

# Catheter-directed thrombolysis for acute pulmonary embolism: Where do we stand?

Catheter-directed techniques, including catheter-directed local thrombolysis (CDT), have emerged as an attractive alternative to surgical embolectomy for patients diagnosed with acute pulmonary embolism (PE), if they are in need of reperfusion therapy but have absolute or relative contraindications to intravenous full-dose thrombolysis.<sup>[1]</sup> Beyond this relevant but clinically narrow scenario, the popularity of catheter-directed reperfusion modalities recently began to extend to patient groups for whom pharmacological or mechanical thrombus removal has not thus far been recommended as first-line therapy by international guidelines.<sup>[2,3]</sup> In particular, CDT is increasingly being performed in patients with intermediate–high-risk PE, namely, those who are normotensive at presentation but exhibit echocardiographic and laboratory signs of the right ventricular (RV) dysfunction.<sup>[4–6]</sup> Is this increasing popularity of CDT justified, and to what extent is this method feasible and affordable at present?

In the recent years, two interventional studies and a large multicenter registry showed that CDT treatment results in recovery of echocardiographically assessed RV function in patients with intermediate- or high-risk PE.<sup>[4–6]</sup> The phase-2 Ultrasound Accelerated Thrombolysis of PE Trial randomized 59 patients with acute main- or lower-lobe PE and a right-to-left ventricular dimension ratio >1.0 to receive unfractionated heparin plus catheter-directed, reduced-dose, ultrasound-assisted thrombolysis of 10–20 mg recombinant tissue plasminogen activator (tPA) over 15 h, or to be treated with heparin alone.<sup>[4]</sup> In this population, ultrasound-assisted thrombolysis led to improvement of subannular right-to-left ventricular dimension ratio at 24-h follow-up without an increase in bleeding complications.<sup>[4]</sup> In another prospective, single-arm multicenter trial enrolling patients with submassive or massive PE, 150 individuals received 24 mg of tPA for up to 24 h with a significant reduction of pulmonary hypertension and anatomic thrombus burden.<sup>[5]</sup> These favorable results are supported by the PERFECT prospective multicenter registry which included 28 patients with massive and 73 with submassive PE receiving purely mechanical or pharmacomechanical thrombus removal.<sup>[6]</sup>

In the current issue of *Lung India*, two interesting case reports describe the successful use of CDT with tPA delivered through EKOS catheters for the initial management of acute PE.<sup>[7,8]</sup> In the first report by Dr. Singh *et al.*, a patient with intermediate–high-risk PE received continuous infusion at 0.5–1 mg/h for 3 days until

normalization of mean pulmonary artery pressure.<sup>[7]</sup> In the other report, Dr. James *et al.* described the successful use of CDT in a patient with extensive bilateral PE and recent hemorrhagic stroke.<sup>[8]</sup> These reports highlight a key issue related to reperfusion treatment, notably the target populations which might benefit from catheter-directed thrombus removal techniques carrying a (possibly) more favorable risk-to-benefit ratio than intravenous thrombolysis. In fact, the PEITHO trial previously revealed that systemic thrombolysis does not lead to significant early net clinical benefit if used as first-line treatment in patients with intermediate–high-risk PE and does not influence the risk of developing late complications, such as chronic thromboembolic pulmonary hypertension and death.<sup>[9,10]</sup> In contrast, systemic thrombolysis still represents the mainstay of treatment for hemodynamically unstable patients who are characterized by a high risk of early death if the right ventricle is not immediately relieved from the pressure overload.<sup>[2,3]</sup> With respect to catheter-directed reperfusion techniques, both (presumed) noninferior efficacy of CDT, compared to systemic thrombolysis, in high-risk PE, and its superior safety in intermediate–high-risk PE as suggested by the results obtained thus far, remain to be confirmed by studies in larger patient populations. Availability of such data will, over the long-term, be the prerequisite for sustaining the spread and justifying the economic coverage by health systems of CDT worldwide. In a recent European annualized model estimating venous thromboembolism-associated costs, it has been calculated that the median costs for the management of a single episode of major bleeding were almost 2.5-fold higher than those for acute PE, therefore largely contributing to the annual spending.<sup>[11]</sup> This economic perspective reinforces the concept of optimizing the safety of treatment and, more specifically, reperfusion options in acute PE.

Catheter-directed reperfusion techniques are perceived as low-risk interventions in terms of major bleeding, and this also appears to be supported by the reports published in *Lung India*.<sup>[7,8]</sup> This, however, does not mean that CDT can safely be performed anywhere and by anyone. In patients receiving systemic thrombolysis in PEITHO, the 7-day rate of major bleeding was between 8.3% (by GUSTO criteria) and 11.5% (by ISTH criteria);<sup>[9]</sup> a similar rate (9.9%) was described in a recent meta-analysis by Marti *et al.*<sup>[12]</sup> In comparison, available data for CDT reported rates of major (moderate to severe GUSTO) bleeding ranging from 0% to 10% in recent interventional studies.<sup>[4,5]</sup> The results of a recent meta-analysis of 35 interventional and observational (“real world”) studies on CDT calculated a

pooled rate of 6.6% for major bleeding.<sup>[13]</sup> If one considers fatal and intracerebral bleeding events only, none of such devastating events occurred in the interventional ULTIMA and SEATTLE II studies,<sup>[4-6]</sup> while data from meta-analyses suggested event rates of approximately 2.8% in patients undergoing CDT.<sup>[13]</sup> Taken together, these data underline the fact that CDT should be performed only in experienced and qualified centers with high volumes of patients.

Finally, the reports in Lung India also point to the longer times of preparation and performance of CDT compared to peripherally administered systemic thrombolysis. This might limit the use of CDT in severely compromised patients in need of immediate reperfusion. The results of the OPTALYSE PE study (NCT02396758), which is testing different dosages and treatment durations in patients with acute submassive PE, and of the RE-SPIRE study (NCT02979561), will provide more insights on this topic.

Whether CDT will ultimately establish itself as the better alternative to systemic thrombolysis for high-risk PE patients, and to standard anticoagulation in selected intermediate–high-risk patients, remains to be established. The safety profile of CDT, which will ultimately determine the impact of this intervention in terms of net clinical benefit, will also play a major role in justifying reimbursement by health systems. On the basis of the current knowledge, interventional reperfusion treatment can already be considered in both PE risk categories on an individual basis provided that local expertise is available.

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### Conflicts of interest

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