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Review Article

Catheter-Directed Treatment for Pulmonary Embolism in Light of Current Evidence

Abstract

Pulmonary embolism (PE) is the leading cause of in-hospital morbidity and mortality and accounts for approximately 100,000 deaths in the United States and 300,000 deaths in Europe annually. Although societal guidelines for low- and high-risk PE are well established, the present management of submassive (intermediate)-risk PE is evolving. Catheter-directed thrombolysis (CDT) represents a viable treatment option for treatment of submassive PE given its ability to rapidly reduce right heart strain with an acceptably low rate of major hemorrhagic complication. The current review aims to discuss the existing guidelines and literature supporting CDT for PE and also to examine upcoming areas of future research to support its adoption in the algorithm for the management of submassive PE.

Keywords: *CDT, pulmonary thrombolysis, submassive PE*

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Introduction

Pulmonary embolism (PE) is a life-threatening entity that occurs in approximately 60–70/10,000 individuals.[1] It is the leading cause of in-hospital morbidity and mortality and accounts for roughly 100,000 deaths in the United States per year.[2,3] In Europe, this figure is even larger, responsible for over 300,000 deaths annually, of which only 7% are diagnosed antemortem.[3] Moreover, mortality related to PE may potentially be higher than currently estimated as the majority of sudden deaths are typically attributed to a cardiac origin as opposed to PE.

At present, the severity of PE is stratified into three risk thresholds: low, intermediate, (submassive), and high (massive). Low risk is defined as PE in the absence of right heart strain. Submassive is defined as PE resulting in right heart dysfunction without systemic arterial hypotension (systolic blood pressure [SBP] >90 mmHg) and represents up to 25% of patients presenting with PE.[4] Conversely, massive PE is defined by the presence of central PE associated with right ventricular (RV) strain and sustained systemic arterial hypotension (SBP <90 mmHg for at least 15 min) and/or the presence of central PE requiring inotropic support.[5]

Risk stratification guides subsequent treatment and the expected outcome of a patient presenting with PE. The goals of treatment are primarily focused on the reduction of mortality and secondarily on the prevention of PE recurrence and late-onset chronic thromboembolic pulmonary hypertension.[2] The established guidelines for low-risk PE (i.e., anticoagulation) and high-risk PE (i.e., aggressive clot which includes systemic thrombolysis, catheter-directed thrombolysis (CDT), and/or surgical thrombectomy) are generally well-accepted strategies.[6] In recent years, however, the primary area of uncertainty with respect to management has centered around submassive PE. Treatment algorithms ranging from anticoagulation alone to systemic thrombolysis have been studied for submassive PE with varied results and conclusions.[7-9]

CDT is an emerging treatment option that has recently shown promise for patients with submassive PE.[10] CDT utilizes an endovascular approach to locally deliver a thrombolytic agent within the thrombus itself to facilitate fibrinolysis. This technique has shown to accelerate the reversal of right

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heart strain caused by PE at 24–48 h while also mitigating the bleeding risk associated with systemic thrombolysis.[3] Direct delivery of a lytic agent into and around the clot can reduce the amount of drug being used, thereby reducing the risk of subsequent systemic bleeding. Nevertheless, the role of CDT in submassive PE continues to evolve, while prospective data remain limited. This review aims to examine the current CDT guidelines and existing literature for the treatment of PE and explore upcoming avenues of research in the field to potentially support its utilization.

In the past 3 years, three landmark prospective studies established the safety and efficacy of CDT for PE, laying the foundation for CDT in submassive PE: ULTIMA, SEATTLE II, and PERFECT.[10-12] ULTIMA was a prospective randomized trial that included 59 patients with central PE and echocardiographic RV-to-left ventricular (LV) diameter (RV/LV) ratio ≥1.0.[10] Patients were randomized to receive unfractionated heparin only (n = 29) or systemic heparin along with ultrasound-assisted CDT (USAT) of 10–20 mg of recombinant tissue-plasminogen activator (t-PA) infused over 15 h (n = 30). The trial found USAT to be significantly superior to anticoagulation alone in reversing RV dilation at 24 h, without an increase in bleeding complication.[10] The significance of RV function is important as a meta-analysis by Cho *et al*. demonstrated that short-term mortality is increased for PE patients with RV dysfunction.[13] SEATTLE II was a single-arm, multicenter trial that evaluated the safety and efficacy of USAT. The trial included 150 patients, 31 of which had acute massive PE and 119 had submassive proximal PE with a RV-to-LV diameter ratio on computed tomography (CT) ≥0.9. The trial similarly found that USAT decreased RV dilation, reduced pulmonary arterial hypertension, decreased anatomic thrombus burden, and minimized intracranial hemorrhage in patients with acute massive or submassive PE.[11] PERFECT was a multicentric registry that prospectively enrolled 101 patients with acute PE (n = 73 submassive; n = 28 massive).[12] Of note, very few exclusion criteria were applied with the intention of presenting a real-world sampling of patients undergoing CDT.[12] Patients in the registry underwent either catheter-directed mechanical or pharmacomechanical thrombectomy and/or CDT with low-dose t-PA or urokinase. The registry similarly found that CDT resulted in improved hemodynamics with relief of right heart strain while reporting no major hemorrhagic or procedure-related complication.

Although these important studies have established the potential for CDT in the management of submassive PE, they remain limited in their ability to conclude definitively that CDT is a clinically beneficial treatment compared to alternative therapies.[14] SEATTLE II and PERFECT were single-arm trials that lacked a comparator group to declare superiority. Both ULTIMA and SEATTLE II were fairly low sample size studies that were neither adequately designed nor powered to assess other clinically relevant variables as mortality or long-term impact on quality of life. Finally, PERFECT was limited by its nonrandomized design and also did not evaluate the long-term outcomes.[14]

Additional studies have aimed to identify the potential benefit of CDT in submassive PE. A recent meta-analysis by Mostafa *et al*. found that submassive patients undergoing CDT showed an all-cause mortality of 3.6% and risk of major bleeding of 0.9%.[15] Additional small (n = 27–55) retrospective studies on submassive PE have found low rates of major hemorrhage (0%–4%) and high rates of technical success.[16-18]

Given these limitations and the paucity of additional clinical data supporting CDT, the American College of Chest Physicians (ACCP) 2016 guidelines on venous thromboembolic disease recommend systemic thrombolysis over CDT unless patients are at higher risk for bleeding or are likely to deteriorate before systemic thrombolysis can take effect. These recommendations are however classified as Grade 2C, signifying a weak recommendation based on a low level of evidence.[6] Other societal guidelines from the American Heart Association and European Society of Cardiology recommend systemic thrombolysis or CDT only in patients in whom imminent cardiac decompensation is evident.[19]

Current societal recommendations such as the ACCP are in place despite established literature demonstrating a bleeding risk of up to 20% with systemic thrombolysis and intracranial hemorrhage risk of 3%–5%.[20] Although CDT appears to mitigate the risk of major hemorrhage compared to systemic thrombolysis, the lack of clinical data supporting its safety in large numbers appears to have prohibited its adoption in contemporary guidelines. Given the need for further investigation, a research consensus panel was convened in December 2015 to determine what avenues of research are needed to justify the utilization of CDT for submassive PE. The panel determined that future trials should focus on identifying clinically impactful and feasible endpoints, determining appropriate selection criteria, maximizing enrollment, and collecting robust safety data regarding CDT.[21]

Choosing a feasible endpoint in the design of submassive PE trials remains challenging. Mortality would appear to represent a logical outcome measure; however, the reported rate of mortality in literature for submassive PE is varied. The International Cooperative Pulmonary Embolism Registry reported a mortality rate of up to 20%; however, the more recent Pulmonary Embolism thrombolysis (PEITHO) trial demonstrated mortality in the range of 1.8%. Furthermore, this >1000 patient trial along with two other meta-analyses did not demonstrate a mortality benefit when comparing systemic thrombolysis to anticoagulation alone.[8,9,22] These results suggest that a large-scale trial to demonstrate mortality benefit with CDT may not be feasible. Alternatively, Sista

et al. have suggested that dyspnea, exercise intolerance, and decreased quality of life following submassive PE may be a more reasonable outcome metric.[14] These symptoms, collectively called "Post-PE syndrome," were shown to occur in a high percentage of patients following a first-time PE.[23,24] Specifically, objective measures such as "6-min walk distance" may represent future endpoints to demonstrate the potential improvement in the quality of life when utilizing CDT for submassive PE.[14]

Triaging patients that may benefit from CDT also remains challenging. The present category of patients who were classified as "submassive" is heterogeneous and can range from asymptomatic individuals with an enlarged RV to acutely symptomatic patients with biochemical evidence of myocardial ischemia headed toward cardiac decompensation. Current prognostic models developed to assess PE mortality such as the Pulmonary Embolism Severity Index (PESI) were derived from low-risk patients and therefore may not be applicable to the submassive patient population and selecting those at risk for decompensation.[25] Additional metrics such as RV/LV ratio and PA pressures are indirect measures that cannot reliably predict progression to RV failure. Recent literature has suggested that more specific models geared to assess the risk for cardiac arrest using vital signs, laboratory values, and age may be more accurate than PESI for predicting 30-day mortality.[25] These scores may therefore be more beneficial in choosing patients that are more likely to benefit from CDT due to higher risk for mortality.

Finally, establishing robust safety data for CDT can help to offset its perceived invasive nature compared to systemic thrombolysis. Although systemic thrombolysis through a peripheral vein has shown to improve hemodynamics compared to anticoagulation alone, it must be weighed against the risk of major and intracranial hemorrhage.[26] The PEITHO trial demonstrated a 11.5% incidence of bleeding in the systemic thrombolysis treatment arm, while a meta-analysis by Wang *et al*. demonstrated a 9.5% incidence of major hemorrhage.[27] This elevated risk in addition to conflicting data surrounding mortality benefit is a likely contributing factor to why systemic lytic therapy is not recommended routinely in submassive PE.[6-9] As continued research shows that CDT may offset the risk of bleeding, it can potentially be used to justify its utilization over systemic thrombolytics. To support this, a recent study by Avgerinos *et al*. retrospectively compared systemic thrombolysis to CDT for both submassive and massive PE, finding improved safety and effect in the CDT arm.[2] Another study by Kolkailah *et al*. demonstrated patients undergoing CDT to demonstrate a zero incidence of intracranial hemorrhage with slower Intensive Care Unit stays and hospital length of stay when compared with those undergoing pulmonary embolectomy.[26] Similar studies performed prospectively will continue to support CDT's place over systemic thrombolysis for submassive PE.

Conclusion

The management of submassive PE is in a current state of evolution, with CDT representing a viable treatment option due to its low rate of hemorrhagic complication and ability to rapidly relieve right heart strain. However, additional prospective data are needed to further justify the use of CDT as a standard of care for submassive PE, specifically with respect to demonstrating superior clinically relevant outcome metrics compared to other alternative treatment options. Future studies will hopefully serve to cement the safety of CDT and also define better prognostic tests to identify patients in whom CDT will be most beneficial. Until then, CDT represents a viable option within the current guidelines for the management of submassive PE patients requiring escalation of care beyond systemic anticoagulation.

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Conflicts of interest

There are no conflicts of interest.

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