Reperfusion therapies in pulmonary embolism–state of the art and expert opinion: A position paper from the "Unité de Soins Intensifs de Cardiologie" group of the French Society of Cardiology

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Reperfusion dans l'embolie pulmonaire: état de l'art et consensus d'experts: position du groupe soins intensifs de cardiologie de la société française de cardiologie

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Abbreviations: CDT, catheter-directed therapy; HRPE, high-risk pulmonary embolism; IHRPE, intermediate-high-risk pulmonary embolism; LV, left ventricular; PE, pulmonary embolism; PERT, pulmonary embolism response team; RV, right ventricle; TTE, transthoracic echocardiography; USAT, ultrasound-assisted thrombolysis; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

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KEYWORDS
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Summary Acute pulmonary embolism is a frequent cardiovascular emergency with an increasing incidence. The prognosis of patients with high-risk and intermediate-high-risk pulmonary embolism has not improved over the last decade. The current treatment strategies are mainly based on anticoagulation to prevent recurrence and reduce pulmonary vasculature obstruction. However, the slow rate of thrombus lysis under anticoagulation is unable to acutely decrease right ventricle overload and pulmonary vasculature resistance in patients with severe obstruction and right ventricle dysfunction. Therefore, patients with high-risk and intermediate-high-risk pulmonary embolism remain a therapeutic challenge. Reperfusion therapies may be discussed for these patients, and include systemic thrombolysis, catheter-directed therapies and surgical thrombectomy. High-risk patients require systemic thrombolysis, but may have contraindications as a result of the high risk of bleeding. In addition, intermediate-high-risk patients should not receive systemic thrombolysis, despite its high efficacy, because of prohibitive bleeding complications. Recently, percutaneous reperfusion techniques have been developed to acutely decrease pulmonary vascular obstruction with lower-dose or no thrombolytic agents and, thus, potentially higher safety than systemic thrombolysis. Some of these techniques improve key haemodynamic variables. Cardiac surgical techniques and venoarterial extracorporeal membrane oxygenation as temporary circulatory support may be useful in selected cases. The development of pulmonary embolism centres with multidisciplinary pulmonary embolism teams is mandatory to enable adequate use of reperfusion and improve outcomes. We aim to present the state of the art regarding reperfusion therapies in pulmonary embolism, but also to provide guidance on their indications and patient selection.

MOTS CLÉS
Embolie pulmonaire ;
Thrombolyse ;
Thrombectomie ;
Techniques reperfusion par cathéter ;
Reperfusion

Résumé L'embolie pulmonaire aiguë est une urgence cardiovasculaire fréquente. Son incidence augmente rapidement tandis que sa mortalité reste stable. Le pronostic des patients à haut risque et à risque intermédiaire élevé reste médiocre sans amélioration au cours de la dernière décennie. Les stratégies de traitement actuelles reposent sur l'anticoagulation pour prévenir les récidives et réduire l'obstruction vasculaire pulmonaire. Cependant, la lyse du thrombus sous anticoagulant est lente et ne permet pas une diminution rapide de la surcharge du ventricule droit et des résistances vasculaires pulmonaires chez les patients présentant une obstruction sévère et une dysfonction ventriculaire droite. La prise en charge de ces patients reste un défi thérapeutique et peut amener à discuter des thérapies de reperfusion comme la thrombolyse systémique, les techniques percutanées par cathéter et la thrombectomie

chirurgicale. La thrombolyse systémique est indiquée chez les patients à haut risque en l'absence de contre-indication formelle en raison du risque hémorragique. Mais elle ne devrait pas être utilisée chez les patients à risque intermédiaire élevé malgré son efficacité élevée en raison de complications hémorragiques rédhibitoires. Récemment, les techniques de reperfusion percutanées ont été développées visant à diminuer de manière aiguë l'obstruction vasculaire pulmonaire avec un dose réduite ou sans thrombolytique et en conséquence un profil de sécurité amélioré. Certaines de ces techniques ont démontré une grande efficacité sur les paramètres hémodynamiques clés. Enfin, les techniques de chirurgie cardiaque et le support circulatoire temporaire par ECMO veno-artérielle se sont améliorées et peuvent être utiles dans certains cas. Le développement de centres spécialisés avec une équipe multidisciplinaire est obligatoire afin de permettre une utilisation adéquate de la reperfusion pour améliorer le pronostic des patients. Ce document vise à faire un état de l'art concernant les thérapies de reperfusion de l'embolie pulmonaire tout en discutant leurs indications et la sélection des patients.

Background

Pulmonary embolism (PE) is the third most common cause of acute cardiovascular emergency, and has high rates of morbidity and mortality [1]. Although progress has been made regarding diagnosis with biomarkers and imaging, therapeutic advances are scarce, and lag far behind the improvement in outcome obtained in acute coronary syndromes [2]. In fact, while the incidence of PE is increasing, prognosis has not improved in recent years, and remains poor in higher-risk patients [3].

The prognosis of patients with high-risk PE (HRPE) and intermediate-high-risk PE (IHRPE) is poor, even though they account for, respectively, 2—4% and 10—15% of all PE cases in the emergency ward, with 30-day mortality rates of 34.8% and 8.2%, and 30-day major bleeding rates of 23.9% and 9.6% [4,5].

Although aggressive therapy with systemic thrombolysis has resulted in great improvements in the treatment of pulmonary obstruction, it is associated with a dramatic increase in bleeding; in particular, prevention of intracerebral bleeding has been implemented in clinical practice for intermediate-risk patients with PE [6]. Over the last few years, new percutaneous interventions have been developed to enable a quick and significant reduction in pulmonary obstruction, with potentially enhanced safety compared with systemic thrombolysis [7]. These interventions may improve the outcome of higher-risk patients with PE, and were accordingly upgraded in the recent guidelines to a IIb level of recommendation [3]. In addition, in patients with severe haemodynamic instability (patients with refractory circulatory collapse or cardiac arrest), the updated guidelines support venoarterial extracorporeal membrane oxygenation (VA-ECMO) to optimize end-organ function in combination with surgical embolectomy or catheter-directed therapy (CDT) [3].

One major advance in the guidelines is their promotion of PE centres and multidisciplinary care for PE. In fact, PE is a complex condition, and a significant proportion of its morbidity and mortality is related to concomitant diseases. To improve the prognosis of PE, we may need to proceed as is done in acute coronary syndromes, with dedicated PE centres, a network of care, protocols for reperfusion and increased use of reperfusion in selected patients. Based on the available evidence, we aim to provide the state of the field regarding existing reperfusion therapies, and guidance on their appropriate use.

PE risk stratification

Severe PE or HRPE is defined by cardiac arrest, obstructive shock (i.e. systolic blood pressure < 90 mmHg or requirement of vasopressors to achieve a systolic blood pressure > 90 mmHg despite adequate filling status) accompanied by signs of end-organ hypoperfusion or persistent hypotension (i.e. systolic blood pressure < 90 mmHg or systolic pressure drop by 40 mmHg for > 15 minutes, if not caused by new onset arrhythmia, hypovolemia or sepsis) [3]. High-risk PE accounts for < 5% of all acute PE cases, and constitutes a medical emergency; it is associated with a 30% risk of in-hospital death, particularly during the first hours.

In addition, among initially haemodynamically stable patients, approximately 10% may experience early clinical and haemodynamic deterioration, with an overall in-hospital PE-related mortality risk of approximately 50% in this subgroup of patients who undergo deterioration [5]. Risk stratification of acute patients with PE allows physicians to accurately identify those with an elevated risk of death or major complications. For patients without cardiogenic shock or cardiac arrest, advanced risk stratification with a combination of clinical variables (i.e. tachycardia, mild hypotension, hypoxemia, age and previous cardiorespiratory disease) using the simplified PE severity index, biomarkers reflecting myocardial injury (troponin) and imaging of right ventricular (RV) dilatation and dysfunction allows physicians to identify, among initially clinically stable patients, those with the highest risk of subsequent deterioration (patients with IHRPE). Such patients might benefit from intensive monitoring and, in selected cases, from reperfusion therapy (Fig. 1) [3].

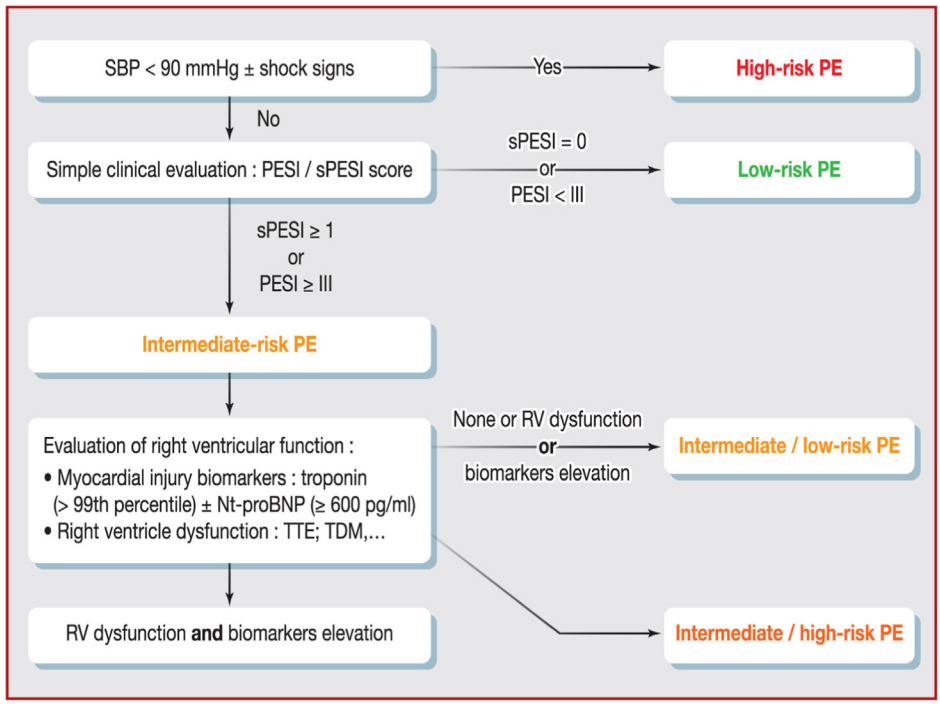

Figure 1. Assessment of pulmonary embolism severity according to the 2019 European Society of Cardiology guidelines for the diagnosis and management of acute pulmonary embolism [3]. NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PE: pulmonary embolism; PESI: pulmonary embolism severity index; RV: right ventricle; SBP: systolic blood pressure; sPESI: simplified pulmonary embolism severity index; TDM: tissue Doppler echocardiography method; TTE: transthoracic echocardiography.

State of the art reperfusion therapies

Acute PE interferes with both circulation and gas exchange [3]. RV failure secondary to acute pressure overload is considered the primary cause of death in HRPE. As shown in Fig. 2, mild increases in vascular obstruction may translate into a large increase in RV pressure. While anticoagulation and natural fibrinolysis may require up to 7 days to significantly reduce pressure, systemic thrombolysis and other reperfusion therapies have been shown to be much quicker. This is the rationale for the use of reperfusion therapy in patients with haemodynamic impairment and RV dilatation. Three types of reperfusion therapies are available: systemic thrombolysis, CDT and surgical thrombectomy.

Systemic thrombolysis

The benefit of systemic thrombolysis is related to the quick reduction in vascular obstruction, translating into immediate improvement in RV haemodynamics. It must be acknowledged that this benefit is related to the quick action of systemic thrombolysis, and is limited to the first days of PE, because anticoagulation alone achieves a similar haemodynamic benefit within 7 days [8,9]. Systemic thrombolysis is mostly efficient within the first 2 days of acute PE, but it can still be successful within the first 15 days [8,10]. Of note, unsuccessful thrombolysis has been reported in 8% of patients with HRPE [10]. The gold-standard treatment for thrombolysis is recombinant tissue type plasminogen activator, based on the available evidence [3]. Systemic thrombolysis remains the reperfusion technique with the highest level of evidence.

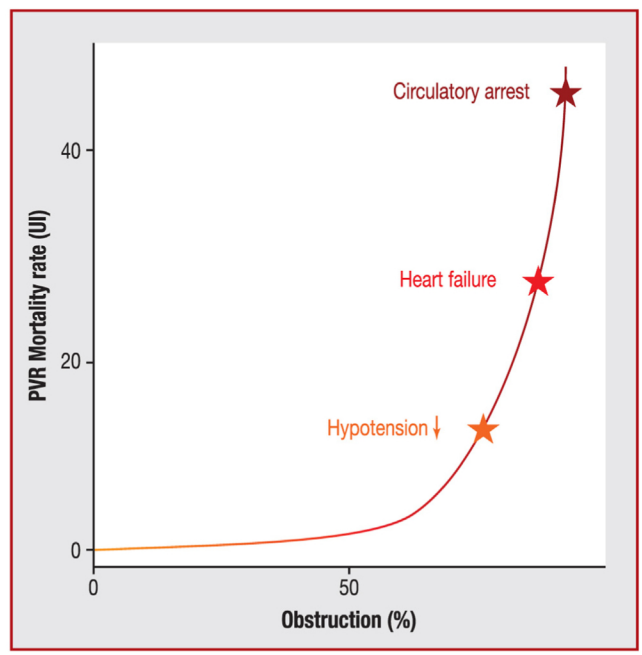

Figure 2. Physiopathology of pulmonary embolism severity. Early pharmacological reperfusion is partial, but can avoid cardiogenic shock and circulatory arrest by lowering pulmonary vascular resistance (PVR). IU: international units. [Journal: please change to IU in figure].

Systemic thrombolysis is associated with an increased risk of major bleeding episodes, particularly intracerebral bleeds (2—3%)—a fourfold increase compared with that of

Table 1 Contraindications for systemic thrombolysis according to the 2019 European Society of Cardiology guidelines [3].

Absolute	Relative
History of haemorrhagic stroke or stroke of unknown origin	Transient ischaemic attack in previous 6 months
Ischaemic stroke in previous 6 months	Oral anticoagulation
Central nervous system neoplasm	Pregnancy or first postpartum week
Major trauma, surgery or head injury in previous 3 weeks	Non-compressible puncture sites
Bleeding diathesis	Traumatic resuscitation
Active bleeding	Refractory hypertension (SBP > 180 mmHg)
	Advanced liver disease
	Infective endocarditis
	Active peptic ulcer

SBP: systolic blood pressure.

anticoagulant alone, particularly in patients aged over 65 years [11,12]. Of importance, some patients are considered at high bleeding risk and should not receive systemic thrombolysis (Table 1).

Systemic thrombolysis is the gold standard in HRPE based on a single very small study that included 11 patients and was terminated prematurely because of a higher rate of death in patients assigned to the placebo group [13]. A meta-analysis and a large registry confirmed these results [14]. Thereafter, alternative protocols for thrombolysis—particularly protocols with reduced doses of thrombolytics, such as 30 mg of recombinant tissue type plasminogen activator—were tested [15]. However, despite encouraging results regarding bleeding episodes in particular, there is a lack of adequately powered trials to enable the recommendation of such alternative protocols [15,16]. The PEITHO-3 trial will soon assess the efficacy and safety of a reduced dose of alteplase (0.6 mg/kg, not exceeding 50 mg, intravenously over 15 minutes) on top of low-molecular-weight heparin compared with low-molecular-weight heparin alone in patients with acute IHRPE and an elevated risk of early death, haemodynamic collapse or PE recurrence.

In patients with IHRPE, the PEITHO trial randomized patients to systemic thrombolysis or unfractionated heparin alone. In this trial, although systemic thrombolysis significantly reduced the risk of haemodynamic deterioration, it was associated with a large increase in major bleeding episodes [6]. Therefore, despite its high efficacy, systemic thrombolysis is not recommended in patients at an increased risk because of safety issues (class III) [3].

CDT

Based on the results of the PEITHO trial, showing the efficacy of more aggressive therapy in IHRPE, CDT was developed to achieve similar efficacy for clot reduction and haemodynamic improvement with a lower bleeding risk compared with systemic thrombolysis [3,6].

Schematically, two principles are reported: a mechanical method to retrieve thrombi through aspiration or thrombectomy; and in situ fibrinolysis assisted by different catheters. Most of these devices have demonstrated the ability to reduce pulmonary artery obstruction and improve haemodynamic variables, with variable safety and efficacy. These techniques require a team experienced in endovascular techniques (interventional cardiologists or radiologists). Pulmonary angiography enables thrombus localization (most often femoral), and guides pulmonary artery reperfusion. However, clinical outcome data from randomized trials are lacking for all of these techniques. We have summarized the available evidence for the most studied devices in Table 2 [7,17–23].

Mechanical methods

Catheter-based mechanical methods can be divided into thromboaspiration and fragmentation.

For thromboaspiration, suction thrombectomy allows aspiration of the thrombus into the lumen of catheters of varying diameters with discharge into an aspiration container. These devices may be of particular interest in the case of active bleeding preventing surgical procedures and in situ fibrinolysis. However, caution is warranted, as the use of these devices has been associated with sudden death, arrhythmias, shock or distal embolization. In addition, significant blood loss has been reported.

The principles of mechanical thrombectomy include clot fragmentation, fragmentation with aspiration and rheolytic thrombectomy. However, these techniques may cause distal embolisms, which may increase pulmonary vascular resistance and RV strain. Recent data have suggested an increased risk of major adverse events, including deaths or haemodynamic deterioration, with the use of the AngioJet™ device (Boston Scientific, Marlborough, MA, USA) in PE care. It is therefore the object of a black box warning from the FDA in this clinical setting.

In situ fibrinolytic therapy

Transcatheter thrombolysis directed into pulmonary thrombi has the theoretic advantage of supplying a high local concentration of the agent in the clot, with lower systemic exposure. This technique was already being used in the early 2000s, and aims to reduce the thrombolytic dose and thus bleeding complications. However, despite numerous protocols and devices, few data are available [3,6,17,23].

Ultrasound-assisted thrombolysis (USAT) is another option for achieving pulmonary reperfusion using ultrasound associated with local thrombolysis. A randomized trial comparing USAT with unfractionated heparin reported that USAT was associated with increased RV/left ventricular (LV) ratio reduction and improved haemodynamic variables [21]. A recent meta-analysis of trials assessing this technique reported a large decrease in mean pulmonary artery pressure and a reduction in the RV/LV ratio in patients with HRPE and IHRPE compared with heparin alone. In this meta-analysis, the rates of major and intracerebral bleeding were low (< 0.5%), although the bleeding risk remains to be clarified [21,24]. However, the actual superiority of USAT over

Table 2 Overview of available catheter-directed therapies.

Desobstruction principle	Device; vendor [reference]	Mechanism	Technical considerations	Study design; endpoints
Thromboaspiration	AngioVac™; AngioDynamics, Latham, NY, USA [17]	Veno-veno bypass; funnel-shaped inflow tip to engage thrombi and aspirate	26-French access for inflow; 16- to 20-French access for outflow; requires perfusion team	Single centre, case reports ($n = 5$)
	FlowTriever; Inari Medical, Irvine, CA, USA [23]	Nitinol discs engage and mechanically retrieve clot with simultaneous aspiration	20-French catheter; must manage blood loss associated with large-bore aspiration	Single arm, multicentre ($n = 106$); reduction in RV/LV ratio, 3.8% major adverse events
	Indigo® System; Penumbra, Alameda, CA, USA [18]	Mechanical clot engagement with mechanized aspiration	8-French catheter	Retrospective, single arm, single centre ($n = 54$); mean PAP, major adverse events
Mechanical thrombectomy	Amplatz™ thrombectomy device; Microvena, St. Paul, MN, USA [19]	High-speed impeller	6-French catheter	Case reports
	Aspirex® thrombectomy catheter; Straub Medical, Wangs, Switzerland [22]	Rotating spiral inside a catheter	8-French catheter	Single centre, single arm ($n = 16$); mean PAP, RV/LV ratio
In situ fibrinolytic therapy	Uni-Fuse™; AngioDynamics, Latham, NY, USA [20]	CDF	4- to 5-French catheter	Single centre, prospective ($n = 18$); RV/LV ratio
	EkoSonic™; Boston Scientific, Marlborough, MA, USA [21]	USAT	5-French catheter	Multicentre, randomized, prospective ($n = 59$); RV/LV ratio

CDF: catheter-directed fibrinolysis; LV: left ventricle; PAP: pulmonary artery pressure; RV: right ventricle; USAT: ultrasound-assisted thrombolysis.

other CDT devices has not been evaluated, and clinical outcome data are lacking [25].

In a retrospective analysis, investigators compared CDT and systemic thrombolysis in acute patients with HRPE and IHRPE. After propensity matching, patients undergoing CDT had a lower rate of hospital mortality and major bleeding episodes than those undergoing systemic thrombolysis [21,26].

Surgical thrombectomy

Surgical thrombectomy in acute PE usually requires cardiopulmonary bypass without aortic cross-clamping and cardioplegic cardiac arrest, and involves incision of the two main pulmonary arteries, with the removal or suction of fresh clots. Compared with repeat fibrinolysis, surgical thrombectomy is associated with a trend toward higher in-hospital survival, uneventful evolution and lower PE recurrence after fibrinolysis failure [10]. Thus, the usual indications for surgical thrombectomy are contraindication for or failure of fibrinolysis (grade Ib recommendation) [3,27]. The surgical procedures require general anaesthesia and sternotomy in critically ill patients with haemodynamic instability, which may be associated with significant mortality and morbidity. The indications for surgical thrombectomy are limited to PE because of proximal or intracardiac thrombi.

In practice, the results of surgical thrombectomy are highly variable according to patient selection, the timing of implementation, and the experience of the surgical and medical teams. Although fibrinolysis has reduced bleeding rates compared with systemic thrombolysis, surgical management may induce serious potential complications including tamponade, atrial fibrillation and right heart failure [28]. Interestingly, recent studies reported that the in-hospital mortality of patients with PE undergoing

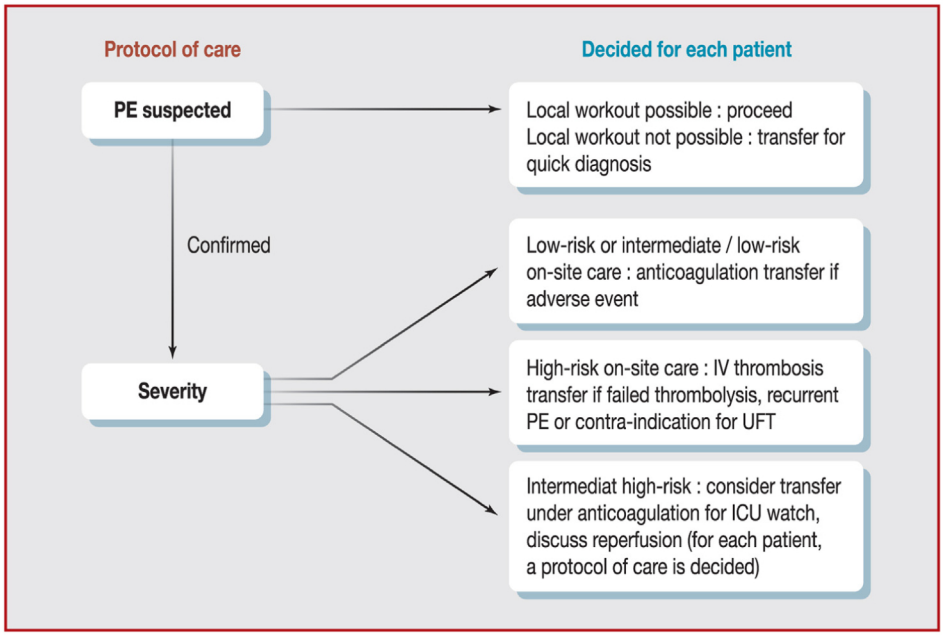

Figure 3. Suggested protocol for discussing, transferring and managing patients with high-risk and intermediate-high-risk pulmonary embolism. ICU: intensive care unit; IV: intravenous; PE: pulmonary embolism; UFT: unfractionated heparin.

surgical thrombectomy in dedicated PE centres was 3—6%, and that the 1-year mortality rate was 15—23% [27—32]. The improvement in surgical techniques and in the management of critically ill patients may explain these results.

Some authors recommend thrombectomy in cases of intracardiac and/or intra-patent foramen ovale thrombi as first-line therapy [29,31,32]. However, dedicated randomized trials comparing surgical thrombectomy and other reperfusion techniques are needed, and thus the level of evidence for its use remains low.

VA-ECMO

In most patients with severe disease, temporary circulatory support (VA-ECMO) may be used to allow the transfer or referral of the patient to a dedicated team [33].

The use of VA-ECMO in unstable patients with PE seems appealing from a physiopathological point of view, because of the heart — lung block with extracorporeal circulation associated with an oxygenator. This feature ensures rapid circulatory and respiratory stabilization, saves time for thrombus lysis and provides a bridge to endovascular or surgical reperfusion. However, evidence is weak, with most studies being small and old series, with very disparate results related to a lack of standardization in patient selection, techniques and timing of implantation and management. ECMO should be considered in patients with very severe disease with refractory circulatory collapse or cardiac arrest (30—100% of patients) [33,34]. The reported hospital survival ranged from 25% to 100% (34). A recent large multicentre retrospective series focused on HRPE suggested that standalone VA-ECMO tended to be associated with a higher mortality than ECMO in combination with reperfusion therapy (relative risk of 30-day all-cause death 1.47, 95% confidence interval 0.98—2.20; $P = 0.06$) [33].

Owing to the intensive resource consumption and the complexity of the technique, multidisciplinary selection of patients is mandatory. Life expectancy of < 1 year, previous cardiac arrest with an unknown no flow duration and high lactate at implantation were associated with higher mortality. Such variables should be taken into consideration before making a decision about VA-ECMO implantation [35].

Thus, given the level of evidence (grade IIb) and the high rate of complications (bleeding and infection, especially with use over longer periods), VA-ECMO may be considered by an experienced team in combination with surgical embolectomy or CDT in refractory circulatory collapse or cardiac arrest; it may be discussed for patients with HRPE or IHRPE who deteriorate when thrombolysis is contraindicated or has failed [3]. Again, the potential benefit of this technique is derived from observational data, and is not backed by randomized trials.

Expert opinions

Critical role for PE centres and multidisciplinary PE response teams (PERTs)

PE is at the intersection of several specialties; it involves cardiologists, chest specialists and intensivists, as well as specialists in haemostasis, oncology and imaging, cardiovascular surgeons and emergency physicians.

Given the lack of formal evidence in many fields of PE management, to adequately manage these patients, the development of a multidisciplinary PE response team (PERT) is key to providing optimal acute and long-term care [3]. In fact, improving outcomes requires reducing not only PE-related death, but also the morbidity and mortality of associated diseases, such as cancer. PERTs should develop protocols of care for acute patients with PE, depending on

the severity of PE and the patient's condition, but should also determine the necessary associated care, including haematological work-ups, cancer screening and the potential need for long-term anticoagulant therapy. In addition, such teams can help in decisions about timing and type of reperfusion therapy. Similar to cardiogenic shock teams, such multidisciplinary care and regional networks are likely to improve clinical outcome [36].

PERTs should work within an organized regional network of care with other hospitals, and in coordination with emergency transport services to help to diagnose and classify acute PE, as well as to select patients who should be transferred to the PE centre and/or require reperfusion and to decide on the optimal technique. Within a PE centre, all reperfusion therapies should be available (including percutaneous techniques), with staff members trained and able to deal with all of them and their complications around the clock. The literature suggests that PE centres provide up-to-date and homogenous care for patients with PE and increase reperfusion rates [37—39].

Consistently, the recent guidelines on PE support recommend the development of such PERTs and centres (grade IIa recommendation) [3]. A standardized protocol of care should be used within a network of care to determine who should be transferred and considered further for reperfusion (Fig. 3). Such protocols should be updated according to the scientific literature and self-assessment of PERT results. Although these structures are backed by guidelines and observational data, their ability to improve outcomes remains unconfirmed.

Table 3 Which reperfusion technique to use in patients with high-risk and intermediate-high-risk.

Systemic thrombolysis	Patients with HRPE
	Patients with IHRPE who deteriorate
Surgical embolectomy	Patients with HRPE with contraindications to systemic thrombolysis
	Patients with IHRPE who deteriorate
Percutaneous reperfusion	Patients with HRPE with contraindications to systemic thrombolysis
	Patients with HRPE with a high bleeding risk
	Patients with IHRPE:
	who deteriorate
	who do not improve over the first 24 hours
	with severe respiratory distress
	with thrombus in transit
	with kidney or liver injury
	with RV/LV $\geq$ 1.3
	with sPAP > 50 mmHg
	with severe RV hypokinesia (onde, etc.)

HRPE: high-risk pulmonary embolism; IHRPE: intermediate-high-risk pulmonary embolism; LV: left ventricle; RV: right ventricle; sPAP: systolic pulmonary artery pressure.

Selection of patients for reperfusion therapy

Owing to the differences in benefits and risks between reperfusion techniques, they need to be discussed for each patient, and selected according to the patient's profile. Systemic thrombolysis remains the gold standard for HRPE. In those with an excessive risk of bleeding or with a contraindication for systemic thrombolysis, another technique should be considered [3].

Patients with IHRPE who have severe respiratory distress and/or marked RV dysfunction are at high risk of secondary haemodynamic instability and death [6]. Among these patients, the selection of those who may benefit from reperfusion and the means to obtain it should be determined by the multidisciplinary team based on risk-benefit assessment and according to local expertise (Fig. 3 and Table 3). The following factors should be considered when determining the need and means [3,40]: haemodynamic instability of the patient; age and co-morbidities; computed tomography and/or echocardiography findings regarding RV dilatation, RV function, pulmonary artery pressure, localization of thrombi and thrombus burden; local resources, including availability of the surgical team and the type of percutaneous reperfusion techniques; experience of the surgical and intensivist team; bleeding risk; and contraindications for fibrinolysis (recent major surgery, peripartum, recent stroke, etc.; Table 1).

To improve the management of patients, PE centres should have a validated local protocol that can be applied to most patients. A multivariable evaluation is needed to determine who should benefit from an intervention (Fig. 4).

Timing of reperfusion therapy

Early and efficient doses of pharmacological treatment can avoid RV dysfunction and severe events in HRPE and IHRPE [3].

In HRPE, systemic thrombolysis by alteplase infusion is recommended (100 mg in 2 hours or 0.6 mg/kg in 15 minutes; maximum dose 50 mg), and should be started as soon as possible, as the risk of sudden cardiac arrest resulting from RV failure is high. In HRPE not suitable for intravenous thrombolysis, either surgical or percutaneous reperfusion could be proposed [41], surgery being mainly intended for cases of intracardiac thrombus.

In the case of in-hospital cardiorespiratory arrest within an institution with access to VA-ECMO support, thrombolysis should be considered to allow rapid haemodynamic and respiratory stabilization, and a reperfusion strategy including CDT or surgery should be determined as a secondary option.

For IHRPE, the current guidelines recommend rescue systemic thrombolysis in the case of clinical deterioration. As an alternative to rescue thrombolytic therapy, surgical thrombectomy or percutaneous catheter-directed embolectomy should be considered with issues such as hypotension without hypoperfusion, a requirement for high oxygen supply, severe RV dilatation or high pulmonary artery pressure,

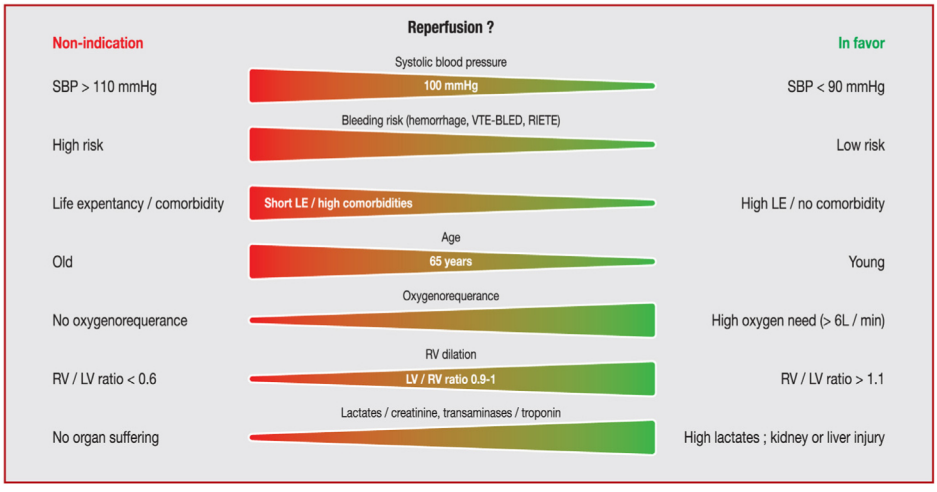

Figure 4. Multivariable evaluation of reperfusion technique indication. HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; LE: life expectancy; LV: left ventricle; REITE: Computerized Registry of Patients with Venous Thromboembolism; RV: right ventricle; SBP: systolic blood pressure.

Table 4 Monitoring of patients with severe pulmonary embolism.

	Efficacy of reperfusion	Complications		
		Medical therapies	Catheter-directed thrombolysis techniques	VA-ECMO
Clinical examination	Regression of clinical signs of shock; regression of clinical signs of right heart failure	Evidence of bleeding (abdominal distension, flank haematoma, impairment of neurological status); arterial and other venous thrombosis	Bradycardia; haemoptysis; vascular access; diuresis and urine aspect (rust-coloured)	Pupil examination; leg cannula (inspection, palpation, measurement of leg circumference)
Biological variables	Lactate; NT-proBNP	ACT; platelets; haemoglobin	Haemoglobin; plasma free haemoglobin; creatinine	Haemoglobin; plasma free haemoglobin
Imaging	TTE: (decrease in RV/LV dimension ratio; sPAP; and cardiac flow); CTPA: (decrease in RV/LV dimension; and Qanadli score to evaluate filling defect)	Any major bleedings	TTE (pericardial effusion); ultrasonography (site puncture complications); CT scan (any major bleeding and arterial injury)	TTE

ACT: activated clotting time; CT: computed tomography; CTPA: computed tomography pulmonary angiography; LV: left ventricle; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; RV: right ventricle; sPAP: systolic pulmonary artery pressure; TTE: transthoracic echocardiography; VA-ECMO: venoarterial extracorporeal membrane oxygenation.

kidney or liver impairment or high lactate concentrations. In most PE centres, ''preventive'' percutaneous techniques are performed, based on PERT decisions and protocols, to prevent decompensation and reduce length of stay in the intensive care unit. To date, these types of approaches are mainly carried out in the context of studies or prospective registries within expert institutions aimed at clarifying the real-world role of these techniques, and dedicated trials are warranted to demonstrate the efficacy and safety of these protocols.

When surgery or percutaneous interventions are proposed by the PERT, unfractionated heparin should be preferred [3]. Anticoagulants should be started as soon as possible after the diagnosis is suspected. For HRPE, unfractionated heparin is recommended with the following dose regimen: a bolus of 80 IU/kg + infusion of 18 IU/kg/h (activated partial thromboplastin time 2—2.5 times normal value or factor Xa inhibitor at 0.3—0.7 IU/mL). In patients with IHRPE, curative doses of low-molecular-weight heparin or fondaparinux should be preferred over unfractionated

heparin during the first 24—48 hours, and oral anticoagulant therapy (non-vitamin K antagonist oral anticoagulant or vitamin K antagonist) can be prescribed when clinical improvement is obtained.

Monitoring of acute PE and reperfusion techniques

The monitoring of severe patients with PE includes assessment of the efficacy of reperfusion and of the occurrence of complications related to the reperfusion techniques (Table 4).

The efficacy of reperfusion will be assessed by clinical examination (regression of right heart failure and cardiogenic shock), biological variables (improvement of organ dysfunction and lactate decrease) and RV imaging (transthoracic echocardiography and, in some cases, computed tomography to assess RV/LV dimension or residual thrombi).

Regarding complications, physicians should be aware of the high risk of bleeding induced by systemic thrombolysis and anticoagulation, and the specific complications of CDT and thrombectomy techniques with or without VA-ECMO [40,42]. Analyses of clinical variables, biological markers of haemolysis, leg ischaemia and kidney function should be performed at least twice a day. The identification of complications and their severity should lead the PERT to discuss the risk-benefit ratio for continuing such therapies.

Conclusions and perspectives

The guidelines released recently by the European Society of Cardiology are in favour of the development of PE centres within a regional network and a multidisciplinary PE team to provide multidisciplinary care and appropriate reperfusion techniques to improve the outcome of higher-risk patients with PE. In most severe and unstable patients, the use of VA-ECMO as salvage therapy should be considered as a bridge to reperfusion therapy. While surgical thrombectomy remains an option, its availability is limited; therefore, catheter-directed treatments represent a promising alternative, with low morbidity and mortality. Percutaneous reperfusion techniques have seen advances, and should be proposed in patients with HRPE with a contraindication for intravenous thrombolysis; they should also be discussed in patients with IHRPE who deteriorate under anticoagulation, as an alternative to systemic thrombolysis. The newly developed percutaneous techniques have promising potential in the care of such patients, as they provide quick and significant haemodynamic improvements with low rates of bleeding. Ultrasound-facilitated catheter thrombolysis has a higher level of evidence for these indications compared with the other percutaneous techniques. However, these techniques are limited by the lack of randomized clinical trials demonstrating their clinical benefit (see Appendix).

Future trials should aim to establish whether catheter-directed therapies have a clinical benefit, and which patients should be selected for these procedures . In the meantime, while the guidelines are enhancing the level of evidence for reperfusion in PE, it is critical that PE networks and centres be developed.

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References

[1] Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. Circ Res 2016;118:1340—7.
[2] Puymirat E, Simon T, Steg PG, et al. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA 2012;308:998—1006.
[3] Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543—603.
[4] Ebner M, Kresoja KP, Keller K, et al. Temporal trends in management and outcome of pulmonary embolism: a single-centre experience. Clin Res Cardiol 2020;109:67—77.
[5] Secemsky E, Chang Y, Jain CC, et al. Contemporary Management and Outcomes of Patients with Massive and Submassive Pulmonary Embolism. Am J Med 2018;131:1506—14 [e0].
[6] Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402—11.
[7] Zarghouni M, Charles HW, Maldonado TS, Deipolyi AR. Catheter-directed interventions for pulmonary embolism. Cardiovasc Diagn Ther 2016;6:651—61.

[8] Becattini C, Agnelli G, Salvi A, et al. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res 2010;125:e82—6.
[9] Konstantinides S, Tiede N, Geibel A, Olschewski M, Just H, Kasper W. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. Am J Cardiol 1998;82:966—70.
[10] Meneveau N, Seronde MF, Blonde MC, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. Chest 2006;129:1043—50.
[11] Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA 2014;311:2414—21.
[12] Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 2015;36:605—14.
[13] Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streptokinase and Heparin versus Heparin Alone in Massive Pulmonary Embolism: A Randomized Controlled Trial. J Thromb Thrombolysis 1995;2:227—9.
[14] Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. Circulation 2006;113:577—82.
[15] Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest 1990;98:1473—9.
[16] Goldhaber SZ, Agnelli G, Levine MN. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis. An international multicenter randomized trial. The Bolus Alteplase Pulmonary Embolism Group. Chest 1994;106:718—24.
[17] Al-Hakim R, Park J, Bansal A, Genshaft S, Moriarty JM. Early Experience with AngioVac Aspiration in the Pulmonary Arteries. J Vasc Interv Radiol 2016;27:730—4.
[18] De Gregorio MA, Guirola JA, Kuo WT, et al. Catheter-directed aspiration thrombectomy and low-dose thrombolysis for patients with acute unstable pulmonary embolism: Prospective outcomes from a PE registry. Int J Cardiol 2019;287:106—10.
[19] Dudzinski DM, Giri J, Rosenfield K. Interventional Treatment of Pulmonary Embolism. Circ Cardiovasc Interv 2017:10.
[20] Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129:479—86.
[21] Pei DT, Liu J, Yaqoob M, et al. Meta-Analysis of Catheter Directed Ultrasound-Assisted Thrombolysis in Pulmonary Embolism. Am J Cardiol 2019;124:1470—7.
[22] Pollak JS. Catheter-Based Therapies for Pulmonary Emboli. Clin Chest Med 2018;39:651—8.
[23] Tu T, Toma C, Tapson VF, et al. A Prospective, Single-Arm. Multicenter Trial of Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism: The FLARE Study. JACC Cardiovasc Interv 2019;12:859—69.
[24] Tapson VF, Sterling K, Jones N, et al. A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism: The OPTALYSE PE Trial. JACC Cardiovasc Interv 2018;11:1401—10.
[25] Rao G, Xu H, Wang JJ, et al. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute pulmonary embolism: A multicenter comparison of patient-centered outcomes. Vasc Med 2019;24:241—7.
[26] Arora S, Panaich SS, Ainani N, et al. Comparison of In-Hospital Outcomes and Readmission Rates in Acute Pulmonary Embolism Between Systemic and Catheter-Directed Thrombolysis (from the National Readmission Database). Am J Cardiol 2017;120:1653—61.
[27] Neely RC, Byrne JG, Gosev I, et al. Surgical Embolectomy for Acute Massive and Submassive Pulmonary Embolism in a Series of 115 Patients. Ann Thorac Surg 2015;100:1245—51 [discussion 51-2].
[28] Azari A, Beheshti AT, Moravvej Z, Bigdelu L, Salehi M. Surgical embolectomy versus thrombolytic therapy in the management of acute massive pulmonary embolism: Short and long-term prognosis. Heart Lung 2015;44:335—9.
[29] Celik T, Balta S, Ozturk C, Yildirim AO, Iyisoy A. The best treatment option in the management of patients with acute massive pulmonary embolism: surgery or thrombolysis? Int J Cardiol 2016;214:286—7.
[30] Cho YH, Kim WS. Surgical embolectomy as a first line treatment for acute massive pulmonary embolism. Int J Cardiol 2016;222:785.
[31] Cho YH, Sung K, Kim WS, et al. Management of acute massive pulmonary embolism: Is surgical embolectomy inferior to thrombolysis? Int J Cardiol 2016;203:579—83.
[32] Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg 2005;129:1018—23.
[33] Meneveau N, Guillon B, Planquette B, et al. Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases. Eur Heart J 2018;39:4196—204.
[34] Corsi F, Lebreton G, Brechot N, et al. Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation. Crit Care 2017;21:76.
[35] George B, Parazino M, Omar HR, et al. A retrospective comparison of survivors and non-survivors of massive pulmonary embolism receiving veno-arterial extracorporeal membrane oxygenation support. Resuscitation 2018;122:1—5.
[36] Tehrani BN, Truesdell AG, Sherwood MW, et al. Standardized Team-Based Care for Cardiogenic Shock. J Am Coll Cardiol 2019;73:1659—69.
[37] Carroll BJ, Pemberton H, Bauer KA, et al. Initiation of a Multidisciplinary, Rapid Response Team to Massive and Submassive Pulmonary Embolism. Am J Cardiol 2017;120:1393—8.
[38] Kabrhel C, Rosovsky R, Channick R, et al. A Multidisciplinary Pulmonary Embolism Response Team: Initial 30-Month Experience With a Novel Approach to Delivery of Care to Patients With Submassive and Massive Pulmonary Embolism. Chest 2016;150:384—93.
[39] Rosovsky R, Chang Y, Rosenfield K, et al. Changes in treatment and outcomes after creation of a pulmonary embolism response team (PERT), a 10-year analysis. J Thromb Thrombolysis 2019;47:31—40.
[40] Aissaoui N, Konstantinides S, Meyer G. What's new in severe pulmonary embolism? Intensive Care Med 2019;45:75—7.
[41] Edla S, Rosman H, Neupane S, et al. Early Versus Delayed Use of Ultrasound-Assisted Catheter-Directed Thrombolysis in Patients With Acute Submassive Pulmonary Embolism. J Invasive Cardiol 2018;30:157—62.
[42] Le Gall A, Follin A, Cholley B, Mantz J, Aissaoui N, Pirracchio R. Veno-arterial-ECMO in the intensive care unit: From technical aspects to clinical practice. Anaesth Crit Care Pain Med 2018;37:259—68.