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New Strategies in the Treatment of Pulmonary Embolism

ABSTRACT

KEY WORDS: pulmonary embolism, catheter-based therapy, thrombolysis

Pulmonary embolism (PE) represents a major cause of cardiovascular morbidity and mortality. Over the last few years, there has been an increase in the incidence of PE, while simultaneously the mortality rates associated with PE have been declining. The improved survival rates in PE are likely to result from the better availability of more precise diagnostic methods, better adherence to guidelines and the use of new enhanced therapeutic options. Since hemodynamic compromise is the principal cause of poor outcome in patients with acute PE, early identification of patients at risk and appropriate risk stratification of patients with PE are essential for further management and can direct the use of more invasive treatment strategies. Anticoagulation therapy is the cornerstone of treatment for acute PE, while for hemodynamically unstable patients, systemic thrombolysis is the recommended treatment of choice. However, systemic thrombolysis comes with a cost of increased risk for major bleeding, including possibly fatal intracranial bleeding. Interventional catheter-based therapies with mechanical thrombectomy or catheter-directed thrombolysis with very low doses of thrombolytic offer the possibility for this bleeding risk to be minimized, while sufficient recanalization of pulmonary arteries allows for hemodynamic stabilization and improves the patient's symptoms. The decision when to use interventional procedures over pharmacological treatment is still a matter of debate, especially in the intermediate-high-risk group of PE patients. Ongoing studies comparing one interventional method against another, and catheter-based therapies against anticoagulation are ongoing. While the results of these studies are eagerly awaited, implementations of local hospital protocols for optimal PE treatment with consultations between multidisciplinary specialists in the so-called PE response team are suggested.

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INTRODUCTION

Venous thromboembolism, encompassing deep vein thrombosis and pulmonary embolism (PE), represents the third most frequent cause of cardiovascular disease, with PE being one of the leading causes of death in hospitalized patients. The incidence of PE varies between regions and is reported to range from 39–115 per 100,000 persons, with a higher incidence amongst the elderly. Due to the increasing use of diagnostic high-resolution contrast-enhanced CT of the chest in everyday clinical practice, especially in cancer patients and the aging population, the incidence of PE has been increasing in the last 20 years. However, time trend analysis suggests that case fatality rates of acute PE may be decreasing in the last years *(1)*. This can be explained by more incidental diagnosis of PE and reports of minor subsegmental PE, which may not have the same serious consequences, but also by better patient and physician disease awareness, adherence to guidelines, and possibly also due to the use of new more effective treatment strategies.

Since the pulmonary circulation in healthy individual is a low-pressure and low-resistance circuit, the right ventricle (RV) is especially susceptible to failure in response to sudden increases in vascular resistance, as is seen with acute PE. A failing RV leads to impaired left ventricle filling and increased pericardial pressure from the enlarging right heart. Since the interventricular septum is affected, left ventricular stroke output is also decreased, leading to neurohormonal activation to stimulate the contractility and inotropy of the myocardium. Low cardiac output and pulmonary vasculature obstruction cause ventilation/perfusion mismatch, which contributes to hypoxemia. The reduction in systemic blood pressure together with the rise in RV end-diastolic pressure impairs the right coronary perfusion causing a further imbalance between oxygen demand and myocardial oxygen delivery, which leads to myocardial ischemia, further worsening of RV performance and ultimately death *(1)*.

PATIENT STRATIFICATION AND TREATMENT OPTIONS

Early identification of PE patients that are at risk of hemodynamic compromise and death is of paramount importance, and the stratification of patients based on their clinical state, comorbidities, laboratory markers of myocardial ischemia and presence of right heart dysfunction guides further therapeutic decisions. Incorporating validated clinical scores, such as the Pulmonary Embolism Severity Index (PESI) and the simplified PESI, allows for the assessment of a patient's overall mortality risk and early outcome.

Patients with hemodynamic instability are stratified into a high-risk group, while hemodynamically stable patients are further stratified into a low- or intermediate-risk group based on the above-mentioned criteria.

The intermediate-risk group of patients is further divided into intermediate-low and intermediate-high-risk, with the latter having both positive serum troponin and signs of RV dysfunction on imaging, while the intermediate-low-risk group has none or only one of these criteria, but presenting an elevated PESI score.

Patients with PE, whose condition is hemodynamically stable and who have no RV strain, normal cardiac biomarkers and a low PESI score, are considered to have low-risk PE.

Current treatment guidelines recommend the prompt initiation of anticoagulation therapy in all patients with PE and also recommend systemic thrombolysis (ST) in high-risk PE patients *(1)*. ST is associated with a high risk of major bleeding, including possibly fatal intracranial haemorrhage, therefore, it is estimated that up

to half of high-risk patients do not get ST due to a perceived increased risk of bleeding *(2)*. In patients with intermediate-high-risk PE, thrombolytic therapy with full dose recombinant tissue-type plasminogen activator (rtPA) is associated with a significant reduction in the risk of hemodynamic decompensation or collapse, but it is paralleled by an increased risk of severe extracranial and intracranial bleeding. Smaller studies and meta-analyses have shown a favourable safety profile of ST with a reduced dose rtPA in these patients, which still proved good efficacy, while an ongoing study is set to confirm these findings *(4)*.

With the advancement of interventional therapies, new therapeutic options became available for high- and intermediate-high-risk PE patients who are not candidates for ST. A reperfusion of the pulmonary arteries can be achieved by inserting a catheter into the proximal pulmonary artery and aspirating the thrombus – mechanical thrombectomy (MT). Large bore aspiration catheters are used to remove the thrombus, which can be done quickly and without any patient sedation. Due to the large diameter of the catheter, careful manipulation and continuous patient monitoring during the procedure is suggested *(2)*.

Alternatively, a catheter can be left in place for a few hours, and very low-dose rtPA perfused through the catheter to achieve local thrombolysis with minimal systemic effect. The vast majority of data for the latter procedure in PE patients comes from using an ultrasound-facilitated catheter-directed thrombolysis (CDT). Both MT and CDT are effective in reducing the RV diameter and pulmonary artery pressures after reperfusion, but there is little data on hard clinical outcomes in PE patients, such as death or hemodynamic collapse from randomized controlled trials. The FLAME study, which was a prospective nonrandomized interventional study in high-risk PE patients with hemodynamic instability, has shown that patients who got MT had only a 1.9% in-hospital mortality and a 15.1% probability of clinical deterioration *(5)*. These numbers are much lower than expected in such a high-risk group, but those were selected patients in a nonrandomized study.

While the need for immediate reperfusion therapy in the high-risk group of PE patients is undeniable, this treatment strategy is less clear in the intermediate-risk group. As stated before, ST is effective, but its use was counterbalanced by increased risk of bleeding. It is still not known whether using interventional catheter-based therapies (CBT), MT or CDT, offers a better safety and efficacy profile than ST or even anticoagulation alone. There are ongoing studies that will hopefully answer this question. Meanwhile, implementations of local hospital protocols for optimal PE treatment with consultations between multidisciplinary specialists in the so-called PE response team are suggested *(1)*. Considering the patient's clinical state and the risk for hemodynamic collapse and bleeding, a decision is to be made regarding the best treatment option. An analysis of registry data has identified certain patient characteristics that are correlated with worse outcomes in intermediate-high-risk PE patients. These are elevated serum lactate levels, tachypnoea, sinus tachycardia, systolic blood pressure below 110 mmHg or shock index (pulse/systolic blood pressure) above 1, elevated markers of RV function and ischemia (elevated troponin, elevated B-type natriuretic peptide, reduced RV function), central and large thrombus burden (saddle PE), concomitant proximal deep vein thrombosis or a right heart thrombus *(6)*. Currently, CBT should be considered for patients with high-risk PE in whom thrombolysis is contraindicated or has failed. Failure after ST has been reported in up to 8% of patients and is defined as no hemodynamic improvement after two to four hours. CBT is also

a treatment option for initially stable patients in whom anticoagulant treatment fails, i.e., those who experience hemodynamic deterioration despite adequately dosed anticoagulation, and should be considered when no improvement is achieved after 24–48 hours of initial anticoagulation *(2)*.

In patients with intermediate-risk PE and after CBT, a full dose of parenteral anticoagulation, preferably with low-molecular-weight heparin, is recommended. For stable patients, a switch to a direct oral anticoagulant (DOAC), such as apixaban, edoxaban, rivaroxaban, or dabigatran is also possible. In intermediate-risk PE patients, a change to a DOAC after 72 hours of parenteral anticoagulant is safe, while in low-risk PE patients, an upfront DOAC therapy with apixaban or rivaroxaban is possible *(7)*.

CONCLUSION

PE treatment is evolving with new CBTs offering an effective and fast reperfusion of pulmonary vasculature in patients with high- or intermediate-high-risk PE. While these procedures are already performed in everyday clinical practice, their benefit is still to be proven. Results from ongoing randomized trials will hopefully give us a better insight into whom we should treat more aggressively and whether these procedures provide any benefit to PE patients in the long term.

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