Intensive Care Treatment of Pulmonary Embolism: An Update Based on the Revised AWMF S2k Guideline

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Abstract

Acute pulmonary embolism (PE) remains a significant cause of morbidity and requires prompt diagnosis and management. The prognosis of affected patients depends on the clinical severity. Therefore, risk stratification is imperative for therapeutic decision-making. Patients with high-risk PE need intensive care. These include patients who have successfully survived resuscitation, with obstructive shock or persistent haemodynamic instability. Bedside diagnostics by means of sonographic procedures are of outstanding importance in this high-risk population. In addition to the treatment of hypoxaemia with noninvasive and invasive techniques, the focus is on drug-based haemodynamic stabilisation and usually requires the elimination or reduction of pulmonary vascular thrombotic obstruction by thrombolysis. In the event of a contraindication to thrombolysis or failure of thrombolysis, various catheter-based procedures for thrombus extraction and local thrombolysis are available today and represent an increasing alternative to surgical embolectomy. Mechanical circulatory support systems can bridge the gap between circulatory arrest or refractory shock and definitive stabilisation but are reserved for centres with the appropriate expertise. Therapeutic strategies for patients with intermediate- to high-risk PE in terms of reduced-dose thrombolytic therapy or catheter-based procedures need to be further evaluated in prospective clinical trials.

Keywords

- pulmonary embolism
- critical care
- therapeutic thrombolysis
- right-sided heart failure

Introduction

Pulmonary embolism (PE) is the third most common cause of acute cardiovascular emergency and has high rates of morbidity and mortality.[1,2] PE is attributed to the clinical picture of venous thromboembolism, which considers the close pathophysiological relationship between deep vein thrombosis (DVT) and PE.

PE spans the entire spectrum between asymptomatic and immediately fatal disease. Fast and efficient-risk assessment and risk-adapted treatment are of particular importance when managing acute PE.[3] This review refers to the current guidelines of the European Society of Cardiology,[4] the current S2k guideline "Diagnostics and Therapy of Venous Thrombosis and Pulmonary Embolism" of the AWMF (Association of the Scientific Medical Societies),[5] and a recently published position paper of the German Cardiac Society.[6] In this regard, the present article focuses on acute PE requiring intensive care treatment in the adult patient and does not address this clinical picture in children nor discusses serious complications of extremity thrombosis or thrombosis in the inferior or superior vena cava or neither refers to specific populations such as pregnant women. Other articles in this issue specifically address risk factors of VTE and the diagnostic strategies that form the basis for further therapeutic

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decisions and are therefore not discussed again in this paper to avoid redundancy.

Epidemiology

Exact data on the incidence of VTE in Germany are lacking.[5] The annual incidence rate of PE ranges between 75 and 269 cases per 100,000 individuals as shown by studies in Western Europe, North America, Australia, and Southern Latin America, with individuals 70 years of age or older having an incidence of up to 700/100,000.[3,7] The prognosis and severity of clinical presentations of PE correlate with the extent of right ventricular (RV) strain, which in turn is determined by the extent of thrombotic obstruction of the pulmonary circulation and concomitantly by preexisting cardiac diseases such as ischemic heart disease or RV, left ventricular, or biventricular heart failure. Preexisting lung diseases, such as chronic obstructive pulmonary disease, can also have a significant impact on the clinical course of a patient with PE. Between 2005 and 2015, the incidence of PE in Germany increased from 85/100,000 population/year in 2005 to 109/100,000 in 2015. During the same period, in-hospital case fatality rates decreased from 20.4 to 13.9%. The overall proportion of patients treated with systemic thrombolysis increased from 3.1% in 2005 to 4.4% in 2015.[8] While age-adjusted mortality for PE continues to decline, for people beyond the age of 80 it increases exponentially and dramatically to >100 deaths per 100,000 per year. Among women aged 15 to 55 years, PE is one of the leading causes of death.[5,9]

Pathophysiology

The thin-walled RV pumps the entire systemic venous return into the pulmonary circulation for gas exchange. RV function integrates preload, afterload, contractility, pericardial constraint, interaction with the left ventricle, and cardiac rhythm.[10] Under normal conditions RV afterload is very low. In the setting of either pressure overload or volume overload, RV mechanics and function are substantially altered and may lead to RV failure. In acute PE, mechanical obstruction of pulmonary vasculature along with vasoconstriction due to the release of vasoactive mediators such as thromboxane A2 and serotonin by endothelial cells and platelets result in sudden RV afterload increase.[11] Of note, significant increases in pulmonary arterial pressure (PAP) do not occur until more than 40 to 50% of the pulmonary arterial pathway is occluded.[12] Acute compensatory mechanisms of the right heart to an increase in pressure and resistance of the pulmonary pathway include an increase in myocardial wall tension and inotropy and neurohumoral-mediated systemic vasoconstriction.[13] This compensatory increase in PAP aims to improve perfusion of the (partially) occluded pulmonary circulation, but in a nonpressure-adapted RV, it is possible only in the short term up to a maximum mean pressure of about 40 mm Hg.[13,14]

In addition to a decrease in cardiac output (CO) caused by a decrease in the ability of the RV to compensate for the increased afterload, gas exchange is impaired primarily by increased dead space ventilation (ventilated areas are no longer perfused) and thus a functional right-to-left shunt. This is clinically reflected in hypoxaemia. Furthermore, in about 30% of patients, the foramen ovale reopens as a result of the increase in right cardiac pressure, which aggravates the existing hypoxaemia as a mechanical right-to-left shunt.[15]

Increased RV wall tension together with a reduced oxygen supply to the myocardium, increased oxygen demand because of increased afterload, heart rate and systemic hypotension aggravate RV ischaemia and lead to further neurohumoral activation at the systemic and intracardiac levels. Increased RV wall tension together with a reduced oxygen supply to the myocardium as well as increased oxygen demand as a consequence of increased afterload, heart rate and systemic hypotension aggravate RV ischaemia and lead to further neurohumoral activation at the systemic and intracardiac levels. The mismatch between RV pressure and RV ejection fraction causes a progressive decrease in left ventricular preload.[5] Another important concept of RV failure is ventricular interdependence. As a consequence of increased RV wall tension, RV contraction time increase and continue while the left ventricle is already in early diastolic phase, leading to a leftward shift of the interventricular septum, compromising left ventricular filling and CO, as well as adding mechanical inefficiency to the RV.[11] Moreover, pericardial tension increases. Progression of RV failure brings the heart into a fatal vicious circle, increasing further oxygen demand and decreasing oxygen supply and triggers haemodynamic instability and tachyarrhythmias that finally leads to systemic hypoperfusion and shock and left untreated causes death in acute PE (►**Fig. 1**).[11]

Knowledge and understanding of the pathophysiological consequences, both at the cardiac and especially at the systemic level, are indispensable prerequisites for efficient diagnosis and, ultimately, targeted therapy aimed at thrombotic obstruction of the pulmonary circulation while addressing the haemodynamic effects through intensive care measures.

Risk Stratification

Risk stratification of patients with acute PE is mandatory not only for determining the appropriate therapeutic management approach but also to determine whether the patient needs further care in an intensive care unit (ICU) or at least in a monitoring area (e.g., intermediate care unit [IMC]). Initial risk stratification is based on clinical symptoms and signs of haemodynamic instability (►**Table 1**), which indicate a high risk of early death. Patients after surviving cardiovascular arrest, with obstructive shock or persistent hypoperfusion are classified as high-risk PE and should certainly continue to be monitored and treated in an ICU. Risk-adapted diagnostics are then derived from the risk stratification. The potentially high (early) mortality of acute PE makes an immediate algorithm-based diagnostic approach inevitable. When acute PE is clinically suspected, simple and readily available means can be used to classify the patient as high-risk, intermediate-risk, or low-risk PE (►**Table 2**).[13]

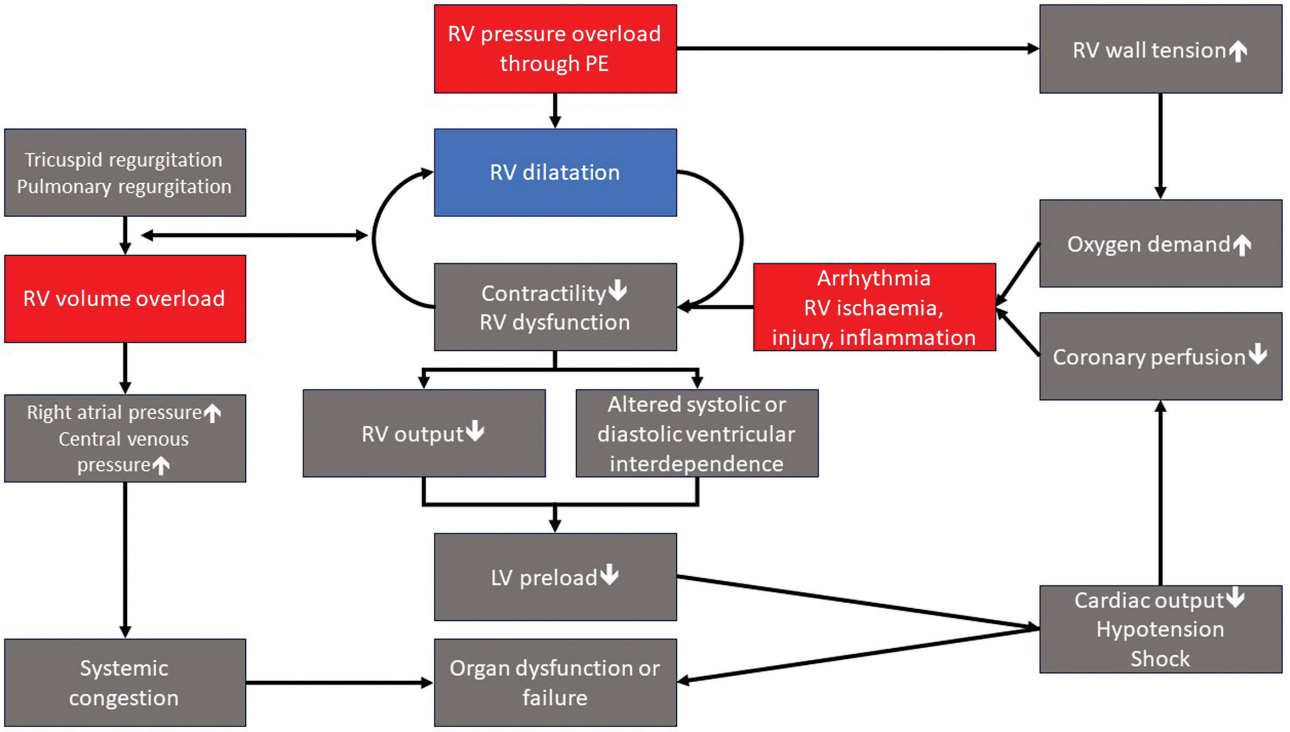

Fig. 1 Pathophysiology of acute right ventricular failure. LV, left ventricular; PE, pulmonary embolism; RV, right ventricular.[10]

Diagnostic Procedure in High-Risk Pulmonary Embolism

Clinically unstable patients with an urgent suspicion of PE cannot be referred to the usual diagnostic procedures. These patients must be diagnosed as quickly as possible, as they must be offered causal therapy without delay. Elaborate procedures such as computed tomography pulmonary angiogram, which may put the patient at additional risk and which may also mean a loss of time, should be avoided. Haemodynamically unstable or mechanically ventilated patients with later proven PE were never included in diagnostic studies.[11]

Biomarkers such as troponin, B-Type Natriuretic Peptide (BNP) or N-terminal prohormone of BNP (NT-proBNP) support the clinician in a more refined risk stratification. Troponin elevation, as the laboratory correlate of relevant myocardial ischaemia, indicates increasing severity of PE. Similarly, BNP/NT-proBNP elevations are a clear indicator of RV strain in PE. A meta-analysis reported an odds ratio (OR) of 5.24 for early mortality in patients with elevated troponin (both I and T).[16]

Sonographic procedures that can be performed at the bedside, such as echocardiography, lung ultrasound, and duplex sonography of the veins, can be used quickly. These methods not only allow a diagnosis to be confirmed but are also extremely helpful in the differential diagnosis of patients' haemodynamic instability (e.g., left heart failure, pericardial tamponade, or acute valve insufficiencies).[5] The proof or exclusion of an RV strain is of utmost importance. In the absence of RV strain signs, massive PE can be ruled out as the cause of clinical instability and an alternative diagnosis should be sought. However, if there is any doubt that the echocardiographically detected RV dysfunction is an acute event (such as in a condition of known chronic lung disease or chronic thromboembolic pulmonary hypertension) or if

Table 1 Definition of haemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation)[4]

Cardiac arrest	Obstructive shock	Persistent hypoperfusion
Need for cardiopulmonary resuscitation	Systolic BP < 90 mm Hg or vasopressors required to achieve a BP ≥ 90 mm Hg despite adequate filling status	Systolic BP < 90 mm Hg or systolic BP drop ≥ 40 mm Hg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	

Abbreviation: BP, blood pressure.

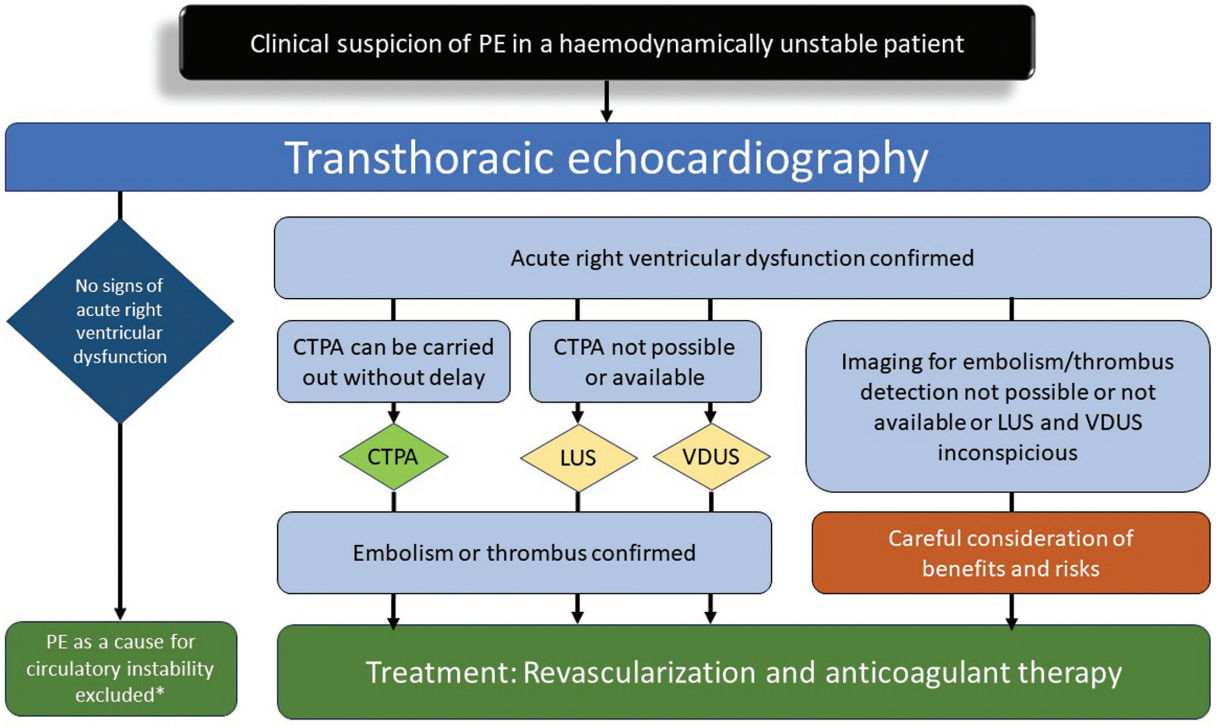

Fig. 2 Diagnostic algorithm for suspected PE in haemodynamically unstable patients. Reproduced from Linnemann et al.[5] *Absence of right ventricular strain can exclude only the presence of a haemodynamically relevant pulmonary embolism. Smaller embolisms are still possible. CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; LUS, lung ultrasonography; VDUS, venous duplex ultrasonography.

no meaningful findings can be obtained for technical reasons (e.g., emphysema, extreme obesity), patients must undergo further imaging diagnostics if PE is still suspected.[5]

The objective here is to directly detect the embolus or the underlying thrombosis (►**Fig. 2**). It is rarely possible to directly visualise a thrombus in the right heart (so-called transit thrombus) or in the central parts of the pulmonary arterial pathway echocardiographically. Therefore, with the ultrasound device available at the bedside, a sonography of the lower extremity veins and, with appropriate expertise, also a lung ultrasonography (triple point-of-care-ultrasonography) should be performed immediately after the echocardiography in haemodynamically unstable patients. The presence of RV strain signs on echocardiography together with sonographic evidence of an embolus and/or DVT are considered conclusive of a thromboembolic event as the cause of the haemodynamic instability; therapy can be initiated without further delay.[5] However, echocardiography does not provide "perfect" specificity for PE diagnosis, especially after cardiac arrest. RV dilatation and injury in patients with cardiac arrest may indeed be related to the cardiac arrest and not to specific causes of the arrest. Sustained cardiac arrhythmias, hyperkalaemia, hypovolaemia, and hypoxia may also cause RV dilatation.[11]

To conclude, it can be stated that in acute life-threatening situations, the sole detection of RV strain may be sufficient in

Table 2 Risk stratification and 30-day mortality for proven pulmonary embolism[4,5,43]

Early mortality (within 30 d)	Shock or hypotension haemodynamic instability	sPESI ≥ 1	RV dysfunction in TTE or CTPA	Cardiac biomarkers (e.g., troponin, NT-proBNP)	Proportion of patients[43]	
High (>20%)		Yes	Yes	Yes	Yes	12%
Intermediate	Intermediate–high	No	Yes	RV dysfunction and biomarker elevation		30%
	Intermediate–low	No	Yes	Normal RV function and biomarkers or RV dysfunction or biomarker elevation		37%
Low (<1%)		No	No	No	No	22%

Abbreviations: CTPA, computed tomography pulmonary angiography; NT-proBNP, N-terminal pro-B-natriuretic peptide; RV, right ventricular; sPESI, simplified Pulmonary Embolism Severity Score; TTE, transthoracic echocardiography.

individual cases to assume PE and initiate therapy if further imaging for direct embolism or thrombus detection is not feasible or available and other causes of haemodynamic instability are excluded or unlikely.[5]

The results of the (bedside) imaging, considering the biomarkers already mentioned, allow an additional risk assessment in patients who are still haemodynamically stable but show right heart strain on imaging and have elevated biomarkers at the same time. These patients are classified in an intermediate- to high-risk group (►Table 2). Close monitoring is recommended in these cases to permit the early detection of haemodynamic decompensation or collapse and consequently the need for rescue reperfusion therapy.[4]

Treatment for Patients with High-Risk Pulmonary Embolism

PE Patients with high or intermediate–high risk must be monitored in an ICU. In addition to basic monitoring with continuous electrocardiogram recording and continuous measurement of oxygen saturation, continuous invasive arterial blood pressure measurement should be performed in haemodynamically unstable patients. In view of the required therapeutic anticoagulation and against the background of a possibly necessary thrombolysis, the indication for the insertion of central venous catheters must always be critically reviewed in view of the associated risk of bleeding.

Hypoxaemia and haemodynamic instability up to obstructive cardiogenic shock as an expression of acute right heart failure must be stabilised. Therapy directed at the pathophysiology of PE must take all available measures to reduce the afterload for the RV. The cause-oriented therapy is to be seen in a reduction or removal of the PEs. Extracorporeal membrane oxygenation (ECMO) therapy can be used in patients with refractory obstructive shock or during resuscitation[17] but should be restricted to specialised centres with sufficient experience in the provision of this therapy. Determination of the optimal treatment strategy should be individualised, risk-adapted, and based on interdisciplinary consensus. Specialised Pulmonary Embolism Response Teams (PERT) have been established in numerous hospitals for this purpose. Meta-analyses on the efficacy of PERT currently show a trend towards a survival benefit, particularly so in intermediate- and high-risk patients.[5,18,19] The establishment of multidisciplinary PERT in German hospitals is recommended.[4] They pursue the overall goal of coordinating and accelerating treatment decisions and their implementation in acute, potentially life-threatening PEs (high and intermediate–high risk). In doing so, the expertise and resources available in the respective hospital are to be optimally used and, if necessary, cooperation partners (e.g., virtual conference) or the criteria for transfer to a qualified centre are to be determined.[6]

Oxygen Therapy and Ventilation

Hypoxaemia is one of the features of severe PE and is mostly due to the mismatch between ventilation and perfusion. A relevant right-to-left shunt through a patent foramen ovale or an atrial septal defect can be the cause of severe hypoxaemia or respiratory failure that cannot be controlled by conventional oxygen administration.[4,10] Administration of supplemental oxygen is indicated in patients with PE and $SaO2 < 90\%$.[4] Regardless of the delivery system (nasal cannula, venturi mask, high-flow cannulae, ventilation masks), treatment should be directed towards a target range for peripheral oxygen saturation of 92 to 96%.[5,20] Noninvasive positive-pressure ventilation may open up atelectatic areas and reduce the pulmonary vascular shunt. It should always be remembered that noninvasive positive pressure ventilation also increases RV afterload. Application of positive end-expiratory pressure can worsen RV function. This is due to a decrease in venous return and an increase in afterload as a result of compression of the pulmonary vessels.

Intubation is required in many PE patients with haemodynamic instability and impending respiratory failure.[5] Patients with RV failure are frequently hypotensive or are highly susceptible to the development of severe hypotension during induction of anaesthesia, intubation, and positive-pressure ventilation.[4] In high-risk PE patients who are intubated, 19% have cardiac arrest on induction and another 17% have cardiac arrest shortly afterwards.[21–23] The compromised left ventricle can only adapt to the consequences of induction of anaesthesia to a limited extent and, in addition, any induction drug can aggravate preexisting hypotension by attenuating the sympathetic response.[5] If intubation is needed, anaesthetic drugs more prone to cause hypotension should be avoided for induction.[4] Postintubation hypotension should be anticipated and, if possible, avoided by appropriate combination of induction drugs including, e.g., ketamine and vasopressors at adjusted dosages.[5] Tidal volumes of approximately 6 mL/kg lean body weight should be used in an attempt to keep the end-inspiratory plateau pressure < 30 cm H_2O.[4] Hypercapnia increases RV afterload. Therefore, low $PaCO_2$ values should be aimed for when ventilating patients with acute right heart failure.[5]

Volume Therapy

Even patients with acute RV failure in PE may still be preload dependent in occasional cases. However, volume loading has the potential to overdistend the RV and ultimately cause a reduction in systemic CO. Cautious volume loading (≤ 500 ml fluid) may be appropriate if low arterial pressure is combined with an absence of elevated central venous filling pressures. Ultrasound imaging of the inferior vena cava (IVC) can be helpful in deciding for or against volume administration. A small and/or collapsible IVC in the setting of acute high-risk PE may suggest a low-volume status.[4] A passive leg raising (PLR) test may indicate volume responsiveness but should only be performed after floating clots in the pelvic venous circulation have been ruled out to prevent further venous thromboembolism. The major advantage of a PLR is the reversibility of the volume effect on the RV. Usually, however, the volume effect of the PLR should be checked against the invasively measured stroke volume.[24,25]

Vasopressor and Inotrope Treatment

Vasopressors and/or inotropes are indicated in acute RV failure with haemodynamic instability.[10] Vasopressors such as norepinephrine (NE) are primarily indicated to restore blood pressure and improve cerebral, coronary, and other organ perfusion.[10] NE stimulates both the α1 and β1 receptors and, through them, exerts its systemic vasopressor and inotropic or chronotropic effects, respectively. Although stimulation of the α1 receptor can lead to pulmonary vascular vasoconstriction, an actual increase in the pulmonary vascular resistance (PVR) is only likely to occur at higher doses above 0.5 µg/kg/min.[26] Vasopressin, a nonsympathomimetic vasoconstrictor, functions through stimulation of V1 receptor. Through a nitric oxide–dependent mechanism, vasopressin's stimulation of the V1 receptor can also result in a PVR reduction.[26] However, data for vasopressin are lacking in acute right heart failure.[10]

Dobutamine, levosimendan, and phosphodiesterase III inhibitors improve contractility and increase CO. Based on the results of a small series, the use of dobutamine may be considered for patients with PE, a low cardiac index, and normal blood pressure; however, raising the cardiac index may aggravate the ventilation/perfusion mismatch by further redistributing flow from (partly) obstructed to unobstructed vessels.[4] Dobutamine may reduce blood pressure; in that case, a vasopressor, such as NE, is recommended. Levosimendan may favourably affect RV–arterial uncoupling by combining RV inotropy and pulmonary vasodilation. Phosphodiesterase III receptors are absent in the pulmonary vasculature. Thus, phosphodiesterase III inhibitors exert a positive inotrope effect on the RV without the deleterious effects on PVR that occur with catecholamines. Similar to dobutamine, these drugs may aggravate arterial hypotension and should be combined with noradrenaline if needed.[10] Authors of a Cochrane analysis summarise that there are no convincing data to support specific inotropic agents or vasodilators in terms of mortality benefits in acute right heart failure.[5,27]

Vasodilators

Vasodilators decrease pulmonary artery pressure and PVR but may worsen hypotension and systemic hypoperfusion due to their lack of specificity for the pulmonary vasculature after systemic (intravenous [IV]) administration. Currently, no recommendation can be made for IV vasodilators.[4] The same applies to inhaled vasodilators such as nitric oxide or prostanoids. Randomised controlled trials (RCTs) for PE treatment with inhaled vasodilators are lacking. Therefore, no recommendation can be made in favour or against therapy with inhaled vasodilators.[5]

Mechanical Circulatory Support

The temporary use of mechanical cardiopulmonary support, mostly with venoarterial extracorporeal membrane oxygenation (VA-ECMO), may be helpful in patients with high-risk PE, and circulatory collapse or cardiac arrest and may be considered in combination with surgical embolectomy or catheter-directed treatment.[4] Up to now no RCTs testing the efficacy and safety of these devices in the setting of high-risk PE have been conducted to date. Use of ECMO is associated with a high incidence of complications, even when used for short periods, and the results depend on the experience of the centre as well as patient selection. The increased risk of bleeding related to the need for vascular access should be considered, particularly in patients undergoing thrombolysis. ECMO might also induce adverse effects such as reduction in bronchial arterial blood flow, reduction in pulmonary blood flow/transpulmonary gradient, and worsening of lung ischaemia.[11] In a meta-analysis of 29 observational studies, increased mortality was seen when patients were older than 60 years, did not receive surgical embolectomy and were treated after cardiac arrest.[28] Overall, the indication for VA-ECMO should be extremely rigorous and the initiation and execution of such invasive therapy should be reserved for centres with the appropriate expertise. VA-ECMO is not a stand-alone causal treatment procedure for acute PE with circulatory instability. Rather, it can be used in combination with catheter-based intervention or surgical embolectomy.[4] The use of ECMO can help to bridge the time until reperfusion and, if necessary, also enable transport to a qualified centre.[6]

Anticoagulant Therapy

Anticoagulation with unfractionated heparin (UFH) at therapeutic dosages, including a weight-adjusted bolus injection, should be initiated without delay in patients with high-risk PE.[4] These patients usually receive systemic thrombolysis or invasive reperfusion. In view of this and the fact that UFH have a shorter half-life and can be better controlled, they should be used preferentially in the haemodynamically unstable patient. Low-molecular-weight heparins should be used with utmost caution in this situation and always taking into account renal function, which can be compromised in the further course of the disease, especially in haemodynamically unstable patients with obstructive cardiogenic shock.

Reperfusion Therapy

Systemic Thrombolysis

Thrombolytic therapy leads to faster improvements in pulmonary obstruction, PAP, and PVR in patients with PE, compared with UFH alone; these improvements are accompanied by a reduction in RV dilation on echocardiography.[4] The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for 6 to 14 days.[4] In a meta-analysis of 21 trials involving 2,401 patients with high- or intermediate-risk PE, systemic thrombolysis plus heparin was shown to reduce both mortality (OR: 0.58; 95% confidence interval [CI]: 0.38–0.88) and PE recurrence (OR: 0.54; 95% CI: 0.32–0.91) versus therapeutic

anticoagulation with heparin alone.[29] However, thrombolysis increases the risk of major bleeding (OR: 2.84; 95% CI: 1.92–4.20) and even more so of intracranial haemorrhage (OR: 7.59; 95% CI: 1.38–41.7).[29] A total of 9.4% of patients treated with thrombolytic therapy experience a major bleeding complication,[29] and intracranial haemorrhage occurs in approximately 2% of patients.[30,31] For this reason, thrombolysis is clearly indicated in high-risk PE patients, as the risk of PE-related death or life-threatening complications is greatly increased in the first hours or days after diagnosis.[5] The impact of thrombolytic treatment was investigated in the Pulmonary Embolism Thrombolysis (PEITHO) trial in normotensive patients with intermediate-risk PE, defined as the presence of RV dysfunction and elevated troponin levels.[31] Thrombolytic therapy was associated with a significant reduction in the risk of haemodynamic decompensation or collapse, but this was paralleled by an increased risk of severe extracranial and intracranial bleeding. In the PEITHO trial, 30-day death rates were low in both treatment groups, although meta-analyses have suggested a reduction in PE related and overall mortality of as much as 50 to 60% following thrombolytic treatment in the intermediate-risk category.[32,33] The current recommendation for thrombolytic therapy in PE patients at intermediate–high risk is that thrombolytic therapy should only be given in the event of haemodynamic deterioration.[5] Streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA) are available in Germany for systemic thrombolysis in acute PE (►Table 3). The absolute and relative contraindications must be strictly followed (►Table 4). At present, no RCTs are available that compare reduced dosing of thrombolytics with the approved dosing. It is anticipated that such an approach would be equally effective in reducing thrombus burden in the pulmonary arteries with fewer bleeding events. The empirical evidence is currently insufficient for definitive conclusions. Currently, in the context of a large multicentric RCT (PEITHO-3; ClinicalTrials.gov identifier: NCT04430569), a reduced-dosage regimen with rt-PA (i.e., 0.6 mg/kg is being compared with a maximum dosage of 50 mg) with anticoagulation alone in PE patients at intermediate–high risk.[34]

Table 3 Validated thrombolysis regimens for therapy of acute pulmonary embolism[5]

Substance	Dosage regimen
Alteplase (rt-PA)	Bolus injection of 10 mg over 1–2 min, followed by 90 mg over 2 h or 100 mg over 2 h or accelerated: 0.6 mg/kg over 15 min
Streptokinase	250,000 IU over 30 min, followed by 100,000 IU/h for 12–24 h or accelerated: 1.5 million IU over 2 h
Urokinase	4,400 IU/kg over 10 min, followed by 4,400 IU/kg/h for 12–24 h or accelerated: 3 million IU over 2 h
(Tenecteplase)	Weight-adapted regimen with bolus injection of 30–50 mg over 5–10 s (dosage as in acute myocardial infarction, validated in a prospective study, but currently not approved in Germany for the treatment of acute PE [as of January 2023])

Abbreviation: PE, pulmonary embolism.

Surgical and Endovascular Reperfusion

Surgical pulmonary embolectomy is recommended for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed.[4]

There are no generally accepted criteria for failure of thrombolysis. Both clinical and haemodynamic deterioration and the absence of clinical improvement 2 to 4 hours after initiation of IV thrombolysis may indicate failure. Echocardiographic signs of deterioration in RV function and a rising lactate level as markers of systemic hypoperfusion should also be considered in an assessment of reperfusion success.[6]

As an alternative to surgery, catheter-based techniques such as endovascular thrombus fragmentation and thrombectomy procedures as well as catheter-directed local thrombolysis (CDT) should be considered in this patient group.[4] No randomised comparative studies of systemic thrombolysis and CDT in high- or intermediate-risk PE patients are available yet. Similarly, no RCTs were found

Table 4 Absolute and relative contraindications to thrombolysis[5]

Absolute contraindication	Relative contraindication
• History of intracranial haemorrhage • Ischaemic stroke within the last 6 months • CNS neoplasia with increased risk of bleeding • Severe trauma, surgery, or head injury within the last 3 mo • Haemorrhagic diathesis • Active, potentially threatening bleeding after lysis • Allergy to thrombolytic agent	• TIA within the last 6 mo • Oral anticoagulation • Pregnancy or delivery within the last 7 d • Resuscitation with cardiac massage • Uncontrolled hypertension (RRsyst >180 mm Hg • Severe hepatic disorder • Infective endocarditis or pericarditis • Oesophageal varices • Active gastroduodenal ulcers • Acute pancreatitis • Arterial aneurysms • Recent puncture at noncompressible puncture site

Abbreviations: CNS, central nervous system; RRsys, systolic blood pressure; TIA, transient ischaemic attack.

comparing the use of CDT with anticoagulation alone in high-risk PE patients.[4] A recent network meta-analysis of observational studies and RCTs involving patients with intermediate- to high-risk PE showed a reduced mortality rate when utilising CDT compared with other therapeutic procedures without significant additional bleeding risk.[35] The indication for catheter-based treatment of acute PE requires—like IV thrombolysis—a manifest or impending circulatory instability. It is therefore an acute situation, so that reperfusion treatment (in analogy to acute ST elevation myocardial infarction) should begin as soon as possible after indication. For this purpose, patient transfer to a hospital with the option of intervention can be considered/discussed.[6]

The endovascular mechanical procedures for thrombus fragmentation or removal use rotational, aspiration-based, hydrodynamic, or suction-based thrombectomy. The aim is to improve right ventricular function by reducing the size of the thrombus and the thrombus burden.[4] Despite the increased interest in endovascular procedures in recent years, there is a lack of RCTs comparing mechanical procedures with standard-of-care pharmacotherapy in high- or intermediate- to high-risk PE patients.[36] Due to the insufficient empirical evidence available, the individual endovascular procedures cannot be assessed conclusively.[5]

Surgical pulmonary embolectomy is a treatment option for patients with mainly centrally localised thrombi.[5] Recent work reports good acute and long-term success of surgical embolectomy.[37–39] In-hospital mortality is comparable to the rates for thrombolysis and is estimated at 6.8% for patients without prior cardiopulmonary resuscitation.[40] After prior cardiopulmonary resuscitation, by contrast, in-hospital mortality is 46%. No prospective comparative studies of surgical embolectomy and other reperfusion procedures are available.[5] However, considering the complexity and surgical risk associated with this strategy, catheter-based approaches have gained considerable interest over the past decade.[11,41]

In summary, reperfusion therapy by means of catheter-based procedures for mechanical thrombus fragmentation/aspiration, CDT or (if necessary) by means of surgical embolectomy, should be considered (1) in cases of manifest, refractory circulatory instability, (2) after unsuccessful systemic thrombolytic treatment, and (3) in cases of a high bleeding risk and contraindication(s) to systemic thrombolysis.[6]

Treatment of Patients with Intermediate- to High-Risk Pulmonary Embolism

Patients at intermediate–high risk or considered to be at high risk of haemodynamic decompensation, based on clinical presentation or comorbidities, should initially receive therapeutic anticoagulation and circulatory monitoring (usually for 24–36 hours) in an IMC or ICU in order to be able to detect any clinical deterioration necessitating therapy escalation in good time.[5] Developing a superior method to determine who in the intermediate- to high-risk group would benefit from more invasive therapy remains paramount to investigating and further defining treatment for this group.[42] While it is clear that there is benefit in aggressive treatment in the patient who needs it, if patients are not at true risk for decompensation, then aggressive treatment only comes with more risk. It is perhaps not the treatment of PE that needs defining but rather better individualised haemodynamic monitoring and prediction of decompensation that hold the key.[42] In acute PE and initially stable circulatory conditions, haemodynamic deterioration with manifest or impending decompensation or circulatory collapse in the course of the disease is the indication for reperfusion therapy. As a rule, lysis is the standard therapy; alternatively, catheter-based intervention or surgical embolectomy may be considered if indicated.[6]

Conclusion

The management of high-risk PE patients in the ICU remains a challenge despite all diagnostic and therapeutic advances. Precise pathophysiological knowledge of acute right heart failure in PE is required to manage these complex patients. Bedside sonographic procedures play a central role not only in diagnosis but also in the management of therapy. Drug reperfusion by thrombolysis accompanied by therapeutic anticoagulation remains the core element in the treatment of PE in the high-risk situation. Future studies must show whether reducing the dosage of thrombolytics with greater safety has the same effectiveness. Catheter-based procedures will certainly play an increasing role in the therapeutic arsenal in the coming years.

Conflict of Interest

The authors declare that they have no conflict of interest.

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