PE.⁷

A meta-analysis of these techniques for treating massive PE reported a pooled clinical efficacy of > 85%, defined as stabilization of hemodynamics, resolution of hypoxia, and survival to discharge.⁸ Their pooled hemorrhagic complication rate was only 2.4%, with < 1% incidence of intracranial hemorrhage.

Ongoing research for outcomes after catheter-based treatment of PE is being carried out by Dr. William Kuo at Stanford University. The PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) registry is an ongoing, international, multicenter, prospective registry with primary measures to collect and analyze data on the outcomes of patients treated for massive PE, complication rates, and techniques used. This registry may provide adequate support for a randomized clinical trial and a stronger level of recommendation for catheter-based treatment by the ACCP. Analysis of the pooled data is expected in 2014.

**SUBMASSIVE PE**

Submassive PE is defined as that which results in right ventricular (RV) dysfunction but with a maintained systolic blood pressure > 90 mm Hg. RV dysfunction can result from clot burden in the pulmonary arteries that increases the RV pressure. This overload causes RV dilatation/hypokinesis, which can subsequently result in decreased cardiac output and shock, increasing wall tension, and subsequent myocardial ischemia.

Several parameters have been analyzed to determine their impact on the patient’s prognosis. An RV to LV diameter ratio > 0.9 has repeatedly been found to be a strong independent predictor of in-hospital and 3-month mortality, recurrent VTE, and adverse cardiovascular events.⁹⁻¹¹ For submassive PE, the ACCP guidelines recommend anticoagulation as the standard of care. Thrombolysis is only considered if the patient deteriorates or evolves into a massive PE scenario. However, intervening on submassive PE patients with catheter-based therapy may prevent this deterioration, relieve acute symptoms, and hopefully translate to improved outcomes at longer time points.

As of this writing, there are several clinical trials that are underway or have recently been completed. SEATTLE I is an industry-sponsored (Ekos Corporation, Bothell, WA) retrospective study designed to examine the safety and efficacy of ultrasound-accelerated thrombolysis of submassive and massive PE. This multicenter study has now been completed. SEATTLE II is a prospective multicenter study examining the efficacy of the EkoSonic ultrasound-accelerated infusion catheter also in massive and submassive PE patients, with the primary endpoint being reduction of RV:LV ratio posttherapy. This study has also been completed, although results have not yet been reported. SEATTLE II Extension is already being planned and is expected to start later this year, which will examine pulmonary artery pressure at 90 days, with a secondary endpoint being quality of life.

ULTIMA was a prospective, randomized controlled trial in which 59 patients were randomized to anticoagulation alone versus anticoagulation with the EkoSonic device.¹² To be included, patients had to have an RV:left ventricular (LV) ratio > 1 and documented PE in one main or lower lobe pulmonary artery. The maximum dose of tissue plasminogen activator allowed was 20 mg over 15 hours. The primary endpoints were reduction in RV:LV ratio and bleeding complications.
MEDICAL TREATMENT FOR SUBMASSIVE PE

Tenecteplase (TNK) is a thrombolytic agent that binds directly to fibrin and converts plasminogen to plasmin with a half-life of 20 to 24 minutes. In the absence of fibrin, in vitro studies suggest that plasminogen conversion is decreased. This fibrin specificity decreases the systemic activation of plasminogen, resulting in degradation of fibrinogen. TNK has US Food and Drug Administration approval for use as a thrombolytic agent in the treatment of patients with acute myocardial infarction.

Two randomized studies have examined its utilization in the treatment of submassive PE. The larger trial is the PEITHO (Pulmonary Embolism Thrombolysis) study, which was a double-blind, randomized controlled study comparing TNK administration to placebo in patients with intermediate-risk PE (defined as PE-induced RV dysfunction). TNK administration resulted in a statistically significant reduction in death (2.6% vs 5.6%) and hemodynamic collapse (1.5% vs 5%) in the early time period (7 days postrandomization) over placebo. Unfortunately, however, this came at the cost of increased risk of bleeding complications (6.3% vs 1.5%) and intracranial hemorrhage (2.4% vs 0.2%).

TOPCOAT was a smaller randomized trial examining 83 patients with intermediate-risk PE outcomes at 50 days and 3 months and compared TNK with low-molecular-weight heparin to low-molecular-weight heparin alone. This study was terminated early but did find a greater survival rate in the first 5 days, shorter hospital stay, and greater quality of life (based on the SF-36 questionnaire) at 90 days over low-molecular-weight heparin alone.

ENDOVASCULAR TECHNIQUES FOR MASSIVE/SUBMASSIVE PE

Because the main goal of treatment in patients with massive PE is rapid restoration of systemic blood pressure, mechanical fragmentation or clot removal is the mainstay of treatment. Devices such as rotating pigtail catheters, balloon maceration, and rheolytic thrombectomy have been described.

Local infusion of thrombolytics directly into the clot is also believed to provide added benefit. In vitro studies have demonstrated the difficulty in delivering the needed drug to the clot when administered outside of the clot (ie, via peripheral intravenous infusion). When the thrombolytic agent is administered directed into the clot, the total dose is much less than what is needed when administered systemically.

Short infusions (24 hours or less) of thrombolytic agents via multiple sidehole catheters is becoming the standard method for all catheter-based PE thrombolysis. Doses ranging from 0.5 to 1 mg/h per lung are standard. Ultrasound-accelerated infusion catheters (such as the EkoSonic device) are indicated for infusion of medication into the pulmonary arteries and may confer additional benefit over infusion alone. Ultrasound waves emitted by the catheter may cause thinning of fibrin strands in the thrombus, opening more surface area for the thrombolytic agent to act upon (Figure 4).

CONCLUSION

Although most patients with PE have a good prognosis with standard anticoagulation therapy, patients with massive or submassive PE have a much higher risk of mortality and morbidity. In patients with massive PE,
aggressive catheter-based techniques to locally deliver thrombolytics and mechanically debulk or remove clot may be potentially life saving and have a low risk profile. The results of the PERFECT registry are anticipated in 2014 and will hopefully shed additional light on the role of endovascular therapy.

For patients with submassive PE, catheter-directed therapy with thrombolytic agents appears to accelerate clot removal and normalize RV dysfunction faster than anticoagulation alone. TNK thrombolysis via peripheral intravenous infusion appears to also improve outcomes over anticoagulation alone in these patients but at a higher risk of hemorrhagic complications. SEATTLE II Extension is anticipated to start soon to further confirm the ULTIMA findings and to also provide longer-term follow-up and quality-of-life measures.

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