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Review

Venoarterial extracorporeal membrane oxygenation in high-risk pulmonary embolism: A narrative review

Eugene Yuriditsky [a,*], Jan Bakker [b,c,d,e], Carlos L. Alviar [a], Sripal Bangalore [a], James M. Horowitz [a]

[a] Division of Cardiology, Department of Medicine, NYU Grossman School of Medicine, New York, NY, United States of America
[b] Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, NYU Grossman School of Medicine, New York, NY, United States of America
[c] Department of Intensive Care Adults, Erasmus MC University Medical Center, Rotterdam, Netherlands
[d] Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, United States of America
[e] Department of Intensive Care, Pontifical Catholic University of Chile, Santiago, Chile

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ABSTRACT

Emergent reperfusion, most commonly with the administration of thrombolytic agents, is the recommended management approach for patients presenting with high-risk, or hemodynamically unstable pulmonary embolism. However, a subset of patients with a more catastrophic presentation, including refractory shock and impending or active cardiopulmonary arrest, may require immediate circulatory support. Venoarterial extracorporeal membrane oxygenation (VA-ECMO) can be deployed rapidly by the well-trained team and provide systemic perfusion allowing for hemodynamic stabilization. Subsequent embolectomy or a standalone strategy allowing for thrombus autolysis may be followed with decannulation after several days. Retrospective studies and registry data suggest favorable clinical outcomes with the use of VA-ECMO as an upfront stabilization strategy even among patients presenting with cardiopulmonary arrest. In this review, we discuss the physiologic rationale, evidence base, and an approach to ECMO deployment and subsequent management strategies among select patients with high-risk pulmonary embolism.

1. Introduction

High-risk (massive) pulmonary embolism (PE), encompassing, obstructive shock (end-organ hypoperfusion with hypotension or vasopressor requirement), or cardiopulmonary arrest requires an immediate therapeutic strategy [1]. In a recent analysis of the Pulmonary Embolism Response Team (PERT) Consortium registry, in-hospital mortality was approximately 21% in this risk group yet estimated to be significantly higher in prior studies [2]. In the absence of contraindications, emergent thrombolysis is the recommended management approach [1,3]. However, data supporting this recommendation as well as alternative reperfusion strategies are sparce [1,4].

Recently, the term “catastrophic PE” has been used to describe a subset of patients with progressive hypotension despite multiple vasoactive agents, impending or active cardiopulmonary arrest, or persistent shock despite thrombolysis [2,5]. The short-term mortality in this subset is 41%. As thrombolytics and mechanical reperfusion strategies may require some time to improve hemodynamics, emergent circulatory support to restore systemic perfusion may be an appropriate strategy preceding pulmonary arterial reperfusion for select patients.

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) can be implemented rapidly and provide for hemodynamic stabilization in the setting of refractory shock or cardiopulmonary arrest [4,6]. Once placed on ECMO, patients may undergo mechanical reperfusion with surgical or catheter-based embolectomy or await thrombus autolysis on systemic anticoagulation. As most studies examining ECMO in this setting are limited to case series and registries, patient selection, the timing of initiation, and subsequent management strategies are not yet

Abbreviations: CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; PE, pulmonary embolism; PERT, pulmonary embolism response team; RV, right ventricle; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VV-ECMO, venovenous extracorporeal membrane oxygenation.

* Corresponding author at: Division of Cardiology, Department of Medicine, NYU Grossman School of Medicine, 550 First Ave. Kimmel 15, New York, NY 10016, United States of America.
E-mail address: Eugene.yuriditsky@nyulangone.org (E. Yuriditsky).

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well-defined. Here, we review the rationale and evidence base for VA-ECMO in the setting of PE with persistent hypotension or impending/active cardiopulmonary arrest.

2. Physiologic considerations

The RV is a high-volume, low-pressure pump exquisitely sensitive to abrupt changes in afterload. In the absence of preconditioning, the RV cannot mount a mean pulmonary artery pressure > 40–60 mmHg [1,7]. Right ventricular failure ensues with the mechanical obstruction of the pulmonary vasculature over 50% in conjunction with hypoxic vasoconstriction and the release of mediators of vascular tone [7]. Resultant RV dilatation increases myocardial wall tension and alters its contractile properties, leading to decreased left ventricular filling, hypotension, and depressed coronary perfusion [8]. The interplay of these pathologic mechanisms in a vicious cycle of auto-aggravation may progress to circulatory failure, cardiopulmonary arrest, and subsequent death.

VA-ECMO breaks the cycle of acute RV failure by diverting venous blood away from the RV into the ECMO circuit and returning oxygenated blood to the arterial system, providing organ perfusion [4,8]. The circuit functions as a partial cardiopulmonary bypass as some native cardiac function contributes to systemic circulation. The typical peripheral configuration includes a drainage cannula inserted into the femoral vein and a return cannula positioned in a femoral artery [9]. A centrifugal pump withdraws venous blood, advances it through an oxygenator allowing for gas exchange, and returns it to the arterial tree at a typical flow rate of 4–6 l per minute [9]. Indirect RV support is afforded through RV decompression, decreased pulmonary arterial pressure, and restoration of coronary perfusion. Importantly, veno-venous ECMO (VV-ECMO) treats refractory hypoxemia and hypercapnia without offering hemodynamic support. While several reports have described the use of VV-ECMO in acute PE, likely, those patients presented predominantly with hypoxemia (possibly related to alternative pathology), and PE was not hemodynamically significant [4].

By returning oxygenated blood to the aorta, peripheral VA-ECMO may raise left ventricular afterload. Accordingly, patients with concomitant left ventricular dysfunction may experience acute pulmonary edema [10]. The use of a pulmonary artery catheter to measure the pulmonary artery wedge pressure, as well as echocardiography to track left ventricular dimensions and aortic valve opening are useful monitoring approaches [11]. Mitigating strategies, or left ventricular unloading, including the use of inotropes, intra-aortic balloon pump, or a percutaneous microaxial flow pump may be required [12]. In cases of isolated RV failure, such as with acute PE, left ventricular function is generally preserved. Attention to conventional parameters of peripheral perfusion, such as the mixed venous oxygen saturation, lactate levels, capillary refill time, and organ function, are mainstay in monitoring the patient on VA-ECMO and important factors in determining pump speed settings and resultant circuit flows [13].

3. Practical considerations

An exhaustive discussion of the specifics of ECMO deployment and monitoring is outside the scope of this review and has been described elsewhere [13]. With a well-trained team, cannulation can take as little as 10–15 min, making this a suitable approach for rapidly deteriorating patients or those in cardiopulmonary arrest [14]. However, such rapid cannulation requires optimal conditions and may not be realistic for many centers. Ultrasound guidance and percutaneous access allow for ECMO initiation outside procedural areas, including the emergency department or intensive care unit. However, such expertise may be limited, and many centers do not have ECMO programs. The procedure can be performed solely with the use of local anesthesia, obviating the need for intubation and the associated morbidity and mortality in acute RV failure [15].

Contraindications to the initiation of ECMO include unlikely recovery without a viable plan for decannulation, poor life expectancy, and limited vascular access [13]. However, many variables are relative and require more extensive discussion. Several mortality risk scores have been published to assist patient selection [13]. Bleeding and thromboembolic events are the major complications associated with ECMO; bleeding has been reported in upward of 50% of patients and stroke in approximately 10% [13].

While thrombolytics are the preferred reperfusion strategy in high-risk PE, their use is supported by limited evidence [3]. In a study of 8 patients with massive PE, the 4 patients treated with streptokinase experienced clinical and echocardiographic improvement within an hour [3]. However, this timeframe may be inadequate for the rapidly deteriorating patient. In addition, many have contraindications to thrombolytics. Further, elements of chronicity are common in venous thromboembolism and may be responsible for therapeutic failure [16,17]. Alternative reperfusion strategies, such as surgical embolectomy, are associated with poor clinical outcomes in most patients [18]. Rapid stabilization with the deployment of VA-ECMO may, therefore, be the preferred initial approach for the appropriately-selected patient with high-risk PE.

4. When to initiate ECMO in high-risk PE?

Current guidelines support the use of ECMO in patients with PE in refractory shock or cardiopulmonary arrest in combination with surgical embolectomy or catheter-based therapies [1]. However, there are no randomized data, and the timing of initiation, patient selection, and local expertise should be considered. High-risk PE represents a spectrum of disease. Further, thrombolytics may be less efficacious among patients deteriorating to possible cardiopulmonary arrest or already requiring cardiopulmonary resuscitation [19]. In a recent meta-analysis of over 6400 patients with high-risk PE managed with ECMO, those receiving thrombolytics had a mortality of 57% compared to 43% in the total population [20]. However, meta-analyses and registry data are often limited by the lack of a non-ECMO comparison group. Accordingly, there may be rationale for the earlier use of ECMO in select cases of high-risk PE.

Pasrija et al., described a protocolized approach whereby patients with massive PE and either end-organ dysfunction or unclear neurologic status were cannulated for VA-ECMO as an upfront strategy. Compared to historical institutional controls predominantly undergoing an early aggressive surgical approach with embolectomy, 1-year survival was superior (96% v.73%, $p = 0.02$) [18]. Early ECMO allows for rapid restoration of perfusion. As ECMO was used as an initial rather than a salvage therapy, outcomes in this cohort were superior to those reported in other registries [18,19]. Some experts advocate that eligible patients with catastrophic PE should be cannulated for VA-ECMO if available within 30 min rather than an upfront attempt at reperfusion [5]. Failure of thrombolysis among patients with catastrophic PE, previously reported to occur at a rate of approximately 8%, may also warrant ECMO support [5]. How best to identify those most likely to benefit from early ECMO as compared to an initial attempt at reperfusion remains an important question.

Cannulation for ECMO following thrombolytic administration may increase the risk for clinically significant bleeding. In a retrospective analysis of 83 patients with PE treated with ECMO, 18 patients received thrombolytics before cannulation and were more likely to experience major hemorrhage (61% v. 26%, $p = 0.01$). Despite this risk and a high frequency of cardiopulmonary arrest preceding cannulation, survival to discharge was excellent and similar between the two groups (90% v 85%, $p = 0.94$) [21]. The authors argue that antecedent thrombolytic administration should not be an absolute contraindication to ECMO. However, the precise duration of time between thrombolysis and safe cannulation is unknown. Alternative right-sided mechanical circulatory support options, such as the ProtekDuo ® (LivaNova, London, UK) or Impella RP ® (Abiomed, Danvers, MA) require sole venous access and may be considered in such circumstances. However, the role of right-sided mechanical circulatory support in high-risk PE is not well-defined and may be limited by a center's experience [8]. With the limitations in the current evidence base and the need for an individualized approach accounting for patient factors and procedural capabilities, a PERT discussion is essential in selecting an optimal management strategy.

The concomitant use of systemic thrombolytics and ECMO is thought to carry a prohibitive bleeding risk. Further, drug delivery to the thrombus may be limited as most blood bypasses the pulmonary circulation during ECMO support. Lin et al., reported on 13 patients undergoing ECMO for massive PE; 9 patients were treated with simultaneous systemic thrombolysis and 4 received catheter-directed thrombolysis. Major bleeding occurred in 4 of the 13 patient and required early termination of thrombolytic administration and surgical exploration. Despite these complications, 85% of patients survived to discharge [22]. With limited data, safety concerns, and alternative strategies available, this approach cannot be recommended at present.

5. ECMO as a bridge to reperfusion therapies

While the evidence is limited to retrospective studies and registries, guidelines recommend that ECMO be combined with surgical embolectomy or catheter-based therapies in high-risk PE [1]. Most published studies include a significant percentage of patients undergoing a combined approach of ECMO and surgical embolectomy [23]. Several reports have indicated improved survival rates among patients treated with a mechanical reperfusion strategy informing guideline recommendations [17,24,25]. In a study of 36 patients with high-risk PE supported with ECMO, in-hospital survival was 95% among those managed operatively compared to 31% in the remaining cohort. Interestingly, 35% of patients were found to have acute-on-chronic thrombus necessitating combined embolectomy and pulmonary endarterectomy [17]. This finding may explain thrombolytic failure in a proportion of patients with high-risk PE and why ECMO as a standalone approach without mechanical reperfusion may fail in select patients.

Mortality rates among patients treated with ECMO and surgical embolectomy are variable, ranging from 24% to 43% in recent meta-analyses; however significant heterogeneity exists between studies [20,25]. Cardiac arrest before ECMO initiation is commonly associated with increased mortality in this population [26]. In a meta-analysis including 1138 patients with PE managed with VA-ECMO, surgical embolectomy was associated with higher survival (RR 1.96, 95% CI 1.39–0.76) [27]. However, these results may be in part attributed to selection bias with favorable baseline patient characteristics, a lesser severity of illness, and reflective of institutional protocols.

Mounting evidence and increasing experience with catheter-based therapies may alter the preferred reperfusion approach for patients supported on ECMO [28]. Percutaneous embolectomy, by contrast to catheter-directed thrombolysis, obviates the need for any thrombolytic administration. Both approaches spare the morbidity associated with surgery and may be a preferred option in this population. While data are limited, pooled mortality with the use of combined ECMO and catheter-based reperfusion may be lower than that of surgical embolectomy (29% v. 43%) [20].

6. ECMO as a standalone strategy

The use of ECMO with therapeutic anticoagulation as a standalone approach without a subsequent surgical or catheter-based reperfusion strategy is controversial [1,6]. In most published individual series, ECMO is commonly implemented in conjunction with reperfusion therapies [23]. In a French multicenter retrospective study of 52 patients with PE supported with ECMO, 78% of the 18 patients managed with standalone ECMO were dead at 30 days. By contrast, 30-day mortality was 29% among those who underwent surgical embolectomy [24]. In a large German registry of 2197 patients with PE treated with ECMO, risk for in-hospital death was lower among those receiving embolectomy compared to ECMO alone (OR 0.50 v. 0.68) [19]. However, baseline differences in severity of illness as well as selection bias in these retrospective analyses may in part account for the clinical outcomes. Plausibly, a more tailored approach should be considered.

Systemic anticoagulation limits clot propagation allowing for endogenous fibrinolysis with thrombus resolution occuring within a week [29]. In several series, ECMO combined with anticoagulation alone led to autolysis over the course of several days allowing for RV recovery, ECMO decannulation, and reasonable survival rates compared to similar cohorts [15,30,31]. In a study of 21 patients with PE supported with ECMO, 10 of 13 survivors required no further reperfusion therapies [30]. In a study from a large-volume ECMO center including 41 patients with massive PE cannulated for ECMO, 73% demonstrated RV recovery and were decannulated after a median of 6 days without the need for surgical embolectomy [29]. The 90-day survival was 97% in this group. Factors related to thrombus chronicity including prolonged respiratory symptoms (>2 weeks), history of venous thromboembolism, and an enlarged pulmonary artery were predictive of the subsequent need for embolectomy [29].

Surgical embolectomy carries significant morbidity and mortality particularly in the setting of shock and multiorgan failure. In an analysis of 214 patients undergoing surgical embolectomy, mortality was approximately 24% among those with high-risk PE which increased to 32% for patients requiring preoperative cardiopulmonary resuscitation. By contrast, mortality was 9% for intermediate-risk patients undergoing embolectomy [32]. Patients requiring ECMO may be at especially high surgical risk and experience postoperative RV stunning requiring prolonged circulatory support [31]. Accordingly, several experts have advocated for serial echocardiographic assessment of RV function following the institution of ECMO to evaluate for RV recovery and decannulation rather than upfront embolectomy. Persistent RV dysfunction in conjunction with thrombus nonresolution following a period of observation may be an indication for operative management [15]. The role of this more conservative strategy in the current era of catheter-based therapies remains to be seen.

7. Extracorporeal cardiopulmonary resuscitation in pulmonary embolism

Cardiopulmonary resuscitation (CPR) may be less effective in the setting of high-risk PE due to circulatory obstruction. Indeed, survival among patients with PE suffering cardiac arrest is poor. In the French National Cardiac Arrest Registry, those with PE and out-of-hospital cardiac arrest had a 30-day survival of 16% when treated with thrombolytics and only a 6% survival among controls [33].

The initiation of ECMO during cardiopulmonary resuscitation, ECPR, is unsurprisingly associated with a higher mortality in acute PE compared to its use in obstructive shock in the absence of arrest. In an analysis of the extracorporeal life support organization (ELSO) registry, mortality among patients with PE treated with ECPR was 68% compared to 43% among those requiring ECMO outside of cardiopulmonary arrest [26]. This outcome is only slightly better compared to a 71% mortality among all patients treated with ECPR regardless of arrest etiology [26]. Similar statistics are echoed in a large meta-analysis demonstrating a 34% survival rate in this population [27]. However, case series and registry data are heterogenous with some reporting significantly worse clinical outcomes [19].

Cannulation can be performed in as little as 10–15 min during cardiac arrest however this is dependent on procedural expertise as well as patient and team factors [34]. Support should be established within 60 min following the onset of cardiac arrest. Importantly, such ideal circumstances may not be realistic at many centers as delays from the call to team mobilization and cannulation may occur. Further, inability to establish percutaneous access and the necessity of a femoral cut-down approach may lead to additional delays. Locally formulated inclusion criteria for ECPR based on published favorable prognostic markers should be instituted among ECPR programs [34]. Studies have demonstrated decreased mortality with the use of ECPR in the setting of in-hospital cardiac arrest [35]. However, a large randomized trial examining the use of ECPR in the setting of out-of-hospital cardiac arrest presumed to be of cardiac origin did not demonstrate improved survival with favorable neurologic outcomes [36]. As ECPR programs grow, we are challenged with appropriately selecting patients most likely to benefit from this aggressive intervention.

8. Conclusions

Select patients with high-risk PE may benefit from an early ECMO strategy rather than an initial attempt at reperfusion. However, appropriate patient selection is imperfectly defined, and a center's capability is a decisive factor in the early management algorithm. A more individualize approach to subsequent mechanical reperfusion as compared to an ECMO standalone strategy may evolve with the proliferation of catheter-based therapies. Given the paucity of high-quality evidence, a PERT discussion with multidisciplinary expertise is instrumental in selecting the most appropriate therapies for patients with high-risk PE.

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Eugene Yuriditsky: Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Jan Bakker:** Writing – review & editing, Conceptualization. **Carlos L. Alviar:** Writing – review & editing, Conceptualization. **Sripal Bangalore:** Writing – review & editing. **James M. Horowitz:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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