VOLUME - 15, ISSUE - 01, JANUARY - 2026 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Internal Medicine

THE CRITICAL CARE SPECTRUM OF PULMONARY EMBOLISM: EPIDEMIOLOGY, RISK PHENOTYPING, AND MULTIMODAL MANAGEMENT OF THE UNSTABLE PATIENT.

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ABSTRACT Pulmonary embolism (PE) represents a formidable and potentially cataclysmic vascular emergency that permeates the entire spectrum of acute clinical specialties. While PE is only sporadically the precipitating factor for initial admission into the intensive care unit (ICU), those patients who present with this pathology are frequently situated at a precarious threshold of physiological collapse, bearing a disproportionately high risk of mortality. Paradoxically, the condition often manifests as a secondary, insidious complication in patients already hospitalized for unrelated critical illnesses, adding a layer of complexity to an already fragile clinical state. This comprehensive review meticulously interrogates the evolving epidemiology, diagnostic modalities, and prognostic risk stratification of PE, specifically through the nuanced lens of critical care medicine. It navigates the intricate balance required in managing hemodynamically unstable patients, offering a deep dive into prophylactic strategies, sophisticated anticoagulation regimens, and the deployment of systemic fibrinolysis. Furthermore, we evaluate the burgeoning role of advanced interventions, including catheter-directed therapies, surgical embolectomy, and the final frontier of extracorporeal life support (ECLS). By synthesizing these interventions, the review seeks to provide clinicians with a sophisticated framework for mitigating the profound impact of this lethal condition on the most vulnerable patient populations.

KEYWORDS :

INTRODUCTION

Pulmonary embolism (PE) remains one of the most challenging conditions to diagnose and manage in acute care medicine. With an estimated incidence of 40–110 cases per 100,000 population annually [1], PE is associated with substantial morbidity and mortality, reaching up to 22% at 30 days in high-risk presentations [2, 3]. Although a decline in PE-related mortality was observed in Europe between 2000 and 2015 [4], contemporary data from the United States suggest increasing age- and sex-adjusted mortality among young and middle-aged adults [5].

Despite being heavily investigated in emergency departments-where the diagnostic yield remains low, with a true positive rate of approximately 5% [6]-PE continues to be underdiagnosed. A significant proportion of PE-related deaths occur in patients in whom the diagnosis was not made during life [7]. This paradox highlights the ongoing diagnostic complexity of PE. In this narrative review, we provide a state-of-the-art overview of PE in the ICU, focusing on incidence, prevention, clinical presentation, diagnostic strategies, organ support, and specific therapeutic interventions.

Epidemiology

Pulmonary embolism is an uncommon primary reason for ICU admission. A nine-year observational study involving nearly one million ICU admissions in Australia and New Zealand reported PE as the primary diagnosis in approximately one out of every 300 patients [8]. Among 906 consecutive patients with symptomatic PE, 11.7% presented with hemodynamic instability consistent with high-risk PE, while a further 30% required ICU-level care despite initial hemodynamic stability [3]. Other large cohort studies have reported lower rates of hemodynamic instability, closer to 4% [9].

PE may also be identified in patients presenting with otherwise unexplained acute clinical syndromes, including exacerbations of chronic obstructive pulmonary disease (approximately 5%) [10], syncope (4%) [11], and coronavirus disease 2019 (COVID-19), with reported rates as high as 22% in selected cohorts [12].

More commonly, PE develops as a complication during hospitalization, particularly in critically ill patients. Venous thromboembolism (VTE) is a frequent complication of critical illness, with deep vein thrombosis (DVT) occurring more often than clinically apparent PE. However, the true incidence of PE is difficult to determine, as many events are clinically silent. In a cohort of 2,166 ICU patients, 1.4% developed ICU-acquired PE [13], while a neuro-critical care cohort of 2,188 patients reported an incidence of 2.9% [14]. These figures likely underestimate the true burden.

Studies incorporating systematic DVT surveillance using twice-weekly ultrasonography have reported proximal DVT rates as high as 10% [15], with embolization occurring in up to 50% of cases [16]. Furthermore, a recent study employing routine screening chest computed tomography in neuro-ICU patients identified PE in 17.5% of cases [17]. Reported incidence therefore varies widely depending on surveillance intensity and diagnostic criteria, including whether incidental sub-segmental emboli are included.

Assessment of true PE incidence in the ICU is further complicated by the inability of many hemodynamically unstable patients to undergo definitive imaging, such as computed tomography pulmonary angiography.

Patients admitted to the ICU with PE represent the most severe end of the disease spectrum. Although precise data are limited, mortality rates are substantial. In a multicenter study of 2,792 ICU patients with PE, overall in-hospital mortality was 14.1%, increasing to 41% among those requiring invasive mechanical ventilation [8]. Reported mortality in patients with hemodynamic instability ranges from 14% to 58% [9, 19–21].

Risk Factors

Several frameworks have been proposed to group VTE risk factors, including inherited vs acquired and tempo- rary vs permanent classification schemes, but from an ICU perspective use of a strong/moderate/weak risk fac- tor framework is more intuitive. Strong risk factors are associated with an odds ratio (OR) for VTE of greater than 10 and include lower limb fracture, hospitalization for heart failure or myocardial infarction within the past 3 months, hip or knee replacement, major trauma or spi- nal cord injury, and previous VTE. Besides these strong risk factors, we report in the supplementary eTable 1 a list of moderate (OR 2–9) and weak (OR < 2) risk factors relevant to patients in the ICU [18, 22]. The recent global pandemic highlighted COVID-19 as a specific risk factor.

Clinical Presentation

Classic signs and symptoms of PE include dyspnea, chest pain, syncope/pre-syncope, and hemoptysis [23]. Patients admitted to the ICU for PE typically meet criteria for high-risk or intermediate high-risk PE, otherwise they are generally managed on the hospital ward or even as outpatients. High-risk PE is defined by cardiac arrest, the presence of obstructive shock [systolic blood pressure (SBP) < 90 mmHg plus organ dysfunction], or persistent hypotension (SBP < 90 mmHg for more than 15 min, not due to other causes) [18]. Intermediate-risk PE is defined by an at-risk presentation including factors such as tachy- cardia, tachypnea, and hypoxemia (supplementary eTa- ble 2). This is typically quantified using the Pulmonary Embolism Severity Index (PESI) [24]. The presence or absence of right ventricle (RV) dysfunction (RVD) and an elevated troponin level are used to further risk strat- ify patients into intermediate high- or low-risk groups. Intermediate high-risk patients are recommended for ICU-level monitoring, at least initially, as they are at higher risk for delayed clinical deterioration and may warrant consideration for advanced pulmonary reperfu- sion (see "new techniques and perspectives" below) [18]. A risk stratification framework for critically ill patients is proposed in Table 1. The large Australia/New Zealand study included 4% of patients presenting with cardiac arrest, 3% with respiratory arrest, 18% requiring inva- sive ventilation, and 17% admitted after activation of the rapid response team [8].

The clinical presentation of patients who develop PE while already admitted in the ICU for another reason may range from completely asymptomatic, to unexplained respiratory failure, to sudden cardiac arrest and death. Intensive screening protocols suggest that a large major- ity of incidentally discovered emboli will be segmental or sub-segmental and therefore completely asymptomatic [17].

Prevention Of ICU-acquired PE

Pharmacologic Approaches

Approaches to VTE prophylaxis in critically ill patients can be broadly considered as pharmacologic or mechanical; pharmacologic approaches have largely focused on low molecular weight heparin (LMWH) and unfractionated heparin (UFH). A large network meta- analysis aggregated data from 13 large trials (N = 9619) from mixed medical-surgical, surgical, and trauma ICUs [25]. The authors found that LMWH prevented DVT compared to placebo (high certainty), that UFH.

Table 1 Risk Stratification Of Critically Ill Patients With Pulmonary Embolism

A. Pulmonary Embolism Severity Index (PESI)

PESI characteristic	Points assigned
Age, per year	Age in years
Male sex	+10
History of cancer	+30
History of heart failure	+10
History of chronic lung disease	+10
Heart rate ≥110/min	+20
Systolic blood pressure <100 mmHg	+30
Respiratory rate ≥30/min	+20
Temperature <36 °C	+20
Altered mental status	+60
Arterial O_2 saturation <90%	+20

Points scored	PESI risk class	30-day mortality
≤65	Class I	0–1.6%
66–85	Class II	1.7–3.5%
86–105	Class III	3.2–7.1%
106–125	Class IV	4–11.4%
>125	Class V	10–24.5%

B. Simplified Pulmonary Embolism Severity Index (sPESI)

sPESI characteristic	Points assigned
Age >80 years	1
History of cancer	1
History of chronic cardiopulmonary disease	1
Heart rate ≥110/min	1
Systolic blood pressure <100 mmHg	1
Arterial O_2 saturation <90%	1

Points scored	sPESI risk class	30-day mortality
0	Low risk	1.1%
≥1	High risk	8.9%

BPM beats per minute, *mmHg* millimeters of mercury, O_2 oxygen, *SBP* systolic blood pressure, *RR* respiratory rate, *PESI* pulmonary embolism severity index

A: Since no specific scoring systems exist for critically ill patients, indirect information can be gleaned from the original PESI risk stratification data (n=10,354) [22]. Critically ill patients would generally be expected to fall into risk classes 3-5. Risk class for an individual patient can be calculated from the characteristics, with scores summed and mortality thereafter estimated. This may be helpful for the group of intermediate risk patients where systemic fibrinolysis is not indicated, and other therapies beyond anticoagulation are being considered

B: The sPESI scoring system [38]

may prevent DVT compared to placebo (low certainty), and that LMWH was superior to UFH (moderate cer- tainty). Studies specific to PE prevention are scant [26].

Pharmacological prophylaxis with LMWH should be used where possible [27], although questions remain about specific patient populations and the timing of initiation. Early mobilization of patients, whether as part of a prevention strategy or importantly for patients with established PE, is crucial.

Mechanical Approaches

Approximately 5–20% of critically ill patients develop DVT despite pharmacologic thromboprophylaxis [28], and mechanical thromboprophylaxis with intermittent pneumatic compression (IPC) is typically recommended for patients with

a contraindication to LMWH or UFH. While use of IPC reduces DVT compared to placebo, its efficacy appears to be lower than pharmacologic throm- boprophylaxis [29]. Adding IPC to patients already receiving pharmacologic thwromboprophylaxis does not appear to be helpful [30].

Diagnostic Strategy

A clinicopathological study from fifty years ago, per- formed in 101 patients who died from massive PE, reminds us of the urgency mandated by this diagnosis [31]. Many patients (43.5%) died within the first hour after onset of symptoms, bringing to light the concept of a "golden hour" for diagnosing and managing high- risk PE. For patients without clinical instability, the diagnostic pathway has been widely validated [18] using a Bayesian approach combining clinical assessment, D-Dimer level, and imaging tests. A pre-test probabil- ity is calculated using either the revised Geneva [32] or Wells score [33] (or potentially newer scoring systems such as YEARS [34] or 4PEP [35], grouping patients into low (roughly 10% likelihood of PE), moderate (30%), and high (65%) probability groups [36]. Patients with low and intermediate clinical probabilities may be screened with a D-dimer assay, and a negative D-dimer test safely rules out a PE without need for imaging. D-dimer test- ing is inappropriate for most ICU patients, presumably due to the presence of inflammation which may cause it to be elevated. Patients with high clinical probability, or those with a positive D-dimer, should undergo CT pul- monary angiography (CTPA) where possible. While there are other definitive diagnostic modalities available, none are as pragmatic and widely available, and CTPA offers the additional advantage of diagnosing other thoracic abnormalities and visualization of the right heart. Con- cerns regarding acute kidney injury should not be a con- traindication for CTPA when it is deemed necessary [37], however the test does involve patient transport, exposure to radiation, and the small risk of contrast allergy.

For patients admitted with circulatory shock, the clini- cal probability is usually high and D-dimer testing is not helpful in excluding PE. As in-hospital mortality has been reported to be higher in patients without early defini- tive diagnosis [38], patients who are sufficiently stable (or able to be stabilized) should undergo CTPA to rule-in or rule-out PE while also yielding information about alter- native diagnoses [39]. For patients who are too unstable for transport, critical care ultrasonography (CCUS) is generally the best tool available. In this setting, echo- cardiographic evidence of RV overload in a patient with high clinical suspicion may be sufficient to inform a deci- sion about immediate reperfusion without further test- ing. Alternatively, if no signs of RV overload are detected in an unstable patient, PE is very unlikely. Whole-body CCUS might also unearth an alternative cause for shock or dyspnea, such as tension pneumothorax or pericardial tamponade.

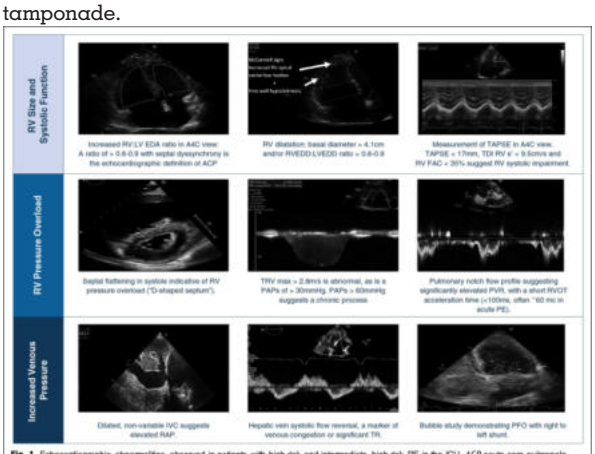

Fig. 1 Echocardiographic abnormalities observed in patients with high-risk and intermediate high-risk PE in the ICU. *ACP* acute core pulmonale, *EDA* end-diastolic area, *EDD* end-diastolic diameter, *FAC* fractional area contraction, *PAPs* systolic pulmonary artery pressure, *PVR* pulmonary vascular resistance, *IVC* inferior vena cava, *PE* pulmonary embolism, *PFO* patent foramen ovale, *RAP* right atrial pressure, *RVOT* right ventricular outflow track, *TAPSE* tricuspid annular plane systolic excursion, *TDI* tissue Doppler imaging, *TR* tricuspid regurgitation, *TRV* tricuspid regurgitation velocity, *TRVmax* tricuspid regurgitation maximal velocity

For a stable patient, unless a thrombus is directly visu- alised, bedside echocardiography is unable to definitively rule-in or rule-out a PE on its own due to the non-spe- cific nature of RVD and a limited negative predictive value. Nonetheless, specific echocardiographic abnor- malities in the correct clinical context can be helpful in increasing or decreasing the probability of PE and may be used to justify empiric treatment for PE if the patient is deteriorating and too unwell for CTPA (Fig. 1). Detec- tion of DVT is also of value in increasing the likelihood of PE. Transesophageal echocardiography (TEE) may some- times confirm the diagnosis by visualizing thrombus in the main or right pulmonary artery or in the right atrium and/or ventricle (clot in transit) [40] (Fig. 2). TEE should not be performed in acutely unwell patients who are not invasively ventilated. Intensivists should be aware that isolated RV dilatation is common after cardiac arrest and return of spontaneous circulation, as well as in critical ill- ness in general, and that this finding is not specific for PE [41].

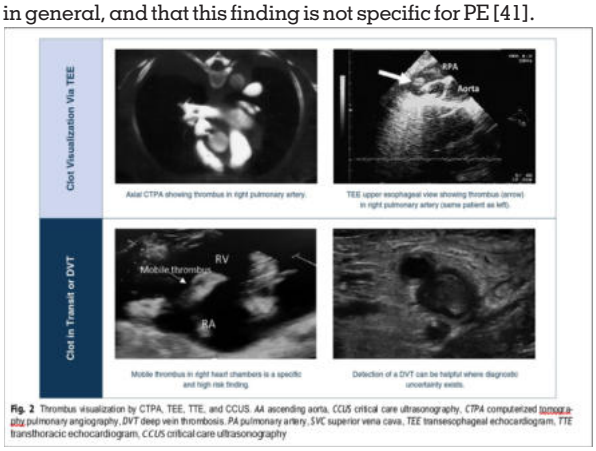

Fig. 2 Thrombus visualization by CTPA, TEE, TTE, and CCUS. *AA* ascending aorta, *CCUS* critical care ultrasonography, *CTPA* computerized tomography pulmonary angiography, *DVT* deep vein thrombosis, *PA* pulmonary artery, *SVC* superior vena cava, *TEE* transesophageal echocardiogram, *TTE* transthoracic echocardiogram, *CCUS* critical care ultrasonography

Although beyond the scope of this article, difficult situations can sometimes arise around the manage- ment of pregnant patients with suspected PE, which remains a leading cause of maternal death. Patients early in their pregnancy can be investigated in the same manner as non-pregnant patients; here D-Dimer is still a good test for low risk patients [42], and CTPA is the most commonly used confirmatory test [43]. Later in pregnancy D-Dimer levels rise naturally, and the test therefore does not perform as well [44]. If a PE is con- firmed, then care must be taken in selecting anticoagu- lant agents, as some are teratogenic. Systemic fibrinolysis can be considered, although pregnancy is considered a relative contraindication. There may be a role for cathe- ter-directed techniques (see below), although there is no data here to guide us.

Assessment Of Severity

Rapid risk stratification is essential in guiding prompt treatments aimed at halting progression to RVD and death [31] [18]. Deterioration may occur anytime within the first 24–48 h, and thus serial risk assessment is cru- cial [20]. Evaluation of severity should include an assess- ment of hemodynamic state and organ perfusion, the identification of RVD, and the integration of biomark- ers such as brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin [18]. Combining these clinical factors with the patient's pre-existing comorbidities ultimately guides individual- ised treatment decisions [21].

Clinical Assessment

Determining whether patients with acute PE should be admitted to ICU depends on a reliable estimate of their mortality risk and potential treatments that may be offered. A simplified version (sPESI) of the PESI scor- ing system groups patients into low (1%, sPESI 0) and high (9%, sPESI ≥ 1) 30-day mortality risk groups based on six simple variables: age, history of malignancy, his- tory of cardiac or pulmonary disease, tachycardia (heart rate ≥ 110/min), hypotension

(SBP < 100 mmHg), and hypoxemia (SaO_2 < 90%) (Table 1) [45]. Low risk patients can generally be managed as outpatients, assuming they meet traditional criteria for hospital discharge. Patients who are not low risk per sPESI criteria should generally be observed in hospital; those with both RVD and an elevated troponin level (considered to be at intermediate high-risk) should be cared for in an ICU, or alternatively a step-down unit with continuous vital sign monitoring available. High-risk patients with hemodynamic instabil- ity or circulatory shock require ICU-level care [18].

Right Ventricular Dysfunction And Overload

Diagnosing right ventricular dysfunction (RVD) and overload involves use of either CTPA or echocardiog- raphy [46]. The ratio of right-to-left ventricle (RV/LV) diameter is easy to acquire by CTPA, and a value of ≥ 1 is associated with a five-fold increased risk of PE-related mortality [47]; reflux of contrast into the inferior vena cava is also an adverse prognostic feature [48]. While CTPA provides a convenient 'snapshot' of RVD, often at the beginning of an ICU admission, it is unsuitable for serial assessment; echocardiography is therefore an indis- pensable tool for intensivists managing patients with PE. CCUS enables temporal assessment of severity as well as the detection of pathology associated with increased risk such as intracardiac shunt through a patent fora- men ovale [49], mobile thrombus [50], or clot-in-transit. Trending changes in RV size and function in response to treatment strategies are key applications of its use. A recent meta-analysis of sixty-three studies of echocar- diography-defined RVD demonstrated increased short- term mortality when RVD is present (relative risk 1.49) [46].

The inextricable link between the RV and pulmonary arterial (PA) circulation has recently brought attention to measures of RV systolic function and their relation to increased afterload in PE, known as RV/PA coupling [51]. In a study of 627 intermediate-risk patients, the non- invasive coupling metric of TAPSE/pulmonary artery systolic pressure (TAPSE/PASP) ratio (with lower values indicating 'uncoupling') performed well and offered bet- ter prognostic information than TAPSE or PASP alone [52].

Biomarkers

In a series of 161 patients admitted to the ICU for PE, 61% exhibited acute core pulmonale and associated metabolic acidosis (here a marker of organ hypoperfusion with increased serum lactate), and this combination of findings served as a powerful predictor of in-ICU mortal- ity [53]. Troponin levels may be used in conjunction with echocardiography to stratify intermediate-risk patients into higher- and lower-risk groups (supplementary eTa- ble 2). Acute hyponatremia has also been identified as a prognosticator of increased mortality [54]. B-type natriu- retic peptide (BNP) or N-terminal-proBNP (NT-BNP), known for their role in diagnosing heart failure, are non- specific for PE and therefore generally unhelpful in the risk stratification process in the ICU.

Organ Support

As anticoagulation, fibrinolysis, and other treatments are being organized, specific management directed towards support of organ systems under the concept of a "golden hour" should be initiated immediately. These interven- tions focus on oxygen delivery, fluid management, and the administration of catecholamines until the pulmo- nary circulation can be re-opened and the RV unloaded (Fig. 3).

Oxygen Delivery

Hypoxemia is usually reversed with nasal oxygen or high-flow nasal cannula in more severely hypoxemic patients; peripheral oxygen saturation (SpO_2) targets of 92–96% are recommended [55]. As the RV is already overloaded by the PE itself, positive pressure ventilation (PPV) may significantly aggravate this physiology even when lung compliance is normal. Invasive mechanical ventilation therefore should be avoided wherever pos- sible and is generally required only in extreme situ- ations such as cardiac arrest, severe encephalopathy (related to shock and cerebral hypoperfusion), refrac- tory hypoxemia, and severe alveolar hypoventilation. Importantly, the recommendation to ventilate patients with plateau pressures (Pplat) not higher than 30 cmH_2O [18] does not apply to this patient population. They usually do not have ARDS and therefore exhibit normal respiratory system compliance. Invasively ven- tilated patients with normal compliance typically have a Pplat as low as 10 cmH_2O; consequently, clinicians should target a Pplat much lower than 30 cmH_2O to further assist in unloading the RV. Tidal volume and respiratory rate should be set to target a normal $PaCO_2$ level, as hypercapnia may cause PA vasoconstriction and RV dysfunction [56]. Positive end-expiratory pres- sure should be avoided, where possible, and specific strategies for the induction of anesthesia and ongoing sedation must be applied to limit the risk of adverse hemodynamic effects [57].

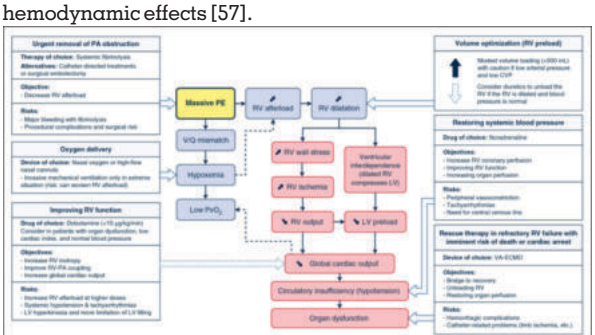

Fig. 3 Pillars of management in patient with high-risk (massive) PE. *CVP* central venous pressure, *LV* left ventricle, *mL* milliliters, *PA* pulmonary artery, *PE* pulmonary embolism, *RV* right ventricle, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation, *V/Q* ventilation/perfusion

Fluid Strategy

While aggressive fluid administration was once con- sidered a cornerstone of care in patients with PE and circulatory shock, a new fluid management approach merits emphasis. RVD limits the beneficial effect of fluid expansion [58], and aggressive fluid administration may be overtly hemodynamically detrimental. Experimental studies support this claim, with fluid expansion shown to induce an increase in RV end-diastolic pressure and a decrease in cardiac index (CI) [59], likely due to ventricu- lar interdependence as an overloaded RV compresses the LV [60]. In patients with PE, a link between larger RV size before fluid expansion and lower CI increases after has been established [61].

The role for central venous pressure (CVP) monitoring is not clear, but clinicians should not administer fluids to achieve any arbitrary CVP target. It has been suggested that clinicians reserve cautious fluid administration only for patients with a CVP < 15 mmHg [62], under the pre- sumption that an elevated CVP represents a contraindi- cation to fluid expansion. However, systemic congestion leading to AKI occurs at a much lower level of CVP here [63], and an initial fluid bolus may increase CVP lev- els significantly, reflecting a large increase in RV stress [61]. RV size as evaluated by echocardiography could be complementary to CVP, and if the RV is severely dilated then IV fluid should probably not be administered. Fluid administration should only be contemplated in the face of circulatory insufficiency with evidence of end-organ dysfunction, and if undertaken then CI and ventricular interdependence should be monitored carefully by echo- cardiographic, clinical, laboratory, and hemodynamic parameters.

Recent studies have evaluated the impact of unloading the RV using diuretics; here most studies involve hemo- dynamically stable patients with intermediate high-risk PE. In a retrospective study of 70 patients who received either furosemide or isotonic saline, only the furosemide group had

an improvement in shock index, SBP, creati- nine level, RV size, and oxygenation at 24 h. There was no significant change in hospital mortality [64].

Catecholamine Strategy

Studies regarding the use of catecholamines in the set- ting of acute PE are scarce, and recommendations must be made mostly on physiologic principles. In addition to re-opening the pulmonary circulation, the corner- stone of improving RV function is to restore a normal blood pressure, therefore improving RV coronary perfu- sion, limiting RV ischemia [64], and allowing for better compensation for an acute increase in afterload. Given these goals, norepinephrine is generally the recom- mended drug, and may be initially safely infused through a peripheral venous catheter at low-to-moderate doses [65]. While low-to-intermediate dose dobutamine was historically considered the preferred drug to improve flow, in a porcine model of PE it increased RV afterload and mechanical work at higher doses (above 10 μg/kg/ min) [66]. Moreover, it may increase LV systolic func- tion in an already normal or even hyperkinetic LV; higher doses therefore should be avoided. Whether there is a role for inodilators such as levosimendan remains to be evaluated, but their potential to lower SBP is a significant limitation to their use. Vasopressin, at low dose (0.01–0.03 U/min), may also improve RV function as it confers advantageous vasodilatory effects on the pulmonary vas- culature, decreasing the pulmonary-to-systemic vascular resistance ratio [67]. Its specific role in managing patients with PE and circulatory failure remains to be tested.

Pulmonary Vasodilators

Although small clinical studies have suggested that inha- lation of nitric oxide (NOi) may improve the hemody- namic state and gas exchange of patients with acute PE [68], no convincing evidence for its clinical efficacy or safety is available to date. A small trial of 78 patients with RVD and without systemic hypotension compared 50 ppm nitrogen (placebo) with 50 ppm NOi for 24 h [69]. At 24 h, 13% of patients in the placebo group and 24% of patients in the NOi group achieved the primary endpoint involving normalization of echocardiographic findings and troponin levels ($p = 0.13$). A randomized explorative trial utilized a single oral dose of Sildenafil 50 mg in patients at intermediate-high risk for PE and found that it did not improve CI but did adversely affect SBP [70].

Anticoagulation

As with non-critically ill patients, immediate therapeu- tic-intensity anticoagulation remains the cornerstone of treatment [71]. There are two main options here: intra- venous UFH or subcutaneous LMWH. Because it can be quickly interrupted and rapidly reversed, UFH has typi- cally been the preferred anticoagulant for ICU patients and should be considered especially for patients who are unstable or deteriorating, and therefore may require thrombolysis or an invasive procedure. LMWH offers ease of administration, a lower risk of bleeding, and more consistent therapeutic effect, and should therefore be the choice for patients who are stable from a hemodynamic and respiratory perspective.

There may be a role for insertion of an IVC filter in select patients. Such filters have been shown to reduce the risk of PE while increasing the risk of DVT, without altering overall mortality [72]. They are typically used in patients with acute PE where an absolute contraindi- cation to therapeutic anticoagulation exists, or where frequent interruptions in anticoagulation (multiple surgeries, for example) will be required in a high-risk patient.

Fibrinolysis

Fibrinolytic treatment (in addition to heparinization) undoubtedly re-perfuses the pulmonary circulation faster than heparin alone in patients with PE. In one of the largest trials, Alteplase administration resulted both in an improvement of lung perfusion as assessed by scin- tigraphy and better RV function [73]. Fibrinolysis also achieves faster improvement in hemodynamic param- eters, with a significant decrease in mean pulmonary artery pressure and an increase in CI after two hours [74]. As such, it is recommended as first line treatment for patients with circulatory shock related to PE unless it is contra-indicated (Table 2) [18]. Absolute contraindica- tions include a history of hemorrhagic stroke, ischemic stroke within the past 6 months, central nervous system neoplasm, major trauma, surgery or head injury in the previous 3 weeks, bleeding diathesis, or active bleeding. Questions often arise over the optimal fibrinolytic regi- men during cardiac arrest. While there is little data to guide us here, a few comments may be made. Fibrinolysis should not be given routinely to every patient in cardiac arrest, but rather should be considered only where sus- picion of PE exists. When given, guidelines recommend a 50 mg bolus dose of Alteplase over 2 min, which can be repeated fifteen minutes later in the absence of ROSC [75, 76].

Data supporting the use of fibrinolytics in intermedi- ate high-risk PE patients is somewhat conflicting. The PEITHO trial demonstrated that fibrinolysis was associ- ated with a significant reduction in a combined outcome of hemodynamic decompensation or death from any cause [78]. However, there was no difference in 30 day mortality due to an increased risk of major bleeding. Indeed, fibrinolysis-treated patients experienced higher major extracranial bleeding (6.3% vs 1.2%) and hemor- rhagic strokes. The risk appears to be higher in patients older than 75 years [78]. As such, the mortality benefit of fibrinolysis in patients with intermediate-risk PE remains controversial, with two further meta-analyses report- ing conflicting results [79, 80]. The 2 year follow-up of patients included in the PEITHO study showed no effect on mortality rates and no apparent reduction in residual dyspnea or RVD [81]. Recent guidelines statements rec- ommend against the use of fibrinolysis in this population [18].

These results underline the need to improve the safety of thrombolytic treatment in the population with inter- mediate high-risk PE. A first strategy could be to use a reduced dose of fibrinolytics, with promising early results related to lowering the risk of bleeding and recurrent PE, and improving pulmonary circulation, CI, and residual vascular obstruction at 24h [82, 83]. A post-hoc analy- sis of the PEITHO trial identified a potential target population that could potentially benefit from this strat- egy; these patients exhibit at least one of the following parameters: initial SBP < 110 mmHg, respiratory rate > 20 breaths/min (or, as a surrogate, an arterial oxygen satu- ration < 90% on room air) at presentation, or a history of chronic heart failure [84]. Patients defined by at least one these clinical parameters, plus a hemodynamically stable PE with RV/LV > 1 on CTPA, and an elevated car- diac troponin level represent the target population of the ongoing PEITHO-3 trial that will assess the efficacy and the safety of a reduced dose of Alteplase (0.6 mg/kg to a maximum of 50 mg) [85].

Table 2 Evidence for systemic thrombolysis in various at-risk patient populations

Patient risk class	Patient presentation	Evidence	Studies	Comments
High-risk Massive PE	Hemodynamic instability	Full-dose intravenous fibrinolysis reduces mortality and is the standard of care	Marti (2014) [69]	1. dPA is generally the preferred agent 2. "Full-dose" is most commonly defined as 100 mg of dPA over 2 h 3. Catheter-directed treatment or surgical embolectomy may be considered if fibrinolysis is con- traindicated
Intermediate high-risk Sub-massive PE	No hemodynamic instability Higher risk PESI or sPESI, Positive troponin level and RHD on echo on CT	1. Benefits of full-dose fibrinolysis are offset by a roughly equal increase in major bleeding and is therefore not recommended 2. Other treatment regimens, including reduced-dose throm- bolysis and catheter-directed therapy, require further study	Meyer (2014) [68]	1. Significant heterogeneity in studies, systemic reviews, and meta-analysis limits confidence in conclusions [77] 2. Thrombolysis does not seem to reduce the risk of CTEPH [71] 3. These patients should generally be admitted to ICU or a monitored step-down unit
Intermediate low-risk	No hemodynamic instability Higher risk PESI or sPESI, Positive troponin level or RHD on echo on CT (or neither, but not both)	Fibrinolysis not recommended	No evidence clearly supporting fibrinolysis	1. These patients should generally be admitted to hospital for observa- tion
Low-risk	No hemodynamic instability. Lower risk PESI or sPESI. Neither positive troponin nor RHD	Fibrinolysis should not be given at any dose under any circum- stances	No evidence supporting fibrinolysis	1. Many of these patients can be discharged home with close follow-up

CT computerized tomography, *CTEPH* chronic thrombo-embolic pulmonary hypertension, *ICU* Intensive care unit, *PE* pulmonary embolism, *PESI* pulmonary embolism severity index, *RHD* right heart dilatation, *rtPA* recombinant tissue plasminogen activator, *sPESI* simplified pulmonary embolism severity index

Mechanical Support

In patients with massive pulmonary embolism remain- ing in shock despite thrombolysis or in case of throm- bolysis contraindication, mechanical circulatory support with veno-arterial extracorporeal membrane oxygena- tion (VA-ECMO) or temporary right ventricular assisting devices (RVAD) may be considered [86].

By draining blood from the right atrium and reinfusing it into the arterial system, VA-ECMO may help to sta- bilize patients with refractory shock, providing a bridge to recovery or other therapies. Consideration of ECMO in combination with mechanical pulmonary recanaliza- tion (either using catheter-directed treatment or surgical embolectomy) in patients with PE and refractory shock or cardiac arrest received a Class IIb recommendation [18], yet these recommendations were mainly based on retrospective observational studies. While some studies report improved survival with VA-ECMO in the setting of acute high-risk PE, including the use of extracorporeal cardiopulmonary resuscitation (ECPR) [87–89], a recent meta-analysis failed to show a short-term survival ben- efit [90]. Significant heterogeneity exists between studies with regards to patient selection, indication for ECMO, institutional expertise, and options for remote cannula- tion. Additionally, patients who required ECMO were likely overrepresented by the most unstable patients, including those who had suffered cardiac arrest; indeed a significant proportion of such patients were actually cannulated during cardiac arrest [89, 91]. In a study com- paring surgical pulmonary thrombo-embolectomy (PTE) to VA-ECMO support, the occurrence of cardiac arrest before ECMO or surgery portended a poor prognosis, irrespective of the therapy used [92].

While some authors have suggested the use of ECMO as a stand-alone support to allow physiological fibrinoly- sis to take place, VA-ECMO is merely a form of life sup- port and reperfusion therapy is still mandatory [89]; a multicenter study reported higher mortality in patients supported with ECMO alone [88]. In a systematic review investigating the optimal reperfusion therapy in patients requiring ECMO, similar results were reported, with worse outcomes in the ECMO-only group potentially mediated by increased hemorrhagic complications [93]. In the largest meta-analysis, age below 60 and surgical PTE were associated with a better prognosis [90]. How- ever, these results may be confounded by treatment bias, as one cannot exclude that patients considered for surgi- cal intervention were at lower risk of mortality regardless of the intervention. Many questions remain regarding the use of VA-ECMO in patients with high-risk PE.

Temporary mechanical circulatory support devices dedicated to RV failure may be an attractive option as RV function often improves sufficiently in a short period of time to allow for device removal and mechanical assis- tance may decrease myocardial oxygen consumption and accelerate recovery. Most literature detailing the use of percutaneous RVADs (pRVAD) was limited to retro- spective single-center or small multicenter studies using various pump technologies. The use of pRVAD was recently reported in 4 patients with persistent cardio- genic shock and severe RV failure from massive PE [94]; the authors described an improvement of haemodynamic parameters and RV function allowing decannulation in all patients. Others have reported the use of an Impella rotary pump device to support the failing RV in acute PE [95], however potentially inserting such a device through a thrombus can lead to multiple emboli and placement is associated with some procedural risk. Many questions remain regarding the use of such devices in patients with high-risk PE and more data is required to determine which mode of support is most effective.

Surgical Embolectomy

In unusual cases, surgical PTE may be an option, albeit one associated with significant mortality and morbidity [96]. After failure of fibrinolysis, PTE was associated with a trend toward higher in-hospital survival and lower PE recurrence compared with repeat dose fibrinolysis [97]. Thus, the usual indications include a contraindication or failure of fibrinolysis, but the procedure can only be undertaken in the presence of proximal or intra-cardiac thrombus burden [18]. Some authors recommend PTE as the first line therapy in cases of intracardiac or intra- patent foramen ovale thrombi [98]. In practice, results are highly variable according to patient selection, timing of implementation, and experience of the surgical team. Although bleeding rates are reduced compared to sys- temic thrombolysis, surgical management may induce serious potential complications including tamponade, atrial fibrillation and right heart failure [18]. However, with the improvement of surgical and resuscitation techniques, the outcome of surgery has improved, with a 3–6% in-hospital and a 15–23% 1-year mortality in dedicated PE centers [99]. In the sickest patients, use of temporary circulatory support (VA-ECMO) may be used to allow transfer to a specialized site [88]. Surgical PTE lacks dedicated randomized trial data, and thus indica- tions for its use remain uncommon.

New Techniques And Future Perspectives

The role of newer advanced therapies for pulmonary embolism (PE) (Fig. 4) has yet to be clearly defined, particularly in the critical care setting [18]. Important gaps in the existing literature include a paucity of randomized controlled trials, limited mortality and patient-centered outcomes data, incomplete understanding of sex-based differences and racial disparities in disease presentation and treatment response [100], and a lack of long-term follow-up. These limitations are especially relevant in the ICU, where patients with intermediate- and high-risk PE represent a uniquely vulnerable population.

Further complicating management is the rapid expansion of catheter-based reperfusion strategies [101]. Although systemic fibrinolysis remains the recommended first-line therapy for high-risk PE, only a minority of hemodynamically unstable patients currently receive this treatment. This is largely due to absolute or relative contraindications and concerns regarding hemorrhagic complications, highlighting the need for alternative strategies that mitigate bleeding risk.

Compared with systemic fibrinolysis, catheter-directed therapies (CDT) offer potential advantages, including enhanced thrombus dissolution through the combination of higher local fibrinolytic concentrations and mechanical disruption, while potentially reducing major bleeding-particularly intracranial hemorrhage. CDT encompasses a heterogeneous and rapidly evolving group of interventions. One or more catheters may be positioned in the main, right, or left pulmonary arteries, allowing for local delivery of fibrinolytic agents via bolus dosing or continuous infusion. Protocols vary widely, and high-quality comparative data remain limited. In addition to local drug infusion, a range of devices can be deployed to aspirate, macerate, or fragment thrombus, either mechanically or with ultrasound assistance.

Among these approaches, ultrasound-facilitated catheter-directed fibrinolysis is the most extensively studied, predominantly in patients with intermediate-risk PE [104–107]. Other catheter-directed thrombolytic techniques have also demonstrated promising early results [18]. Mechanical catheter embolectomy techniques-including thrombus maceration and aspiration-have gained particular interest, as they may obviate the need for fibrinolytic therapy altogether. However, it is important to note that available studies have relied primarily on surrogate efficacy endpoints, most

commonly changes in the right ventricular-to-left ventricular (RV/LV) diameter ratio before and after intervention[101]. Procedural complications are partly attributable to the use of larger-bore catheters, with associated risks of vascular access complications and blood loss during aspiration.

Current clinical practice guidelines provide limited recommendations for these newer reperfusion techniques, reflecting the lack of robust supporting evidence, and generally restrict their use to patients in whom systemic thrombolysis is contraindicated or has failed [18]. Several randomized controlled trials powered to assess clinical efficacy and safety outcomes are currently underway, including studies of ultrasound-facilitated catheter-directed fibrinolysis [98] and multiple mechanical catheter embolectomy devices. Additional trials focusing specifically on ICU populations with intermediate- and high-risk PE are needed.

While awaiting the results of these pivotal studies and subsequent guideline updates, multidisciplinary pulmonary embolism response teams (PERT) play a critical role in individualized decision-making for complex PE cases and are increasingly recommended [18].

CONCLUSION

In the crucible of critical care, the management of pulmonary embolism (PE) remains a formidable diagnostic and therapeutic enigma. For the clinician, the mandate is twofold: the swift identification of this life-threatening pathology and the nuanced navigation of its most perilous forms. This includes high-risk PE, defined by overt hemodynamic collapse, and the more deceptive intermediate-high-risk category, where a veneer of stability often masks an unpredictable trajectory toward clinical deterioration. In the face of high-risk scenarios, the priorities are stark: aggressive circulatory stabilization and the immediate deployment of reperfusion therapies to restore pulmonary patency. Conversely, the intermediate-high-risk cohort necessitates a more contemplative vigilance. Since the wholesale administration of systemic fibrinolysis remains contentious in these patients, the clinician must act as a sentinel-monitoring for subtle shifts in physiological reserve while judiciously evaluating the burgeoning role of catheter-directed interventions. While we are witnessing a renaissance in venous thromboembolism (VTE) care, significant gaps in our collective understanding persist. To truly honor the vulnerability of the critically ill, future inquiry must transcend simple metrics and embrace rigorous, patient-centered randomized trials. By focusing on long-term functional recovery and holistic outcomes, the medical community can refine these complex strategies, ultimately transforming a diagnosis of PE from a moment of crisis into a pathway toward meaningful survival.

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