Society of Interventional Radiology Position Statement on Catheter-Directed Therapy for Acute Pulmonary Embolism

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ABBREVIATIONS

CDT = catheter-directed therapy, CTEPH = chronic thromboembolic pulmonary hypertension, LV = left ventricle, PE = pulmonary embolism, PERFECT = Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis: Initial Results from a Prospective Multicenter Registry, PPS = post–pulmonary embolism syndrome, RCT = randomized controlled trial, RV = right ventricle, SEATTLE II = A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism, TPA = tissue plasminogen activator, ULTIMA = Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism

STATEMENT

The Society of Interventional Radiology (SIR) considers the use of catheter-directed therapy (CDT) or thrombolysis to be an acceptable treatment option for carefully selected patients with massive (ie, high-risk) pulmonary embolism (PE) involving the proximal pulmonary arterial vasculature, in accordance with multidisciplinary guidelines (1–4). SIR defines acute proximal PE as new main or lobar emboli identified on radiographic imaging within 14 days of PE symptoms. In addition, SIR encourages the investigative use of CDT and new endovascular techniques in prospective outcomes studies and clinical trials, with particular attention to patients with acute submassive (ie, intermediate-risk) PE.

BACKGROUND

Acute PE is a common life-threatening condition that represents a severe manifestation along the spectrum of venous thromboembolic disease, and PE is the third leading cause of cardiovascular mortality in the United States (1). Acute PE is currently classified into three categories: low-risk, submassive (ie, intermediate-risk), and massive (ie, high-risk) (2).

Low-risk PE is defined by the absence of right heart strain and systemic arterial hypotension. The majority of patients diagnosed with PE present to the hospital without hypotension or heart strain, and these patients with low-risk PE (< 1% short-term mortality rate) can be successfully managed with prompt initiation of therapeutic anticoagulation (3).

Submassive or intermediate-risk PE is defined by the presence of right heart dysfunction in the setting of normal blood pressure, and this represents as many as 25% of all cases of acute PE. Currently, the greatest uncertainty in the PE treatment algorithm concerns the risk stratification and management of submassive PE. A recent randomized controlled trial (RCT) (4) in patients with submassive PE demonstrated a 5.6% rate of clinical deterioration (ie, death or hemodynamic decompensation) within 7 days and a 3% 30-day mortality rate with anticoagulation alone. In interpreting these findings against the background of previous studies, it should be noted that, for conventional and aggressive PE therapies, contemporary studies report lower mortality rates than older studies. In addition, RCTs have tended to report lower mortality rates than observational studies, which may result in part from selection of healthier populations (ie, strict inclusion/exclusion criteria) and closer subject monitoring in the RCTs. As such, earlier observational studies reported higher rates of mortality and rapid clinical deterioration in submassive PE populations treated with anticoagulation alone (5,6). Nevertheless, considering all the studies to date, it is clear that the estimated mortality risk from submassive PE is substantially higher than that associated with low-risk PE, but that the vast majority of patients survive, perhaps as a result of contemporary advances in medical care (5–7).

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Massive or high-risk PE is characterized by the presence of sustained systemic arterial hypotension defined by a systolic blood pressure < 90 mm Hg for at least 15 minutes or requiring inotropic support (2), and these patients carry a mortality risk of 25%–65% (8). As a result of the critical nature of high-risk PE, there is a current consensus that aggressive clot removal strategies be considered including systemic thrombolysis, CDT, and/or surgical embolectomy in select patients depending on risk/benefit assessment, presence of contraindications to such therapies, and available local expertise (2,3,9).

RATIONALE OF CDT FOR MASSIVE PE

Although systemic thrombolysis is currently indicated for the treatment of acute massive PE, many patients cannot receive systemic thrombolytic therapy because of contraindications. Even when patients with acute PE are prescreened for absolute contraindications, the rate of major hemorrhage associated with systemic thrombolysis has been estimated at 9.2%, with a 1.5% risk of intracranial hemorrhage reported in a metaanalysis of RCTs (7), and observational studies (4,5,10,11) have shown that these bleeding risks may be higher among real-world populations. Although systemic thrombolysis can be initiated in a shorter time frame than CDT, the full dose generally takes 2 hours to deliver, and possible advantages of CDT could include the ability to use a lower thrombolytic drug dose and obtain faster lysis as a result of the targeted intrathrombus drug delivery and the addition of mechanical treatment (ie, pharmacomechanical CDT) (3,12).

In a meta-analysis of 594 patients with acute massive PE treated with modern CDT (ie, use of low-profile devices < 10 F, mechanical fragmentation, and/or aspiration of emboli with or without the use of thrombolytic drugs) (12), clinical success was achieved in 86.5%, with success defined as the stabilization of hemodynamic parameters, resolution of hypoxia, and survival to hospital discharge. The analysis was limited because most of the identified studies were retrospective in design, most were small with heterogenous methods, and there were no randomized trials (although RCTs might pose an ethical challenge in patients with massive PE); nevertheless, there was no significant difference in clinical success rates between the prospective and retrospective study groups. In the same study (12), 96% of patients received CDT as the first adjunct to heparin with no previous systemic tissue plasminogen activator (TPA) infusion, and 33% of cases were initiated with mechanical treatment alone (ie, fragmentation and/or aspiration of emboli) without local thrombolytic agent infusion. In addition, the estimated rate of major complications associated with modern CDT was 2.4%, and most complications were attributed to the use of rheolytic thrombectomy with the use of an AngioJet (Possis Medical, Minneapolis, Minnesota) device (12). The highest complication rates occurred in the 68 patients who underwent CDT with the AngioJet rheolytic thrombectomy device, including 27 minor complications (40%) and 19 major complications (28%), with 5 procedure-related deaths (12); 76% of all major complications recorded in the study (19 of 25) were directly attributed to AngioJet rheolytic thrombectomy despite the fact that it was used in only a small percentage (11%) of the 594 patients studied (12). In this meta-analysis (12), use of the AngioJet device was the only catheter-based treatment associated with procedure-related deaths, and the device currently carries a black-label warning from the Food and Drug Administration (13), stating "There are reports of serious adverse events, including death, associated with cases where the [AngioJet] catheter was used in treatment of pulmonary embolism."

RATIONALE OF CDT FOR SUBMASSIVE PE

Among patients with submassive PE, the initial goal of treatment escalation with thrombolysis is to reduce mortality from PE without increasing the risk of treatment-related complications. Although a recent meta-analysis of randomized trials (7) demonstrated a survival benefit with use of systemic thrombolytic therapy in submassive PE, these data also revealed a much higher risk of major bleeding complications compared with anticoagulation alone. Therefore, the risk-to-benefit ratio of systemic thrombolysis in the submassive PE population is uncertain with regard to clinical decision-making. It is reasonable to hypothesize that delivering a lower overall thrombolytic agent dose via catheter could mitigate the risk of major bleeding complications (14). Interestingly, a previous study on flow dynamics (15) demonstrated that a systemically administered drug makes little contact with an obstructing embolus, and most of the drug flows away from the obstructing clot (ie, Venturi effect) toward the open nontarget vessels. Pharmacologic CDT overrides the Venturi effect because a soft, flexible catheter with multiple side holes is directly inserted under image guidance into the thrombosed target vessel to provide direct intraclot drug infusion. A potential advantage with CDT is targeted drug delivery into the clot to achieve low-dose thrombolysis, which may reduce bleeding risk (14). Therefore, relative to systemic drug therapy, local CDT may improve drug effectiveness, allow a lower drug dose to be used, and result in fewer bleeding complications.

DISCUSSION

Despite some limitations of available evidence (12), CDT is currently considered an acceptable treatment option (as are systemic thrombolysis and surgical embolectomy) for highly selected patients with massive PE (2,3,9). This largely reflects the imminent risk of death and the juxtaposition of a large degree of uncertainty with the estimates of safety and efficacy of CDT and surgical therapy versus the bleeding risk associated with systemic thrombolysis. However, the optimal treatment strategy for submassive PE is still evolving. The 2011 American Heart Association guidelines (2) state that "[systemic] Fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe [right ventricular] RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications… Either catheter embolectomy or surgical embolectomy may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction, or major myocardial necrosis)." The 2014 European Society of Cardiology guidelines (9) state that "Surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative, 'rescue' procedures for patients with intermediate/high-risk PE, in whom hemodynamic decompensation appears imminent and the anticipated bleeding risk under systemic thrombolysis is high." The 2016 American College of Chest Physicians guidelines (3) state: "In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy… Patients who have a higher risk of bleeding with systemic thrombolytic therapy and who have access to the expertise and resources required to do CDT are likely to choose CDT over systemic thrombolytic therapy." A complete summary of these guidelines is included in the **Appendix**.

Because systemic thrombolysis carries a significant risk of major hemorrhage, current guidelines have tempered the indication for use of systemic thrombolysis for intermediate-risk PE, suggesting that it be used only when there is cardiac enzyme leak and/or impending hemodynamic collapse (2,3,9). This causes a dilemma because patients with moderate to severe RV strain are still at risk of sudden cardiac collapse and death before the development of cardiac enzyme leak and impending life-threatening shock (5,6); by then, it may be too late to escalate treatment. Other patients with submassive PE may have severe and persistent pulmonary symptoms (eg, severe hypoxia, tachypnea, and dyspnea on exertion) that is not relieved by therapeutic anticoagulation. In such scenarios, the availability of a treatment option with a more favorable risk-to-benefit profile than systemic thrombolysis would be optimal. It is possible that CDT meets this criterion; however, current estimates of the safety and efficacy of CDT are based on exceedingly limited data and therefore carry major uncertainty. For this reason, even though it is reasonable to target escalation of care to individual patient circumstances (especially for cases bordering on massive PE physiology that are associated with a low risk of bleeding), CDT cannot be firmly recommended for these patient groups at present. Further prospective studies are needed to address these issues, following the lead of three early prospective studies (16–18).