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Progress in Interventional Radiology Treatment of Pulmonary Embolism: A Brief Review

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Abstract

Pulmonary embolism represents a common life-threatening condition. Prompt identification and treatment of this pathological condition are mandatory: in case of massive pulmonary embolism and hemodynamic instability or right heart failure, interventional radiology treatment for pulmonary embolism is emerging as an alternative to medical treatment (systemic thrombolysis) and surgical treatment. Interventional radiology techniques include percutaneous endovascular catheter directed therapies, as selective thrombolysis and thrombus aspiration, which can prove useful in case of failure or infeasibility of medical and surgical approaches.

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INTRODUCTION

Venous thromboembolism (VTE), clinically presenting as deep vein thrombosis (DVT) or pulmonary embolism (PE), is the third most frequent acute cardiovascular syndrome globally, after myocardial infarction and stroke ^[1]. Approximately one third of all patients with a new diagnosis of VTE have PE, with or without DVT ^[2]. PE can be defined as the occlusion of the pulmonary arteries or its branches with embolic material (thrombus, air, fat, or amniotic fluid) that originates elsewhere in the body. Most commonly, the cause is a thrombus arising from the deep veins of the lower extremities, which travels to the pulmonary circulation. Diagnosis of PE can be subtle, as there are

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no specific symptoms, and clinical presentation varies widely, ranging from asymptomatic to sudden cardiac death, which is seen in 25-30% of patients [3]. There have been many advances in the field of PE in the recent decade(s): the development of new diagnostic and therapeutic strategies, including medical and surgical treatment as well as endovascular therapy, has led to an increasing complexity of patient treatment and, consequently, to the need of optimizing the management of this serious condition.

PHYSIOPATHOLOGY

PE, by definition, is characterized by presence of emboli in the pulmonary arterial circulation. Most emboli originate as thrombi in the deep veins of the lower extremities; the most common site of thrombosis is represented by the calf veins, followed by femoro-popliteal veins, and iliac veins. Less frequently, emboli arise from upper extremity veins, and are typically associated with central venous catheters, intracardiac devices, malignancy, or venous trauma. A smaller percentage of PE is caused by pelvic DVT, but they are generally associated with a predisposing factor such as pelvic infection, pelvic surgery, or pregnancy [4]. When 25–30% of the pulmonary vasculature is obliterated by a thrombo-embolus, pulmonary artery pressure (PAP) begins to increase. However, the mechanical obstruction is not the only element leading to pulmonary hypertension: the disruption of the alveolar-capillary membrane by the thrombi results in decrease of oxygen diffusion, with subsequent hypoxia and release of vasoconstrictors that contribute to the acute development of pulmonary hypertension [5]. The increase of pressure in the pulmonary artery determines heterogeneity of pulmonary perfusion, leading to the simultaneous presence of hypo- and hyper-perfused areas; there will be an imbalance between ventilation and perfusion, generating hypoxemia [6]. Moreover, PE can have significant cardiac and hemodynamic consequences, related to the size of emboli and the presence or absence of underlying cardiopulmonary disease (CPD). In healthy patients, the mean pulmonary artery pressure can be up to 40 mmHg acutely; right ventricle (RV) failure ensues when 50-75% of pulmonary arteries are obstructed [7]. When the degree of pulmonary artery

obstruction exceeds 50-75%, the right heart dilates and the combination of the increased wall stress and cardiac ischemia impair RV function and left ventricular (LV) output, leading to hypotension [8]. The presence of a pre-existing CPD results in diminished pulmonary vascular reserve and hemodynamic compromise at a lower level of pulmonary arterial obstruction.

PULMONARY EMBOLISM RISK STRATIFICATION

The American Heart Association (AHA) and the European Society of Cardiology (ESC) classified PE according to its severity, identifying three main categories [1,9].

Patients with massive (AHA) or high risk (ESC) pulmonary embolism present with hypotension, defined as a systolic blood pressure lower than 90 mmHg, or a drop of > 40 mmHg for at least 15 minutes, or need for vasopressor support.

Submassive (AHA) or intermediate risk (ESC) classifications slightly differ as, according to AHA, patients with submassive PE present with a RV strain with no hypotension. RV strain is defined as: RV dysfunction on echocardiography or computed tomography pulmonary angiography (CTPA), RV injury identified by an increase in cardiac biomarkers as troponins or brain natriuretic hormone. On the other side, the ESC criteria for intermediate-risk PE include patients with a simplified Pulmonary Embolism Severity Index (PESI) score ≥ 1 , regardless of RV strain. The PESI score is based on patient's age, comorbidities, heart rate, blood pressure, and oxygen saturation. Moreover, the ESC sub-classifies intermediate-risk patients in two groups based on RV dysfunction and RV injury (intermediate risk - high), or only one or neither of these findings (intermediate risk - low).

Low risk patients, according to both AHA and ESC, do not meet criteria for the abovementioned risk categories.

MEDICAL AND SURGICAL TREATMENT

Severe pulmonary embolism brings to hypoxaemia due to the ventilation-perfusion mismatch. Therefore, it is advised to use oxygen in patients with oxygen saturation

(SaO₂) < 90%. High-flow oxygen and mechanical ventilation should be taken in consideration when extreme hemodynamic instability is present (i.e. cardiac arrest), even though obtaining a good hypoxemia correction is not completely possible without PE reperfusion techniques [10,11]. Intubation should be considered in patients which are not manageable with non-invasive ventilation [1].

Acute RV failure is a cause of death in high-risk PE patients, due to the reduction of cardiac output. When low central venous pressure is present, modest fluid challenge (< 500 mL) could be an option, increasing cardiac index in these patients [12]. On the other hand, fluid challenge could also over-distend the RV, leading to a reduction of cardiac output, therefore it is recommended to use it wisely [13]. If signs of elevated central venous pressure are present, no volume loading is advised. Vasopressors are often necessary in association with reperfusion treatment (medical, surgical or interventional). Norepinephrine leads to an improvement in coronary perfusion and ventricular systolic interaction, without changing pulmonary vascular resistance (PVR) [14]; the use of norepinephrine should be limited in patients with cardiogenic shock.

Temporary extracorporeal membrane oxygenation (ECMO) could be used in patients with a high-risk pulmonary embolism, cardiac arrest, and circulatory collapse, but its use needs to be further tested with clinical trials [15,16].

Acute pulmonary embolism may lead to cardiac arrest, in which case the current ALS (advanced life support) guidelines have to be followed [17].

Moreover, in patients with intermediate to high-risk of PE, it is advised to start subcutaneous anticoagulation while waiting for diagnostic tests, usually with low-molecular weight heparin (LMWH), fondaparinux or unfractionated heparin (UFH) [18]. Clinical trials with non-vitamin K antagonist oral anticoagulants (NOAC) are ongoing. Vitamin K antagonists (VKAs) are vastly used for oral anticoagulation in recent years; when VKAs are used, LMWH or UFH should be continued associated with oral anticoagulants for more than 5 days until INR (International Normalized Ratio) value reaches 2-3 for 2 days [19].

Regarding reperfusion treatment, systemic thrombolysis leads to fast improvement of the pulmonary obstruction and cardiovascular parameters in patients with PE, compared to medical treatment alone [20,21]. The best results are obtained when reperfusion treatment starts 48 h after symptoms onset; however thrombolysis could be useful even after 6-14 days [22]. Intravenous administration of recombinant tissue-type plasminogen activator (rtPA) is preferred to first generation thrombolytic agents (i.e. urokinase) [23].

Surgical embolectomy in patients with acute PE is performed through cardiopulmonary bypass, with incision of the pulmonary arteries and clots removal. This approach is advised in high-risk PE and in selected intermediate risk patients [1,24].

ENDOVASCULAR TREATMENTS: CURRENT EVIDENCES AND FUTURE PERSPECTIVES

Catheter Directed Thrombolysis

Catheter directed thrombolysis (CDT) gives the ¹ advantage of locally delivering a high concentration of fibrinolytic agent to a great clot surface. This way, fibrinolytic dose can be greatly reduced compared to the systemic one, and side effects are therefore lower. A routine-use diagnostic angiography catheter with multiple holes can be used to deliver the fibrinolytic agent and increase its local blood concentration. This could enhance the efficiency of fibrinolysis, reducing the risk of bleeding. Each pulmonary artery is catheterized with a multihole catheter, and a fibrinolytic agent such as tissue plasminogen activator (tPA) is injected through the clot, at a rate of 1 mg/h for 24h in case of a unilateral PE (single device) and 1 mg/h for 12h if bilateral PE (double device) (SEATTLE II Trial) [25]. A more recent trial, the OPTALYSE PE trial, analyzed the possibility to further lower the dose of tPA with shorter infusions. The total dose was significantly lower, ¹⁶ ranging from 4 to 12 mg per lung, and shorter infusion times (2 to 6 hours) [26].

¹ Efficient systemic administration of heparin is continued throughout the endovascular fibrinolysis procedure. Despite the lack of randomized trial studies comparing

endovascular and systemic thrombolytic therapy, several comparative studies have been carried out. In a meta-analysis of Bloomer *et al*, the rate of intracranial hemorrhage (ICH) with CDT was 0.35%, which is significantly lower than that reported with systemic thrombolytics in other randomized trials (1.46%) [27]. Bloomer *et al* also found that the rate of major bleeding or vascular complication was 4.65%, and the observed mortality rate was 3.4% (12.9% in the massive PE group, 0.74% in the submassive PE group).

In addition, results of an American national registry enrolling 3107 patients which underwent systemic fibrinolytic treatment and 1319 patients undergoing CDT, showed that systemic thrombolysis group had increased rates of bleeding-related mortality (18.1% vs 8.4%), general mortality (14.9% vs 6.12%), and rehospitalization (10.6% vs 7.6%) [28]. According to these data, the risk of fatal bleeding is lower during CDT than in case of systemic thrombolysis. This can be due to the higher (approximately fourfold) dose of fibrinolytic agent used in systemic thrombolysis. However, as these data are extracted from a national registry and not from randomized studies, they should cautiously be taken in consideration. The ongoing PE-TRACT and HI-PEITHO studies are designed to overcome this issue.

Mechanical Thrombectomy

In case of massive PE, the first aim should be to quickly declot the affected pulmonary artery to decrease pulmonary hypertension and the risk of RV failure. Initial fragmentation or thrombectomy by different devices (Table 1) can help reduce the thrombotic load and improve reperfusion. In addition, fragmentation of the clot exposes a greater surface of the thrombus, increasing the efficacy of local or systemic therapies [29].

Current catheters for mechanical thrombectomy or endovascular aspiration are classified based on the mechanism of action:

Rheolytic: AngioJet (Boston Scientific, Massachusetts, USA) working mechanism is determined by aspiration of the thrombus using the Venturi-Bernoulli effect. It creates a

suction effect with high-pressure jets in the catheter's distal holes. Various complications (e.g. bradycardia and heart attack, severe hemoptysis, kidney failure, as well as intra-and peri-procedural deaths) were reported during the use of this device [30]; hence, the use of AngioJet as a first-approach treatment should be avoided. Currently the main indication of this product remains treatment of peripheral venous districts.

Rotational: a relatively new device for treatment of PE is Aspirex (Straub, Wangs, Switzerland). Launched on market in mid 2010, the Aspirex catheter acts as an archimedean screw that rotates inside the catheter lumen; this spiral mechanism provides an aspiration supplied by an active motor. Clinical results are promising; however, only recent studies with small cohorts of patients demonstrated its safety and efficacy, and there is a lack of randomized studies supporting these evidence [31]. Two European case series have been reported, with complete thrombus clearance observed in 83% to 88% of patients with intermediate- and high-risk PE [31,32].

Aspiration: the Indigo mechanical aspiration system (Penumbra, Alameda, United States) is an aspiration thrombectomy catheter system. A large caliber (8 French) catheter with a directional soft tip, allows easy aspiration of the clots in the pulmonary arteries due to the great suction power of a suction pump. Several studies are being performed to evaluate safety and efficacy of this device. The recent Indigo Aspiration System for Treatment of Pulmonary Embolism Trial (EXTRACT-PE), a prospective multicenter study on 119 patients demonstrated a significant reduction in the RV/LV ratio and a low major adverse event rate in submassive PE patients treated with the Indigo CAT8 aspiration system, with a reduction of administered intraprocedural thrombolytic drugs, which were avoided in 98.3% of patients [33]. The indigo CAT8 received FDA approval for PE treatment in December 2019. The system is being monitored to assess its safety even in real-world clinical practice, showing a low incidence of reports linked to the product [34]. FlowTrievers® System (Inari Medical) is another aspiration device: its mechanism features three self-expanding nitinol mesh disks designed to engage, disrupt, and deliver clot to the Triever Aspiration Catheter for extraction. It has been

evaluated in a recent single-arm multicenter trial involving 106 patients (FLARE Study) and appears safe and effective in patients with acute intermediate-risk PE, with significant improvement in RV/LV ratio and minimal major bleeding [35]. In 2021 Inari Medical, Inc. announced enrollment of the PEERLESS randomized controlled trial (RCT) comparing the clinical outcomes of patients with intermediate-high risk pulmonary embolism treated with the company's FlowTrier system vs CDT (NCT05111613). PEERLESS is a prospective, multicenter trial that will include up to 700 patients and 60 centers in the United States and Europe. It will be the first ever RCT to compare mechanical thrombectomy to catheter-directed thrombolysis for the treatment of PE and aims to provide definitive data on interventional treatment options for these patients.

Fragmentation: the EKOSonic system (Boston Scientific, Massachusetts, USA) is an ultrasound-assisted catheter-directed thrombolysis system which was specifically indicated for treatment of pulmonary embolism. The ultrasound waves which depart from the interior of the 5.4 French catheter, can reach and treat the whole thrombus; in addition, fibrinolytic agents infusion can be performed from the catheter, combining the two treatment modalities. The functioning tip of the catheter can be of different lengths, with a range from 6 to 50 cm. Although it has been associated with a relatively safe and effective profile the clinical benefits of this treatment when compared to classical CDT has yet to be proven [25]. Ultrasound-assisted thrombolysis shown, in a randomized trial named ULTIMA, to determine faster decrease of RV/LV ratio in patients with acute onset of intermediate-risk PE when compared to medical treatment, with no occurrence of major bleeding. However, the Authors did not observe variations in 90-day patient's mortality [36].

CONCLUSION

Actual ESC guidelines indicate that in high risk or intermediate/high risk patients (with RV dysfunction at trans-thoracic US or at CT pulmonary angiography, or PESI greater than 1, and positive troponin test), reperfusion treatments should be performed, in

association with prompt hemodynamic support ^[1]. However, systemic thrombolysis is actually considered as the first indication, and as literature evidence states, ¹¹ surgical pulmonary embolectomy is recommended in patients with high risk PE in whom systemic thrombolysis is contraindicated or has failed (level of evidence I). Percutaneous catheter-directed treatment has only level of evidence IIa and, therefore, should be actually conditionally considered after failure or infeasibility of the abovementioned medical and surgical therapies ^[2].

¹⁷ Set up of a multidisciplinary team and of management protocols for high and intermediate/high risk patients with PE should be considered, to promptly and correctly address every PE case.

New perspectives

The 2021' announcement of the multicentric prospective PEERLESS RCT, comparing aspiration thrombectomy *vs* catheter-directed thrombolysis in up to 700 patients will provide real life data on interventional radiology treatments for patients with intermediate-high risk pulmonary embolism. At the same time, US-assisted thrombolysis is proving valuable in intermediate-high risk pulmonary embolism patients with good results and low complication rates ^[36]. However, more prospective studies are needed to shed light on the best interventional radiology treatment for this critical condition, as well as to give the right place in the guidelines to these endovascular and mini-invasive techniques, on par to medical and surgical treatments.

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