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Critical Care Management of Acute Pulmonary Embolism

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Abstract

The unprimed right ventricle is exquisitely sensitive to acute elevations in afterload. High pulmonary vascular tone incurred with acute pulmonary embolism has the potential to induce obstructive shock and circulatory collapse. While emergent pulmonary reperfusion is essential in severe circumstances, an important subset of pulmonary embolism patients may exhibit a less extreme presentation posing a management dilemma. As intensive care therapies have the potential to both salvage and harm the failing right ventricle, a keen understanding of the pathophysiology is requisite in the care of the contemporary patient with hemodynamically significant pulmonary embolism. Here, we review right ventricular pathophysiology, an approach to risk stratification, and offer guidance on the medical and mechanical supportive and therapeutic strategies for the critically ill patient with acute pulmonary embolism.

Keywords

pulmonary embolism, high-risk pulmonary embolism, acute right ventricular failure, pulmonary reperfusion, hemodynamic support

Introduction

Substantial embolic pulmonary vascular obstruction in conjunction with mediators of vascular tone rapidly increase right ventricular (RV) afterload resulting in obstructive shock in the most severe circumstances of pulmonary embolism (PE).[1] High-risk PE constitutes a hemodynamically unstable presentation, associated with high mortality, and requires immediate management most commonly with emergent reperfusion therapies. However, a subset of patients with intermediate-risk PE, those manifesting RV dysfunction but without overt circulatory failure, may experience decompensation and transition to a more severe phenotype.[2] While pulmonary reperfusion is the definitive therapy for the high-risk patient, an understanding of the pathophysiology and circulatory support options is requisite in the care of the patient with hemodynamically significant PE.[1,3]

In contrast to advancements in left ventricular failure, a robust evidence base for the management of acute RV failure in PE is lacking. The majority of the data surrounding volume management, vasoactive agent selection, and ventilatory strategies are rooted in experimental models, small human studies, and case reports.[4,5] However, attention to such variables is mandatory as intensive care interventions may not only rescue the failing RV but in addition cause further injury through adverse changes in ventricular dilatation, interdependence, myocardial wall stress and coronary ischemia, and pulmonary vascular resistance (PVR). Similarly, limited data inform on the optimal reperfusion strategies in high-risk PE; however, evolving therapies are creating possibilities for a more nuanced and personalized approach to care. In this manuscript, we review pathophysiology, risk-stratification, and available management strategies for patients with high-risk PE as they apply to the intensive care unit. In light of the high clinical and logistic complexity of patients with intermediate- and high-risk PE, a multidisciplinary Pulmonary Embolism Response Team (PERT) is essential for developing an optimal management strategy.[6,7]

Pathophysiologic Considerations

The pulmonary vasculature exists as a low-pressure circuit with a resistance less than 10% of its systemic counterpart. Approximately 25%-30% of the pulmonary circulation must be obstructed before pulmonary artery pressure rises, and >50% obstruction is required before RV failure ensues.[8] However, mechanical vascular obstruction is not the sole determinant of PVR in acute PE. Cross-clamping of either the right

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or left main pulmonary artery during surgery causes only a modest rise in pulmonary artery (PA) pressures and generally does not result in RV failure.[8,9] Accordingly, the extent of obstruction does not fully explain the increase in PVR and chemical mediators (ie serotonin, thromboxane-A2, endothelin), humoral factors, and reflexes activated by autologous thrombus (by contrast to ceramic beads or microspheres) contribute to the increase in vascular tone.[10] Further, hypoxemia, acidemia, and hypercapnia contribute to increased vascular tone. Indeed, the percentage of pulmonary vascular obstruction does not alone account for the hemodynamic impact of acute PE.[11]

Historically, the RV was viewed as a passive conduit of limited interest to medicine as a result of several experiments prematurely minimizing its importance. In the 1940s, Starr and colleagues performed extensive cautery of the RV free wall in dogs and were unable to demonstrate a significant increase in central venous pressure and concluded lack of effect on cardiac function.[12] As later evidence has noted an association between RV dysfunction and poor clinical outcomes, we have witnessed a resurgence of data and interest in the RV.

The RV is a high-volume, low-pressure pump exquisitely sensitive to abrupt increases in afterload.[13] Right ventricular geometry is suited to accommodate large variations in venous return with up to a 200% increase over several heart beats.[14] However, as RV ejection leads to an increase in radius of curvature, and therefore wall tension, this chamber is less effective at recruiting the Frank-Starling mechanism and is not well adapted to the acute generation of high pressures.[13,15] In the absence of preexisting cardiopulmonary disease causing a sustained pressure load, the RV can acutely generate a mean pulmonary artery pressure of no more than 40 mmHg.[8]

The function of the left ventricle (LV) and RV are inextricably linked as a result of shared circumferential fibers, the interventricular septum, and the pericardial cavity.[16] The two chambers pump blood in series yet are also connected in parallel. With the former mechanism, the LV can only receive what the RV delivers; a reduction if RV stroke volume must lead to a reduction in LV stroke volume. As pericardial and mediastinal constraints define total biventricular volume, with parallel ventricular interdependence, pathologic RV dilatation results in a leftward interventricular septal shift further impinging on LV filling.[17,18]

An acute rise in RV afterload can result in its failure.[16] Initially, several compensatory mechanisms allow for increased RV contractility in response to its dilatation.[15] Exhaustion of these mechanisms leads to RV-PA uncoupling and circulatory failure. Right ventricular dilatation has several untoward effects: tricuspid annular stretch leading to tricuspid regurgitation and volume loading, an increase in RV wall tension which causes myocardial ischemia, and leftward interventricular septal shift further reducing LV stroke volume.[15,19] The combination of systemic hypotension depressing right coronary artery perfusion pressure and increased RV wall tension together contribute to RV myocardial ischemia.[20] The interplay of these mechanisms, termed auto-aggravation (often referred to as the "RV spiral of death") culminate in hemodynamic collapse (Figure 1).[2] An appreciation of PE pathophysiology informs on critical care interventions both salubrious and detrimental to the acutely pressure overloaded RV.

Risk Stratification and the Identification of Occult Shock

Risk categories may have operational value yet are somewhat artificial as pulmonary embolism severity and the risk of dying is dynamic and falls on a continuum varying between, and within groups.[21] High-risk (formerly "massive") PE encompassing obstructive shock (end-organ hypoperfusion with hypotension or vasopressor requirement), or cardiopulmonary arrest carries a mortality of approximately 21% in modern registry data and requires an immediate therapeutic strategy.[2,22] Patients with intermediate-risk PE, or those without hypotension but with evidence of RV dysfunction by imaging or biomarker data, represent a heterogenous group with short-term mortality ranging from 2% to 17% and a potential rate of 30-day complications in excess of 40%.[23,24] Identifying which normotensive PE patients are of the highest-risk and may suffer from adverse clinical outcomes and benefit from advanced therapies remains the central question in contemporary PE care, so that interventions may be appropriately targeted to this group.[3,5]

Clinical algorithms incorporating demographic, imaging, and biochemical variables while sensitive, often lack the positive predictive value to identify patients who may experience clinical decompensation.[25,26] For the purpose of intensive care unit (ICU) management, establishing which patients may have markers of circulatory failure may be more valuable than simply selecting those who are deemed to be at low risk. Approximately 30%-40% of normotensive patients have a significantly reduced cardiac index (CI) and may be in occult shock.[27–29] In a report of 92 intermediate-risk PE patients undergoing thrombectomy, 40% had a CI $\leq$1.8 L/min/m^2. Importantly, even though this hemodynamic profile was neither readily apparent from biomarkers nor risk scores, it yet may be associated with increased mortality.[27,30] A reliance on binary arterial pressure cut points or vasopressor requirements is inadequate in capturing a severely deranged hemodynamic profile.

Markers of abnormal peripheral perfusion including capillary refill time, skin temperature, and mottling may aid in the identification of shock among normotensive patients.[31] However, these variables have not been specifically assessed with respect to prognosis in patients with intermediate-risk PE. A venous lactate at a cut-off of 3.3 mmol/L has been shown to predict in-hospital adverse outcomes (OR 11.0, 95% CI: 4.6, 26.3) and all-cause mortality (OR 3.8, 95% CI:1.3, 11.3) among normotensive patients with acute PE outperforming the established cut-off value of 2.0 mmol/L.[32] While limited to patients with central venous access, an elevated arterial-to-venous carbon dioxide gradient (CO_2 gap) as a marker of stagnant dysoxia is predictive of a reduced CI in acute PE and does not necessitate pulmonary artery catheterization.[29] Of the macrohemodynamic variables, a mean arterial pressure (MAP) $\leq$ 81.5 mmHg on admission has been

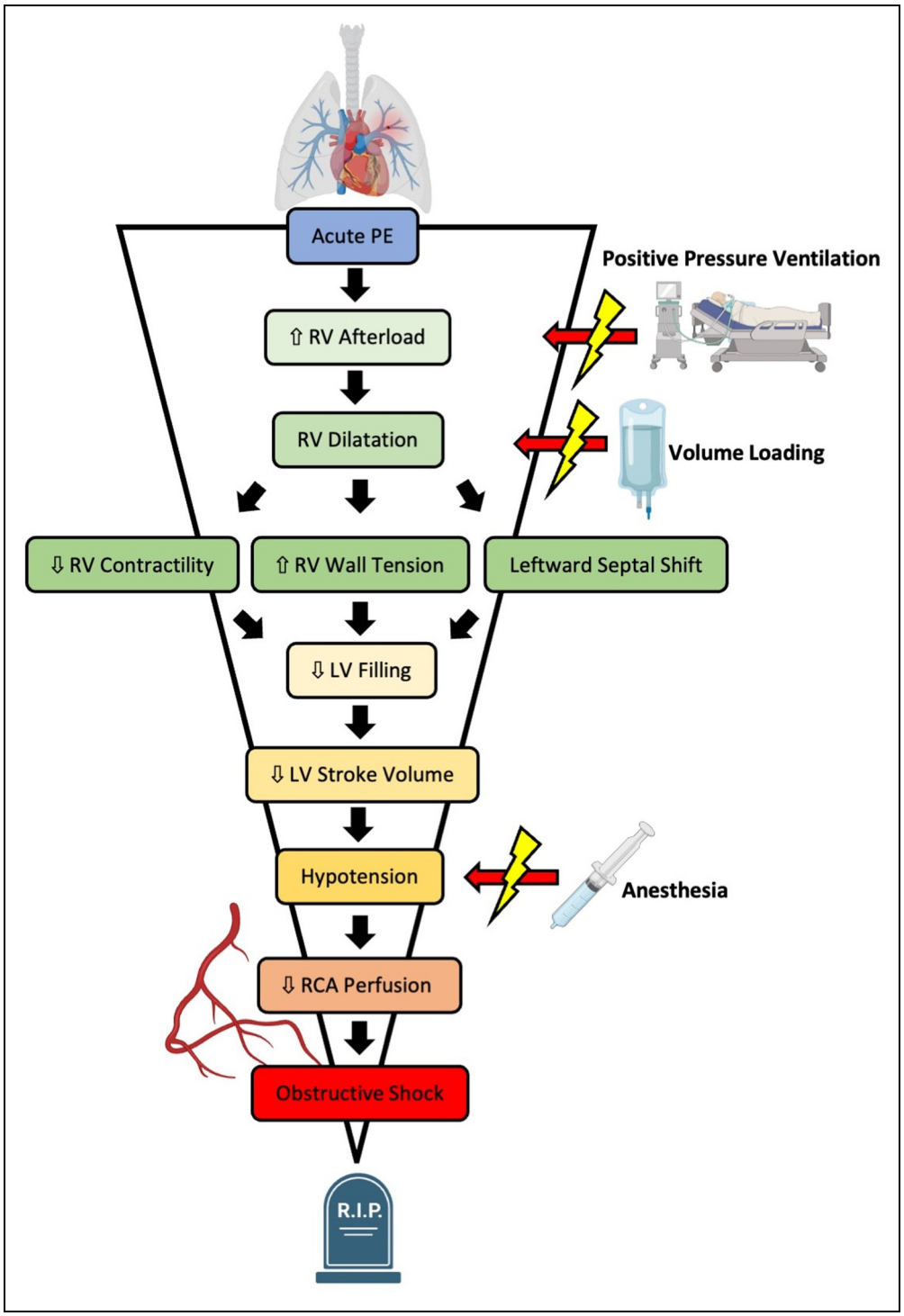

Figure 1. Pathophysiology of acute right ventricular failure in pulmonary embolism. An acute increase in RV afterload following PE leads to RV dilatation resulting in depressed RV contractility, increased RV wall tension, and a leftward shift in the interventricular septum. These effects mediate a decrease in LV filling and therefore stroke volume resulting in systemic hypotension. Consequently, RV ischemic ensures as a result of arterial hypotension and increased RV wall tension leading to obstructive shock. PE – pulmonary embolism, LV – left ventricle, RCA – right coronary artery, RV – right ventricle. Created with BioRender.com.

demonstrated to predict 48-h clinical deterioration among intermediate-high risk patients with a sensitivity and specificity of 77.5 and 95.0, respectively.[33] Attention to conventional hemodynamic parameters and markers of tissue perfusion may be integrated into the clinical evaluation and serially followed as barometers of decompensation.

The assessment of RV structure and function has an important role in the evaluation of the patient with acute PE however,

indices of RV dysfunction are numerous with studies often focused on RV dimensions and rudimentary measures of RV systolic function.[34,35] In a large recent meta-analysis, the RV diameter, RV/LV ratio, and tricuspid annular plane systolic excursion (TAPSE) were among the most studied echocardiographic markers of RV dysfunction. In this analysis, these measures were not associated with mortality among normotensive PE patients.[36] By analogy, two heart failure patients may have a LV ejection fraction of 20% with one ambulatory and another in refractory shock. A more sophisticated and refined approach to the echocardiographic assessment of RV failure may have added value in patient profiling.[35,37]

The left ventricular outflow tract (LVOT) and right ventricular outflow tract (RVOT) velocity time integrals (VTI), both echocardiographic stroke volume surrogates, are strongly associated with adverse clinical outcomes in acute PE.[38,39] In a study of nearly 200 PERT activations, Yuriditsky et al found an LVOT VTI of $\leq$15 cm was associated with in-hospital death or cardiopulmonary arrest (OR 6, 95% CI: 2, 17.9, $P = .0014$). When isolating intermediate-high-risk PE only, 92% of those with poor outcomes had a LVOT VTI $\leq$15 cm whereas only 46% of outcome-negative patients had a reduced LVOT VTI.[40] In a population undergoing mechanical thrombectomy, an LVOT VTI $\leq$15 cm carried a sensitivity and specificity of 92% and 90%, respectively, for the identification of patients with normotensive shock (CI $\leq$2.2 L/min/m^2 with markers of end-organ dysfunction).[40] Ostensibly, the ability to identify occult shock may have meaningful implications with respect to patient monitoring and management.

Right ventricular-pulmonary arterial coupling is a comprehensive index that describes the relationship between ventricular contractility and its afterload.[41,42] While the gold-standard assessment is derived from pressure-volume loops, the ratio of TAPSE to pulmonary artery systolic pressure (PASP) is a validated echocardiographic surrogate. In a study of over 600 patients with acute PE, Lyhne et al found TAPSE/PASP to be a significant predictor of 7- and 30-day mortality outperforming the TAPSE and PASP in isolation.[43]

CT is the gold-standard diagnostic modality for PE in modern practice. While CT may not be available for ICU patients with *de novo* PE (due to risks engendered by traveling to the radiology suite and of contrast administration), most ICU patients are likely to have had a CT. This observation begs the question of whether CT has any role in risk-stratification. CT can show signs, analogous to echocardiography, including chamber dilatation, interventricular septum deflection, and inferior vena cava contrast reflux.[5,44] Many of these markers on CT are binary, however recently, the degree of inferior vena cava contrast reflux on initial CT has been found to be a specific predictor of a low cardiac index and normotensive shock in PE.[44] Overall, several investigations suggest that transthoracic echocardiography has better specificity than CT for assessing PE-related RV dysfunction, which indicates that TTE is likely superior to decide on which patients may need interventions.[45,46] Historically, "clot burden" indices by CT have been assessed, though these can be tedious to calculate, and in general have exhibited suboptimal correlation with clinical events.

Overall, we believe that incorporating non-invasive and dynamic assessments of hemodynamics and more sophisticated metrics of RV performance may identify a more severe hemodynamic profile and a sicker cohort of patients. The future of PE risk-stratification will likely borrow elements of biochemical parameters of the PE, along with CT metrics, and echocardiographic variables that describe consequences to RV function and impacts on overall CI.[35]

Reperfusion Strategies

Patients with high-risk PE require an emergent reperfusion strategy to restore hemodynamics with systemic fibrinolysis being the current recommendation. Selected patients with intermediate-risk PE exhibiting markers of deterioration may similarly benefit.[2,21,47] Given a level of ambiguity with the latter group, multidisciplinary decision-making is essential, and the PERT should be consulted. Among those patient with contraindications to systemic fibrinolytics or in cases of fibrinolytic failure, alternative reperfusion strategies including surgical embolectomy and endovascular therapies are viable options with availability, patient factors, and local expertise determining the specific approach (Figure 2).[47] In select circumstances, interhospital transport may be required to provide the most appropriate therapy for the patient.[48]

Systemic Fibrinolysis

In the mid 1990s, Jerjes-Sanches and colleagues randomized eight patients with high-risk PE to streptokinase versus heparin.[49] Those randomized to streptokinase rapidly improved and survived to 2-year follow-up whereas those treated with heparin died within 1-3 h. This small study is the basis behind the class I recommendation to administer fibrinolytic therapy, in the absence of contraindications, to patients with high-risk PE.[2,50] However, given high odds of bleeding compared to anticoagulation alone, this therapy if commonly withheld even among unstable PE patients in real-world clinical practice.[51] Further, as a subset of high-risk patients may experience rapid deterioration with impending cardiopulmonary arrest, and as this reperfusion strategy may take time for effect, the deployment of venoarterial extracorporeal membrane oxygenation (VA-ECMO) as an upfront approach may have a role, because it immediately decompresses the RV and stabilizes hemodynamics. Analogously, as interventional trial data emerge and the uptake of catheter-based therapies increases, we may see changes in subsequent guideline recommendations for reperfusion strategies in high-risk patients.[52]

Among intermediate-risk PE patients, fibrinolytic therapy has been shown to decrease the composite endpoint of death or hemodynamic decompensation (driven by the latter component) at the expense of major bleeding and intracranial hemorrhage.[53] Correspondingly, fibrinolysis is reserved as a rescue therapy for

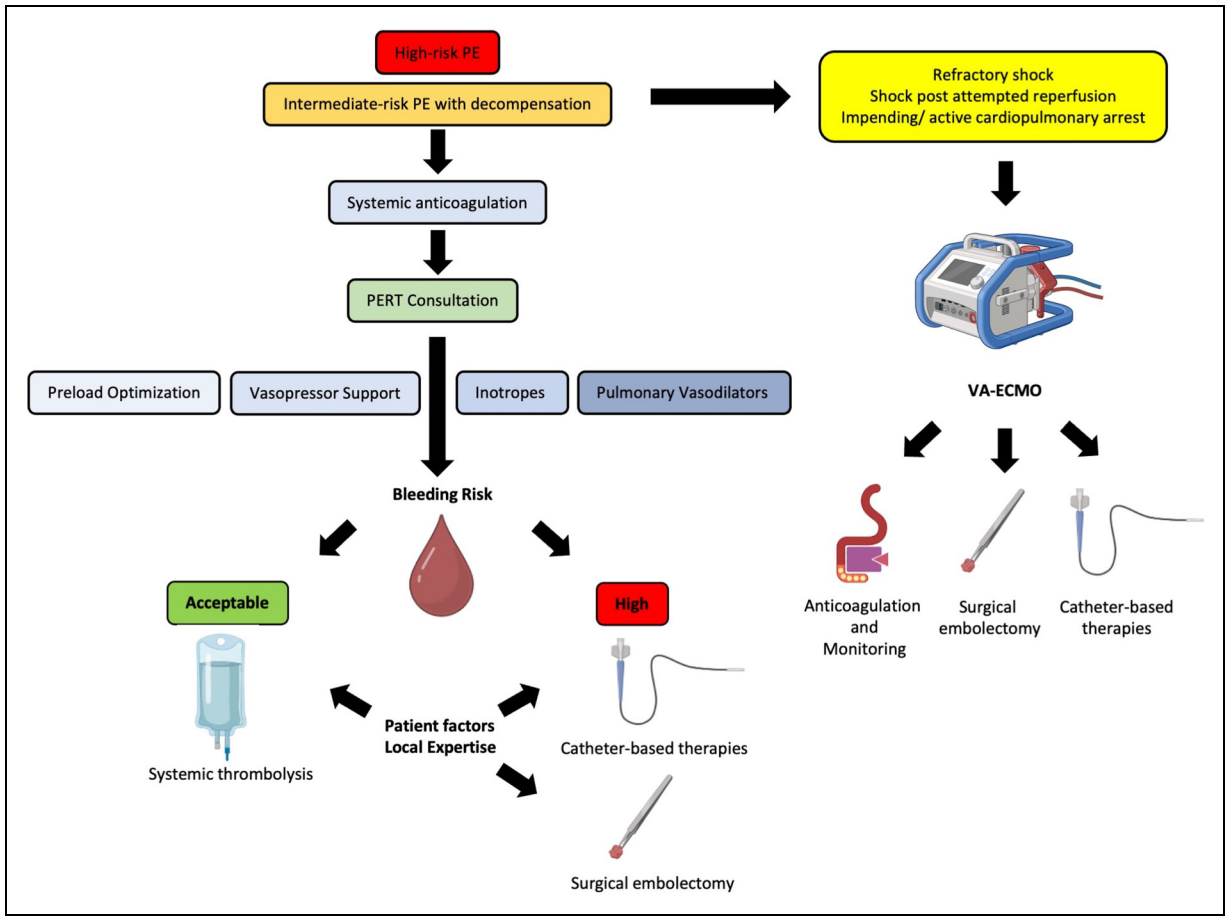

Figure 2. Management of hemodynamically unstable pulmonary embolism. A proposed simplified algorithm for the management of hemodynamically significant pulmonary embolism is illustrated. In determining the optimal reperfusion approach, a multidisciplinary discussion factoring patient characteristics, procedural availability, and local expertise is mandatory. In select circumstances, interfacility transfer may be required. PE – pulmonary embolism, PERT – pulmonary embolism response team, VA-ECMO – venoarterial extracorporeal membrane oxygenation. Created with BioRender.com.

intermediate-risk patients with hemodynamic decompensation despite systemic anticoagulation.[2] Reduced dose fibrinolytics (variably defined across studies) may be associated with an improved safety profile without compromising efficacy however, available evidence is insufficient to support their use in current practice.[54] The currently enrolling Pulmonary Embolism International THrOmbolysis (PEITHO-3) trial aims to evaluate the efficacy of reduced dose alteplase among patients with intermediate-high-risk PE meeting at least one additional marker of severity.[55] If the hypothesis supported by prior smaller studies is confirmed, we may see changes to our current fibrinolytic management approach for this subset of patients.

Surgical Embolectomy

Dr Friedrich Trendelenburg first described surgical embolectomy in 1908. A left anterior thoracotomy was performed followed by the occlusion of the PA and aorta, thrombus extraction, and PA closure.[56] However, as the procedure was often performed with patients in extremis, and as PA occlusion increased afterload to the already failing RV, outcomes with this surgical procedure were dismal. Modern surgical pulmonary embolectomy technique is performed with the use of cardiopulmonary bypass with post-operative mortality ranging from approximately 2%-13% including patients undergoing perioperative cardiopulmonary resuscitation.[56] Surgical embolectomy is reserved for select intermediate- and high-risk patients in whom thrombolysis is contraindicated or has failed.[2] Right heart thrombi and clot-in-transit across a patent foramen ovale may be additional indications.[47] Several case series described the combined use of embolectomy following cannulation for VA-ECMO among certain groups.[57] Despite the high acuity of selected individuals, outcomes are good with respect to RV recovery and survival. However, as surgical embolectomy is limited to institutions with appropriate expertise and as catheter-based options become more commonplace, few patients will be treated with this modality.[58]

Catheter-Based Therapies

Catheter-based therapies have emerged over the last decade as a means of establishing rapid pulmonary reperfusion in the

context of the limitations to alternative strategies.[21,59] Current percutaneous options include aspiration thrombectomy, catheter-directed thrombolysis (CDT), ultrasound assisted CDT, and a combination including pharmacomechanical thrombus fragmentation with CDT and aspiration.[60] Potential advantages to an interventional approach include significantly reduced dose thrombolytics or the avoidance of such therapies altogether with thrombus aspiration.[21] Presently, data informing on the use of these modalities are limited to registries and small trials assessing surrogate outcomes such as changes in the RV/LV ratio.[52,61–63] However, an interventional route may be considered for high-risk patients with contraindications to fibrinolytics or in event of fibrinolytic failure.[2] Certain intermediate-risk patients deemed more likely to experience clinical decompensation may benefit from an interventional approach.[47] However, there is a significant gray zone with respect to this recommendation.

In a recent report from the FlowTriever All-Comer Registry for Patient Safety and Hemodynamics (FLASH) registry composed of 800 patients (77% intermediate-high-risk), only 0.8% of those undergoing catheter-based embolectomy were dead at 30-day follow-up.[64] Several invasive hemodynamic parameters improved immediately post procedure with echocardiographic markers of RV dysfunction and dyspnea scores improving within 48 h. These results were echoed in a prospective registry of high- and intermediate-high-risk patients undergoing CDT where 30-day all-cause mortality was only 1.0%.[65] However, given the very low short-term mortality in this registry, selection bias may have been a contributing factor. The strong safety profile of catheter-based therapies coupled with low mortality rates may shift practice toward a more aggressive upfront interventional approach in intermediate-high risk PE cohorts.[64] However, while observational and real-world data are growing, these alone cannot answer the key questions of whether there should be widespread use of percutaneous PE therapies and for which patients.[66] Accordingly, several randomized trials are underway examining different endovascular modalities with respect to short- and long-term clinical outcomes in intermediate-risk PE.[60]

With respect to high-risk PE patients, interventional data are scant as it is a difficult context for clinical trial design. In a study of 53 high-risk patients treated with percutaneous mechanical thrombectomy, only one patient suffered in-hospital death compared to a 29.5% mortality in the context arm (largely treated with systemic thrombolysis).[67] Among the 63 high-risk patients treated with mechanical thrombectomy in the FLASH registry, multiple hemodynamic variables improved immediately post procedure with all patients surviving to 48 h.[52] While these data are limited, there may be opportunity for a more nuanced approach to the reperfusion of the high-risk patient.[58] Plausibly, endovascular therapies may have an upfront role rather than being reserved for those with contraindications to, or failure of thrombolysis. At present, catheter-based therapies are a potential alternative to systemic thrombolytics as a means to urgently establish pulmonary reperfusion and to rapidly improve hemodynamics. Pending the results of randomized trials, the deployment of these therapies will depend on local expertise and clinical judgement incorporating the degree of hemodynamic disturbance and bleeding risk.

Pharmacologic Hemodynamic Support

PE patients demonstrating hemodynamic compromise require emergent pulmonary reperfusion. Pharmacologic therapies function as a bridge to definitive treatment as well as supportive care for those with persistent RV dysfunction following reperfusion. However, the evidence base surrounding the management of acute RV failure in PE is limited to experimental models and small human studies and often extrapolated from alternative causes of RV dysfunction. Accordingly, an appreciation of pathophysiology is fundamental. An accepted stepwise approach includes optimization of preload, maintenance of systemic and coronary perfusion, augmentation of RV contractility, and a reduction of PVR (Table 1).[4,68,69]

Volume Management and Preload Optimization

The common belief that the RV failure is a preload-dependent state best treated with the administration of fluid is simplistic and inaccurate.[4,70] This ingrained teaching is in part based on the management of RV myocardial infarction which, by contrast to acute PE, is an issue of myocardial performance rather than pressure overload.[71] Targeting a central venous pressure of 8-12 mmHg in acute PE, while advocated by some, is not well supported by the literature.[68] Indeed, an elevated CVP may represent the backpressure to venous return, and we know that static variables poorly predict volume responsiveness.[72] Critically to acute PE patients, RV overdistension with volume loading may impinge on LV filling through parallel ventricular interdependence and depress LV stroke volume.

Literature examining volume management in acute PE is conflicting.[73–76] In a study of 13 patients with massive PE, fluid loading with 500 mL of intravenous dextran resulted in an increase in CI (mean 1.6 L/min/m^2 to 2.0 L/min/m^2).[73] This change inversely correlated with baseline RV end-diastolic area and was independent of baseline CVP. While this study by Mercat and colleagues informs guidelines recommending the administration of $\leq$500 mL fluid to select patients with high-risk PE, it is in conflict with several experimental models demonstrating adverse ventricular interdependence.[77]

By contrast, in a study of 276 patients with intermediate-risk PE, diuresis with the administration of a single bolus of intravenous furosemide resulted in more patients meeting the primary outcome of normalization of hemodynamic and respiratory status as well as simplified Pulmonary Embolism Severity Index variables.[75] These results were echoed in a retrospective study of intermediate-risk patients where diuretics, compared to volume expansion, lead to a decrease in the shock index and an improvement in systemic arterial pressure.[78] Given the conflicting literature, volume management decisions should be empiric and potentially include dynamic indices of volume responsiveness. Whether newer monitoring modalities such as venous excess ultrasound (VExUS) can be applied to the management of the patient with acute PE requires exploration.[79]

Vasopressors and Perfusion Pressure

Myocardial ischemia is part of the final common pathway leading to shock and death in acute PE. The interplay of

Table 1. Pharmacologic Right Ventricular Support.

Pharmacologic agent	Usual dose range	Mechanism of action	Clinical effects	Indications	Adverse effects
Norepinephrine	0.05-0.5 mcg/kg/min	alpha 1 > beta 1 agonism	Peripheral vasoconstriction, increased coronary perfusion pressure, mild inotropy	Hypotension/ Shock (first line)	Arrhythmias, increases in PVR at higher doses
Vasopressin	0.01-0.04 units/min	V (1, 2) agonism	Peripheral vasoconstriction, increased coronary perfusion pressure	Hypotension/ Shock (second line)	Increase in PVR at higher doses
Dobutamine	2-10 mcg/kg/min	beta 1 > beta 2, minimal alpha 1 agonism	Increased inotropy, variable effects on pulmonary vasculature	Low CO following restoration of MAP	Arrhythmias, increase in PVR at higher doses
Milrinone	0.125-0.75 mcg/kg/min	PDE-3 Inhibition	Increased inotropy, decreased PVR and SVR	Low CO following restoration of MAP	Systemic hypotension, prolonged clearance in renal dysfunction
Inhaled nitric oxide	5-20 ppm	sGC activation and cGMP production	Decreased PVR	Short term improvement in oxygenation and PH-associated RV dysfunction	Pulmonary edema (if concomitant LV dysfunction or overload), rebound PH, V/Q mismatch, methemoglobinemia
Inhaled epoprostenol	10-50 ng/kg/min	Multiple, including cAMP production, ET-1 downregulation	Decreased PVR	Short term improvement in oxygenation and PH-associated RV dysfunction	Pulmonary edema (with concomitant LV dysfunction), rebound PH, V/Q mismatch
Intravenous epoprostenol	Initiate at 1 ng/kg/min, up titrate to effect	Multiple, including cAMP production, ET-1 downregulation	Decreased PVR, positive inotropy	PH-associated RV dysfunction	Systemic hypotension, V/Q mismatch (limited role in acute RV shock)

cAMP – cyclic adenosine monophosphate, cGMP: cyclic guanosine monophosphate, CO – cardiac output, ET-1 – endothelin-1, LV – left ventricle, MAP – mean arterial pressure, PDE-3 – phosphodiesterase-3, PH – pulmonary hypertension, PVR – pulmonary vascular resistance, RV – right ventricle, sGC – soluble guanylate cyclase, SVR – systemic vascular resistance, V/Q – ventilation/ perfusion. Reproduced with permission from Yuriditsky, et al Ref #2.

increased RV wall tension and decreased right coronary artery perfusion pressure in the setting of systemic arterial hypotension are the key mediators. In an experimental model, acute pulmonary hypertension was induced by PA constriction until RV failure occurred. With increasing RV pressures, RV myocardial blood flow failed to augment with demand. However, the infusion of phenylephrine as a means of increasing aortic root pressure and therefore right coronary artery perfusion was shown to reverse RV failure.[80] Similarly, balloon occlusion of the descending aorta was demonstrated to restore RV function in an experimental model of PE via similar mechanisms.[20] Both studies highlight the role of coronary ischemia in the acutely pressure overloaded RV and the urgent need to restore systemic arterial pressure and coronary perfusion in such circumstances.

Norepinephrine improves systemic arterial pressure, RV-PA coupling, and exerts positive inotropic effects along with a reduction in PVR at lower doses. In an experimental model of acute PE, norepinephrine restored cardiac output through its vasopressor and inotropic effects whereas volume loading further exacerbated RV dysfunction.[81] Correspondingly, this is the first-line vasopressor in the setting of acute RV failure (as well as first-line in septic and cardiogenic shock).[2,69] However, at higher doses, PVR may increase secondary to norepinephrine, yet this effect varies with across studies.

Vasopressin, a non-catecholamine vasopressor, may induce endothelium-dependent vasodilatation of the pulmonary vasculature, though vasoconstriction ensues at high doses.[69] While the potential reduction in PVR is appealing, as this agent lacks any inotropic effects, it is reserved as a second-line vasopressor in the setting of acute RV failure. Further, data surrounding its use in this setting are generally lacking.[82]

Inotropes and Contractility

Inotropes are considered following the restoration of systemic arterial pressure if cardiac output and peripheral perfusion remain inadequate.[2] Data are limited in acute PE. In experimental models, dobutamine has been shown to restore RV-PA coupling and cardiac output better than norepinephrine.[83] Correspondingly, this agent is recommended for use in patients with acute PE and low cardiac output despite an adequate systemic arterial pressure.[2] At usual clinical doses, effects on PVR are favorable however in excess of 10 mcg/kg/min, PVR may increase.[69,84]

The phosphodiesterase-III inhibitors, milrinone, levosimendan, and enoximone, through an increase in cyclic adenosine monophosphate (cMAP), enhance myocardial contractility and dilate the pulmonary vasculature.[69] Levosimendan is not approved by the FDA for use in any clinical setting. In a porcine model of autologous PE, milrinone and levosimendan both reduced RV afterload and improved its function whereas dobutamine increased cardiac output at the expense of RV afterload and mechanical work at higher doses.[85] However, the reduction of systemic vascular resistance and MAP with milrinone may be a limiting factor and require the co-administration of vasopressors.[69] Inhaled milrinone has been shown to lower PVR without systemic hypotension and may mitigate the ventilation/ perfusion mismatch potentially incurred with systemic administration. This means of delivery has not been studied in the setting of acute PE.[86]

Pulmonary Vasodilators and Afterload Reduction

Beyond thrombus burden, pulmonary vasoconstriction mediated by several vasoactive substances increases PVR in acute PE.[10,87] It follows that pulmonary vasodilators would have a pivotal role in reducing RV afterload. At present, data in support of this hypothesis are limited. Therefore, these agents are typically selected following the optimization of systemic arterial pressure and cardiac output in acute RV failure.[68]

Inhaled nitric oxide (iNO) increases levels of cyclic guanosine monophosphate (cGMP) mediating pulmonary smooth muscle relaxation.[88] Continuous administration at a typical dose of 20 ppm (range 5-20 ppm) decreases PVR without systemic hypotension.[69,87] In a randomized trial of 78 patients with intermediate-risk PE, iNO did not alter the composite endpoint of normalization of RV function and plasma troponin levels. However, in a post-hoc analysis, those treated with iNO were more likely to be free of RV dilatation and hypokinesis on follow-up imaging.[89] Several case reports in acute PE have demonstrated favorable effects.[10] As rebound pulmonary hypertension related to the downregulation of endogenous NO and elevated endothelin-1 levels may occur with abrupt withdrawal of this agent, weaning should be gradual.[88]

Inhaled prostacyclin analogs, specifically epoprostenol, are similar to iNO in their ability to lower PVR. While some case reports and experimental studies have demonstrated favorable hemodynamic effects, a small single-arm study of 14 patients with acute PE did not find improvement in RV dilatation or alternative measures of RV overload.[90] Notably, parenteral administration may be associated with systemic hypotension and ventilation/perfusion mismatch. The preponderance of studies examining inhaled pulmonary vasodilators focus on RV dysfunction in the cardiac surgery population with additional data related to the acute respiratory distress syndrome (ARDS).[69] Correspondingly, the evidence base is too limited to make any specific recommendations regarding their use in the setting of acute PE.[2] Notably, oxygen as a pulmonary vasodilator is being re-evaluated in a dose-dependent manner to impact PVR and RV function in a contemporary PE cohort.[91]

Temporary Mechanical Circulatory Support

The VA-ECMO circuit functions as partial cardiopulmonary bypass, allowing for oxygenation, ventilation, and systemic perfusion. With the typical peripheral ECMO configuration, blood is withdrawn from a femoral vein facilitated by a centrifugal pump, advanced through an oxygenator, and returned to the femoral artery.[4,92] Right ventricular support is provided through RV decompression, a decrease in PA pressures, and restoration of coronary perfusion. Operationally, a well-trained team can perform peripheral ECMO cannulation within 10-15 min even outside procedural areas making this modality a viable option for the rapidly deteriorating patient with refractory circulatory collapse or for one suffering from cardiopulmonary arrest.[2,93]

Recently, the term "catastrophic PE" has been used to describe a subset of high-risk patients with progressive shock despite multiple vasoactive agents, impending or active cardiac arrest, and persistent shock post thrombolysis. This severe presentation carries an in-hospital mortality of 42% in modern registry data yet may be higher by some accounts.[22,58] Some have suggested that VA-ECMO be used as an upfront strategy for this population – particularly as thrombolytics may require time for physiologic effect – thus requiring more nuance in the high-risk PE treatment approach.[58] Further, the administration of thrombolytic therapies prior to cannulation is associated with a significant risk of major hemorrhage compared to patients managed with VA-ECMO upfront and may be associated with increased mortality.[94,95]

Once cannulated, several definitive therapeutic approaches can be considered: 1. Surgical embolectomy, 2. Catheter-based therapies, 3. Systemic anticoagulation with a reassessment of RV function after 5-7 days followed by decannulation, in cases of RV recovery, or additional therapies in cases of persistent RV dysfunction.[57,96] In several series, the latter approach was highly successful with the majority of patients not requiring additional reperfusion strategies.[57,97,98] However, the latest guidelines recommend that ECMO be combined with surgical embolectomy or catheter-based therapies.[2]

Circulatory obstruction may render cardiopulmonary resuscitation less effective in high-risk PE. At institutions with the appropriate expertise, extracorporeal cardiopulmonary resuscitation (ECPR), namely the use of VA-ECMO in the setting of cardiopulmonary arrest, may be considered. In an analysis of the extracorporeal life support organization (ELSO) registry, mortality among patients with PE suffering cardiopulmonary arrest treated with VA-ECMO was 68%, a value similar to that of ECMO in cardiopulmonary arrest regardless of etiology.[99] The use of ECPR among patients with in-hospital cardiac arrest may be associated with improved survival as compared to conventional cardiopulmonary resuscitation.[100]

Alternative temporary mechanical circulatory support modalities (right ventricular assist devices, RVAD)have been used in cases of RV failure related to acute PE however, robust data in their support are significantly lacking.[4] The right-sided microaxial flow RVAD (Impella RP®, Abiomed, Danvers, Mass), can be

inserted percutaneously via femoral venous access propelling blood from the inferior vena cava directly to the PA bypassing the failed RV. Obviating the need for arterial access is a potential advantage. While this therapy may offer hemodynamic improvement, available literature is limited to case reports and small series.[101] Moreover this type of RVAD typically requires fluoroscopy to insert, in direct contrast to the ubiquitous ability to cannulate for peripheral VA-ECMO; this limitation may preclude its use in unstable patients.[4]

A percutaneous extracorporeal centrifugal flow RVAD, ProtekDuo® (LivaNova, UK), allows for blood to be withdrawn from the right atrium and infused directly to the PA using a dual-lumen cannula. As with the Impella RP®, published clinical experience in high-risk PE is limited.[102,103] One major distinction is that while the Protek platform can allow introduction of an oxygenator into the circuit, for combined hemodynamic and respiratory support, the microaxial RVAD pump does not presently allow splicing of an oxygenator into its configuration.[4] However, both RVAD types may be viable options in select circumstances.[58]

Airway and Respiratory Management

The induction of anesthesia, due to sympatholytic effects of medication, as well as the institution of positive pressure ventilation, both have the potential to induce circulatory collapse in patients with RV dysfunction and hemodynamically significant PE.[104] Accordingly, endotracheal intubation should be avoided whenever possible. As hemodynamic, rather than gas exchange issues are the predominant physiologic consequence of acute PE, few patients require invasive mechanical ventilation. Here, we review select approaches to airway management and mechanical ventilation for patients with acute PE at risk for, or with active circulatory failure.

Airway Management

Rapid sequence induction and intubation (RSI) has the potential to induce systemic arterial hypotension resulting in RV ischemia and circulatory collapse. Accordingly, avoiding general anesthesia with an awake approach to tracheal intubation is prefered.[105–108] Beyond the maintenance of vascular tone, preservation of spontaneous ventilation is a key benefit. While considered gold-standard in the management of the predicted difficult airway, a level of operator experience is required.[106]

Johannes and colleagues described an awake bronchoscopic approach to intubation in a series of nine patients with pulmonary hypertension and RV failure with a high rate of success. Topical oropharyngeal anesthesia was accomplished with atomized lidocaine (5 cc of 2%-4%) as well as the application of 5% lidocaine ointment to a Williams airway which was progressed to the oropharynx. With additional lidocaine administered to the vocal cords, an endotracheal tube was advanced over a bronchoscope. Sedation targeting anxiolysis and analgesia was prescribed however, consciousness and respiratory drive were maintained.[105] This approach may not be feasible in the case of the uncooperative patient and challenging among those with significant emesis or secretions obscuring the laryngeal view. Video laryngoscopy, as an alternative to bronchoscopy, is associated with similar success rates in an awake intubation approach.[106]

When RSI is unavoidable, etomidate and ketamine are recommended over propofol as the induction agents of choice to minimize the negative impact on vascular tone and contractility.[108,109] An arterial line should be inserted in preparation for the procedure and hemodynamics should be optimized with vasoactive agents ideally with some margin for an anticipated arterial pressure decline. In the appropriate patient, VA-ECMO should be discussed with the PERT in case of post-intubation hemodynamic collapse. In select patients, femoral venous and arterial access, in anticipation of cannulation, should be established beforehand.[108]

Positive Pressure Ventilation

Positive pressure ventilation has the potential to reduce RV filling and increase afterload inducing hemodynamic collapse in cases of RV failure. Elevated intrathoracic pressures raise resistance to venous return through vascular collapse at the level of the hepatic circulation and superior vena cava.[110] Therefore, elevated pleural pressures may lead to a decrease in RV filling. However, in patients with RV failure, the impact of positive pressure ventilation on afterload may be the predominant contributor to hemodynamic collapse. As the entire pulmonary vascular bed lies within the thorax, it will be similarly affected by changes in intrathoracic pressures. Variations in lung volumes alter characteristics of the pulmonary vasculature and influence its tone. With lung expansion, small alveolar vessels lying within the parenchyma are compressed leading to an increase in their resistance. By contrast, larger extra-alveolar vessels are collapsed at low lung volumes and are pulled open with alveolar expansion. Accordingly, the optimum PVR occurs at functional residual capacity with both atelectasis and alveolar overdistension being detrimental (Figure 3).[111–113]

While many intensivists fear higher values of positive end-expiratory pressure (PEEP) in patients with RV failure, this setting should be individualized to minimize atelectasis and improve gas exchange. In cases of co-existing ARDS, intrathoracic pressure is less readily transmitted to the venous system and therefore higher levels of PEEP may be optimal.[112] Similarly, patients with significant obesity may require higher levels of PEEP to maintain adequate transpulmonary pressure to mitigate atelectasis. Importantly, hypoxemia, hypercapnia, and acidemia raise pulmonary vascular tone and should therefore be avoided.[68,114]

Awake intubation preserves respiratory drive allowing for pressure support ventilation with low PEEP and driving pressure immediately post endotracheal tube insertion. Settings can therefore be titrated slowly to optimize gas exchange and respiratory system mechanics. Echocardiography may be used to monitor RV function both qualitatively and through the use

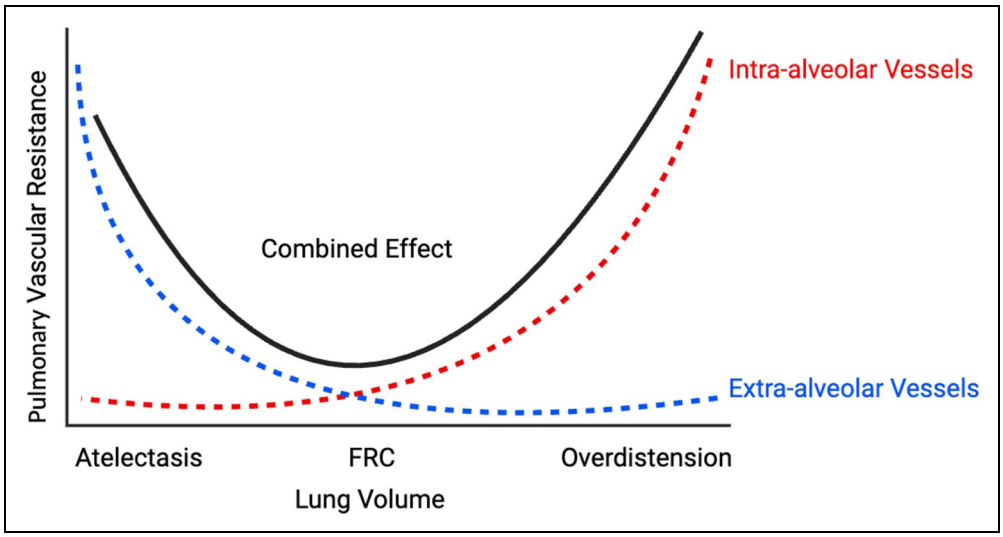

Figure 3. Pulmonary vascular resistance and lung volumes. The relationship between pulmonary vascular resistance and lung volumes is a "U-shaped" or "J-shaped" curve. Intra-alveolar vessels collapse with lung overdistension, raising their resistance. By contrast, extra-alveolar vessels are collapsed at low lung volumes. In sum, optimal pulmonary vascular resistance exists at functional residual capacity (FRC). Therefore, positive end-expiratory pressure and tidal volume settings should be individualized in cases of acute right ventricular failure with a goal of optimizing PVR. Created with BioRender.com.

of the VTI, as a surrogate of stroke volume, with adjustments in ventilator settings.[115] Invasive or minimally-invasive hemodynamic monitoring tools, when available, can be used for the same purpose.

Conclusions

Recent years have seen significant evolution in the management strategies available for patients with hemodynamically significant PE. However, a robust evidence base informing on optimal hemodynamic support and reperfusion therapies is lacking. How best to identify patients most likely to benefit from advanced therapies remains a central question. Accordingly, an understanding of the pathophysiology is imperative as critical care interventions have the potential to both rescue as well as harm the failing pressure overloaded RV. Given the high acuity and complexity of critically ill patients with acute PE, a PERT discussion is essential to develop a nuanced and tailored management strategy.

Abbreviations

ARDS	acute respiratory distress syndrome
CDT	catheter-directed thrombolysis
CI	cardiac index
ECPR	extracorporeal cardiopulmonary resuscitation
ICU	intensive care unit
iNO	inhaled nitric oxide
LV	left ventricle
LVOT VTI	left ventricular outflow tract velocity time integral
PA	pulmonary artery
PASP	pulmonary artery systolic pressure
PE	pulmonary embolism
PEEP	positive end-expiratory pressure
PERT	pulmonary embolism response team
PPV	positive pressure ventilation
PVR	pulmonary vascular resistance
RSI	rapid sequence intubation/induction
RV	right ventricle
RVAD	right ventricular assist device
RVOT VTI	right ventricular outflow tract velocity time integral
TAPSE	tricuspid annular plane systolic excursion
VA-ECMO	venoarterial extracorporeal membrane oxygenation

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