Limitations and Future Perspectives on Pulmonary Embolism: So Far, So Good

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Pulmonary embolism (PE) represents the third most common cardiovascular emergency and, despite continuous diagnostic–therapeutic progress, has high mortality and morbidity rates.[1] In Italy, the estimated annual incidence of PE is around 60,000 new cases, but in autopsy studies the prevalence of unsuspected PE, whether fatal or as a contributing cause of death, is between 3% and 8%.[2]

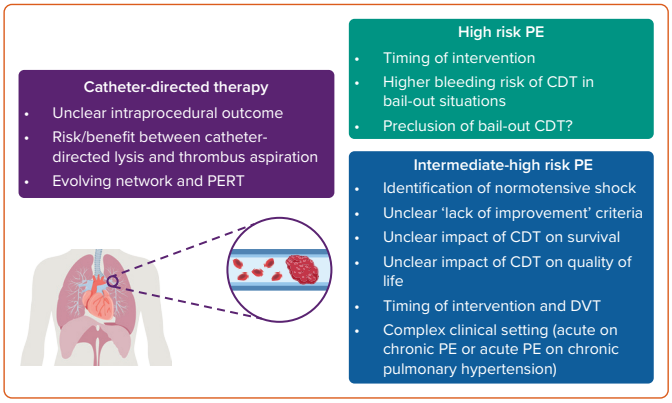
Risk stratification is of paramount importance, allowing diagnostic and therapeutic processes to be guided more accurately. In its latest (2019) guidelines, the European Society of Cardiology (ESC) introduced a new classification for PE based on the expected risk of death in the short term, dividing patients into high-, intermediate- to high-, intermediate- to low- and low-risk categories.[3] High-risk PE is characterised by haemodynamic instability, is associated with a high mortality rate (around 30–60%) and requires prompt and aggressive treatment.[4] Systemic thrombolysis represents the treatment of choice for high-risk PE, but there are relative or absolute contraindications to its use. Almost 40% of PE patients have absolute or relative contraindications to systemic thrombolysis. In this case, according to 2019 ESC guidelines, catheter-directed therapy (CDT) may be a reasonable solution.[3] CDT should be considered for PE patients in whom systemic thrombolysis is contraindicated or has failed.[5] Nevertheless, despite this growing interest and recent studies, comprehensive data are lacking because there are some limitations and pitfalls of this invasive treatment.[6–9]

Risk assessment is fundamental for the precise management of PE. Most of the time this requires a multiparametric approach and, when haemodynamic instability is excluded, risk stratification through prognostic scores, imaging and laboratory data is recommended.[3] The Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI) have been shown to be solid predictors of low-risk PE.[10,11] Conversely, Classes III–V of PESI identify a various spectrum of risk: from intermediate- to low- (mostly Class III) to intermediate- to high-risk patients (Classes IV and V), especially if right ventricle dysfunction and elevated troponin levels are present. In this scenario, a clinical decision for a timely and selected invasive intervention is often a case-by-case call such that the experience of the centre is of utmost importance in choosing the appropriate treatment for the appropriate patient. Moreover, the PESI/sPESI score is insufficient for detecting normotensive shock, which must be clearly recognised in intermediate- to high-risk patients, as they may progress to high-risk status, sometimes without obvious clinical signs.[12]

In this setting, CDT is reserved for patients with thrombolysis contraindication or failure.[3] Indeed, the definition of thrombolysis failure is controversial.[13] Actual expert agreement suggests that thrombolysis failure be defined as the persistence of a 'lack of improvement' criterion at 2–4 hours after the administration of lysis.[13] This is a questionable definition without a clear cut-off; indeed, due to cardiogenic shock, the clinical scenario may evolve rapidly in 2–4 hours and may be fatal for patients. Conversely, patients at intermediate to high risk have a very dynamic clinical presentation characterised by various degrees of haemodynamic compromise (sometimes resuscitated cardiac arrest or sliding towards cardiogenic shock), respiratory failure and right ventricular compromise. Almost 5% of patients at intermediate to high risk may progress to haemodynamic deterioration.[14] Further, up to 10% of patients experience recurrence of PE in the first 1 month after discharge that may be catastrophic and approximately 2% may develop chronic thromboembolic pulmonary hypertension.[9] Appropriate timing criteria for patients at intermediate to high risk lack solid data, especially for late diagnosis when an invasive approach may not be helpful, or at least may be contraindicated. In this regard, adequately powered randomised controlled trials are advised so as to build comprehensive evidence for the acute coronary syndromes.

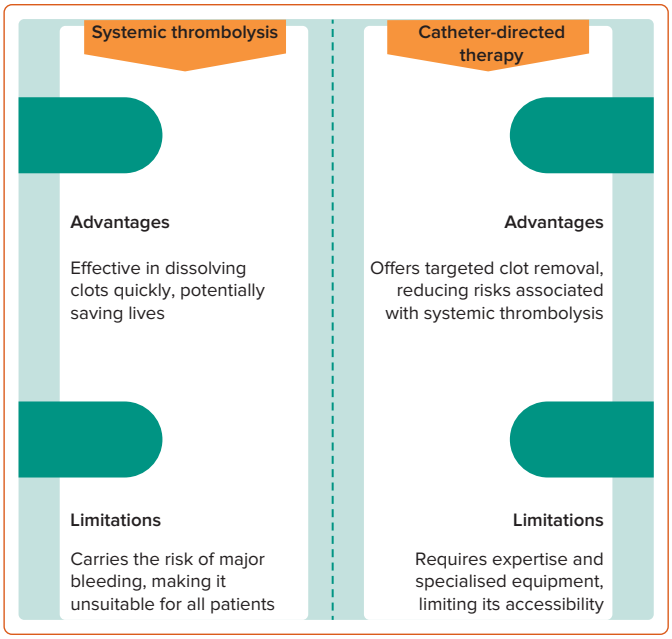
Another point is the absence of standardised definitions of improvement criteria and therapy failure for CDTs, especially in patients at intermediate to high risk. In this scenario, early (or at 30 days) lack of significant improvement in right ventricular size and function or decreases in the right to left ventricle ratio or pulmonary artery systolic pressure after therapy may be considered as therapy failure in this population. Nevertheless, there are no clear validated criteria as yet and no other predictors of failure that are correlated with worse prognosis as exist for no-reflow or thrombolysis in MI flow for ST elevation MI. Furthermore, there is no universally accepted definition of acute or subacute CDT failure in the literature.

Figure 1: Pitfalls in Pulmonary Embolism Intervention



CDT = catheter-directed therapy; DVT = deep vein thrombosis; PE = pulmonary embolism; PERT = pulmonary embolism response team.

Figure 2: Systemic Thrombolysis versus Catheter-directed Therapy



Further studies are needed to evaluate potential markers, especially in the case of 'lack of improvement', to select patients who may benefit the most from interventional therapy. There are no definitive criteria that could help to select this subpopulation, which may be correlated with a higher rate of chronic PE, increased risk of post-PE syndrome and reduced quality of life. Another subpopulation that may benefit from a more advanced therapy is the group of patients with PE on top of chronic pulmonary hypertension for other reasons (e.g. chronic obstructive pulmonary disease, left heart failure). These patients may experience a higher rate of clinical destabilisation, a lower rate of right ventricle recovery and a lower quality of life. The scenario of acute PE on chronic pulmonary hypertension is relatively common in older age, but particularly in the absence of known medical history, a clear pathophysiological definition is very difficult.

As for intermediate- to high-risk PE, in the haemodynamically setting, the role of the PE response team is fundamental in identifying clinical nuance that may inform the choice of CDT or conservative treatment for individual patients (*Figures 1, 2*). The round-the-clock availability of an extracorporeal membrane oxygenation team is necessary due to the non-negligible rate of cardiac arrest during clinical observation or the PE intervention. With this in mind, careful consideration should be given to the organisation of a PE network.[5]

PE bail-out intervention on top of systemic thrombolysis is associated with a higher bleeding rate and although the lysis itself may be ineffective, the consistency of the thrombus changes, becoming more friable.[15] In this specific situation, CDT is much more difficult due to the high risk of thrombus fragmentation and embolisation during aspiration manoeuvres. Indeed, as for intermediate- to high-risk PE, there are no clear criteria indicating 'lack of improvement', even after thrombolysis, and the timing for re-evaluation and bail-out intervention is crucial in this high-risk scenario.

From a technical point of view, the timing of PE (and deep vein thrombosis) is not always easy to define in intermediate- to high-risk patients. Thrombus composition is crucial for safety and efficacy.[16] CDT is much more challenging in the presence of a more aggregate thrombus infiltrated by monocytes, macrophages and fibroblasts, which synthesise collagen.

Another specific situation is disseminated embolic spray, in which case large-bore devices may not be able to reach the distal ramifications of the pulmonary circulation, such that the treatment of distal embolisation and thrombus fragmentation to peripheral vessels remains an unmet need. This is an important consideration for long-term follow-up, especially in preventing late complications of PE, such as pulmonary hypertension caused by chronic thromboembolism and thrombus stratification/hyalinisation in the small vessels. Still, appropriate timing of the intervention is critical in this scenario, and the ESC guidelines recommend early intervention in high-risk patients: within 60 minutes of the diagnosis or up to within 90 min of the diagnosis if the diagnosis is made in a centre that does not perform percutaneous treatment.[3]

Intraprocedural outcomes are another point of uncertainty. Generally speaking, during an interventional procedure, the marker of success should be a predictor of good outcome. Although in high-risk PE with haemodynamic instability, reductions in lactate concentrations and heart rate with an increase in systolic blood pressure could be considered markers of a good prognosis (even in the absence of clear cut-off values), it is much more difficult to predict prognosis in patients at intermediate to high risk. These patients may not be tachycardic and could be normotensive, and it could be difficult to assess the intraprocedural thrombus burden with angiography (thus making hardly a marker). However, pulmonary pressure can be easily evaluated. Taking into account factors that could affect pulmonary pressure, such as blood loss due to the CDT and potential development of anaemia or difference in intraprocedural ventilation, previous studies have reported that a mean drop in mean pulmonary artery pressure of 7 mmHg is associated with <1% mortality at 30 days.[12,17,18]

There are some new advances in the field to help with clinical decision-making. For example, artificial intelligence (AI) is being increasingly used in medicine, mostly to help with decision-making.[19] With regard to PE, the application and focus of AI have been mainly practical to increase diagnostic sensitivity.[20] In addition, there is increasing evidence that AI may play a role in helping physicians stratify the risk of PE.[21,22] Risk assessment and therapy selection remain unmet needs in the field, especially in the grey zone of intermediate- to high-risk PE, where AI could provide support for appropriate therapy selection, especially when to escalate to invasive treatments.

Various ongoing trials in intermediate- to high-risk populations will provide greater insights into the future directions of invasive treatment for PE. Three different types of technology are being investigated versus standard anticoagulation: aspiration thrombectomy, CDT thrombolysis (CDTL) and ultrasound-assisted thrombolysis (USAT).

In the aspiration thrombectomy field, the PEERLESS II trial (NCT06055920) is randomising 1,200 intermediate- to high-risk patients to FlowTriever treatment or standard anticoagulation alone to assess 30-day haemodynamic decompensation and all-cause hospital readmissions, as well as 3-month all-cause mortality, PE-related mortality and major bleeding. The STORM-PE trial (NCT05684796) is comparing patients treated with the recent 12 Fr Indigo (Penumbro) pigtail catheter for mechanical fragmentation and aspiration embolectomy to those treated with standard anticoagulation protocols.

With regard to CDTL, the PRAGUE-26 (NCT05493163) trial is enrolling 558 patients to assess the use of heparin in combination with CDTL versus standard anticoagulation protocols, with the aim of reducing the 7-day incidence of all-cause death, haemodynamic decompensation and PE recurrence. The PE-TRACT trial (NCT05591118), a Phase 3 trial, will evaluate the short-term safety and efficacy of CDTL or mechanical thrombectomy versus standard anticoagulation protocols in 500 patients.

Two specific trials are comparing USAT to standard anticoagulation protocols. The HI-PEITHO trial (NCT04790370) is enrolling 406 patients to evaluate the use of heparin in combination with USAT versus anticoagulation, focusing on the 7-day incidence of all-cause death, haemodynamic decompensation and PE recurrence. The STRATIFY trial (NCT04088292), a Phase 3 trial, is comparing USAT, low-dose systemic thrombolysis and a standard anticoagulation protocol in 210 patients in a three-arm design with the aim of demonstrating reductions in the Miller score, as assessed by pulmonary CT at 96 hours.

In addition to expected new evidence from the upcoming trials, the increasing complexity of medicine warrants decision-making guidance from multidisciplinary teams. To this end, some institutions have created PE response teams consisting of emergency medicine physicians, interventional radiologists, cardiologists and pulmonologists.

There is increasing data that activation of PE response teams is associated with lower mortality rates at 30 and 90 days and reduced readmissions among patients with PE compared with patients without PE response team activation.[23,24] In addition to intrahospital organisation, the development of an emergency PE treatment network, like current networks for the treatment of ST elevation MI, may be the next big step in cardiology, but data are needed. ❑

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