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To ventilate, oscillate, or cannulate?☆

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Abstract Ventilatory management of acute respiratory distress syndrome has evolved significantly in the last few decades. The aims have shifted from optimal gas transfer without concern for iatrogenic risks to adequate gas transfer while minimizing lung injury. This change in focus, along with improved ventilator and multiorgan system management, has resulted in a significant improvement in patient outcomes. Despite this, a number of patients develop hypoxemic respiratory failure refractory to lung-protective ventilation (LPV). The intensivist then faces the dilemma of either persisting with LPV using adjuncts (neuromuscular blocking agents, prone positioning, recruitment maneuvers, inhaled nitric oxide, inhaled prostacyclin, steroids, and surfactant) or making a transition to rescue therapies such as high-frequency oscillatory ventilation (HFOV) and/or extracorporeal membrane oxygenation (ECMO) when both these modalities are at their disposal. The lack of quality evidence and potential harm reported in recent studies question the use of HFOV as a routine rescue option. Based on current literature, the role for venovenous (VV) ECMO is probably sequential as a salvage therapy to ensure ultraprotective ventilation in selected young patients with potentially reversible respiratory failure who fail LPV despite neuromuscular paralysis and prone ventilation. Given the risk profile and the economic impact, future research should identify the patients who benefit most from VV ECMO. These choices may be further influenced by the emerging novel extracorporeal carbon dioxide removal devices that can compliment LPV. Given the heterogeneity of acute respiratory distress syndrome, each of these modalities may play a role in an individual patient. Future studies comparing LPV, HFOV, and VV ECMO should not only focus on defining the patients who benefit most from each of these therapies but also consider long-term functional outcomes.

Abbreviations: ARDS, acute respiratory distress syndrome; CV, conventional ventilation; HFOV, high-frequency oscillatory ventilation; ECLS, extracorporeal life support; VILI, ventilator-induced lung injury; EIT, electric impedance tomography; RM, recruitment maneuver; NO, nitric oxide.

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1. Introduction

Acute respiratory distress syndrome (ARDS) has been traditionally defined as acute severe hypoxemia (Pa_{O_2}/F_{IO_2} “”<200 mm Hg) in the presence of bilateral pulmonary infiltrates on chest radiography that are not primarily caused by elevated left atrial pressures [1]. The most recent revised definition incorporates positive end-expiratory pressure (PEEP), making it more robust [2]. Despite the advances in intensive care management, the ARDS mortality remains high, ranging between 34% and 58% [3-5]. Acute respiratory distress syndrome can be a manifestation of direct lung injury from an infection or aspiration, or indirect injury resulting from an extrapulmonary process [6]. Regardless of the insult, the end result is often a diffuse alveolar damage with the disruption of alveolar capillary integrity resulting in pulmonary edema [7]. The alveolar injury results in the release of proinflammatory cytokines such as tumour necrosis factor, interleukin (IL)-1, IL-6, and IL-8 [8,9]. These cytokines recruit neutrophils to the lungs that mediate further damage to the capillary endothelium and alveolar epithelium [10]. Despite decades of laboratory, animal, and clinical research, our understanding of ARDS is still incomplete.

Mechanical ventilation with low tidal volumes (VTs) and high PEEP often referred to as *lung-protective ventilation* (LPV) is an integral part of ARDS management along with other supportive care [11]. Lung-protective ventilation involves the provision of mechanical ventilation with a plateau pressure of less than 30 cm of water and VTs normalized to predicted body weight [12] to minimize alveolar distension and barotrauma and the addition of PEEP to minimize repeated opening/closure of alveolar units and prevent atelectrauma [13] and biotrauma [14]. There are occasions when LPV fails to provide satisfactory gas exchange while maintaining lung protection. Rescue strategies for severe hypoxemia have been an area of interest and research over the last 2 decades [15]. More recently, oxygenation targets in ARDS themselves are under scrutiny [16], and the optimal targets are yet to be defined. An ideal rescue therapy should improve gas exchange while limiting further ventilator-induced lung injury (VILI), whether it is complementary or not to LPV.

One of the major advances in ARDS management has been the realization that mechanical ventilation induces a number of sequelae, initiated in the lung, which are termed *VILI* [17], but which can become systemic. The development of LPV strategies has led to the subsequent improvement in outcomes [18-22]. The pathogenesis of VILI is complex and represents the shear stress and strain on the pulmonary parenchyma and interstitial and vascular elements. It occurs as a result of cyclical collapse of the unstable alveoli at end-expiration, resulting in shear stress, excessive VTs, excessive distending pressures, and propagation of systemic inflammation with associated other-organ failures [18,19]. Despite LPV having been shown to improve mortality in ARDS [21], it is likely that VILI still occurs through a number of mechanisms. Although there are no objective markers to determine the threshold at which VILI occurs and to quantify it clinically, it may be important to consider long-term functional outcomes in addition to mortality effects when choosing one rescue therapy over another.

The heterogeneous nature of the lung injury may mean that the different modalities of LPV, high-frequency oscillatory ventilation (HFOV), and extracorporeal membrane oxygenation (ECMO) have different effects in individual patients. Conceptually, HFOV delivers very small VTs while maintaining alveolar recruitment and appears to be lung protective. Alternatively, venovenous (VV) ECMO may further minimize VILI by causing little cyclic alveolar closure during tidal breaths, which is often referred to as *lung rest*. More studies are required to guide clinicians about which patient subgroups will benefit and when these therapies should be initiated. This review aims to discuss the available evidence so as to guide physicians to decide the most appropriate rescue therapy strategy in patients with severe hypoxemia refractory to LPV.

2. Lung-protective ventilation—is it adequate?

Mechanical ventilators have now become an indispensable device in the intensive care unit (ICU). These have evolved from being volume and pressure generators to devices that use sophisticated rapid response flow sensors and triggering mechanisms to improve patient comfort and ventilator synchrony [23]. However, their rapid advancement has been based more on engineering developments than clinical results. It should be emphasized that owing to a lack of viable alternate options, mechanical ventilation itself has not been rigorously tested in clinical trials. Similarly, the data on safety, efficacy, and outcomes of various modes of ventilation are limited. There has been significant improvement in survival in the past 2 decades as a result of refinements in ventilator techniques, complimented by improved overall ICU care including restrictive fluid management, early treatment of sepsis, and better source control practices [24].

2.1. Low-tidal-volume ventilation

A low-VT ($\leq$ 6 mL/kg of predicted body weight) and low-pressure (inspiratory plateau pressure $<$30 cm H_2O) strategy is now the standard of care. The ARDS Network study demonstrated an absolute risk reduction in mortality of 9% with this approach [21]. Data from animal studies suggest that VILI can occur even at lower plateau pressures [25], and patients with ARDS may benefit from further reductions in VTs if practically feasible. It is still unclear if this benefit can be extended to patients without ARDS who receive conventional ventilation (CV). There are data suggesting

that mechanical ventilation with conventional VTs contributes to the development of lung injury in patients without ALI at the onset of mechanical ventilation. [26,27]. Mechanical ventilation with conventional VTs was associated with a sustained increase in plasma IL-6 levels in one study [27]. Plateau pressures may not accurately reflect the alveolar distension pressure because a multitude of extrapulmonary factors can affect the plateau pressures [28]. The use of esophageal pressure as surrogate for pleural pressure is also problematic [29]. This is an area that needs further research, despite being the best-studied aspect of the impact of ventilatory strategies on mortality.

Low-VT ventilation is not without risks. Severe hypercapnia and acidosis that follow may result in increased intracranial pressure, depressed myocardial contractility, pulmonary hypertension, and decreased renal blood flow [12]. The risks of permissive hypercapnia have to be balanced against the proven benefits of LPV [21,30] in an individual patient. Often, these associated risks with hypercapnia may lead to failure of LPV regardless of oxygenation and may dictate the choice of the rescue strategy. This is important because extracorporeal respiratory support therapies such as VV ECMO or extracorporeal carbon dioxide removal (ECCOR) techniques may restitute physiology, facilitate ultraprotective ventilation, and potentially reverse the undesirable consequences of permissive hypercapnia. Various novel ECCOR devices are currently available or being investigated, and the details of which can be found elsewhere [31]. These promising techniques are currently not backed by quality evidence and may have a potential role in the future.

2.2. Role of PEEP and recruitment maneuvers

Relatively higher PEEP may keep the alveolar units open at end-expiration, thereby preventing atelectrauma [13] and biotrauma [14]. There are observational studies that have shown harm with PEEP levels below 5 cm H_2O in patients with ARDS [32]. Higher PEEP improves oxygenation and has reduced the need for other rescue therapies such as prone ventilation or inhaled nitric oxide (NO) [30]. A meta-analysis of 3 clinical trials showed improved survival (adjusted relative risk (RR), 0.90; 95% confidence interval [CI], 0.81-1.00) in patients with more severe forms of ARDS who were ventilated with higher PEEP [33]. Recruitment maneuvers (RM) are often attempted to increase the volume of aerated lung, thereby improving gas exchange. A variety of techniques such as periodic sighs, ventilation with high airway pressures, and passive insufflations without ventilation have all been attempted. Such procedures may worsen tidal hyperinflation, with overdistension of compliant sections of the lung tissue, predisposing them to VILI [18,34]. Despite an improvement in oxygenation, clinical trials have not found a survival benefit [35-37], and there is insufficient evidence for routine use of RMs at this stage. Ongoing studies may hold the answers regarding the effectiveness of this bedside intervention [38]. Studies on CV complimented by computed tomography [39] and electric impedance tomography (EIT) [40] have suggested that better recruitment is possible [41], using these techniques. Computed tomography in critically ill patients is not without risks; however, EIT can be an effective bedside tool easily used in the ICU [40]. The potential role of EIT as a real-time guide to lung recruitment is a subject for future research. At the time of writing, the availability of this technique is limited.

2.3. The role of other adjuvant therapies

Adjuvant rescue therapies such as inhaled NO, inhaled prostacyclin [42], steroids [43,44], and surfactant [45] are sometimes used. None have been associated with a clear mortality benefit despite an improvement in oxygenation. The use of these adjuncts may often delay the initiation of HFOV or ECMO. In patients with severe ARDS, early administration of a neuromuscular blocking agent (NMBA), cisatracurium besylate, improved the adjusted 90-day survival and decreased the duration of mechanical ventilation without increasing muscle weakness [46]. These results may highlight the role of optimal neuromuscular paralysis in facilitating LPV and improving outcomes. A recent meta-analysis also found significant benefit with prone positioning in a subset of patients with severe hypoxemia (RR, 0.84; 95% CI, 0.74-0.96) [47]. Results from a recently published randomized controlled trial [48] (Proseva trial) indicate significant mortality benefit with early application of prolonged prone positioning (28 day mortally 16% in the prone group compared to 32.8% in the supine group) in patients with severe and persistent ARDS ($Pao_2/Fio_2 < 150$ with $Fio_2 \geq 0.6$ and PEEP ≥ 5 cm H_2O, who underwent prone ventilation for at least 16h/d) and may significantly affect current practice. The incidence of complications such as accidental dislodgement of tubes, monitoring, and venous access did not differ significantly between the groups. These results may be seen as sufficient evidence for routine use of prolonged prone positioning in patients with severe ARDS and its widespread use may provide the much necessary prospective observational data that may further validate the findings of the Proseva trial. Available evidence does not support the routine use of inhaled NO as a rescue therapy in adults with ARDS [49]. Its use is associated with limited improvement in oxygenation with no improvement in survival and a possible increase in renal dysfunction [50] and nosocomial infections [51]. It should therefore be only a temporizing measure.

Thus, LPV, permissive hypercapnia, optimal fluid, and other supportive management and the use of adjuncts such as NMBAs and prone ventilation may constitute an initial approach to most patients with ARDS. In future, further clarity on oxygenation targets and minimally invasive ECCOR techniques may potentially further extend the role of LPV and may impact the use of HFOV and VV ECMO as rescue therapies.

3. High-frequency oscillatory ventilation—is it just another ventilator?

High-frequency oscillatory ventilation involves maintenance of relatively constant mean airway pressure by using very small VTs (1-3 mL/breath) at a very high frequency (300-900 breaths/min). This is accomplished using rapid pressure oscillations [52]. Minimal variations in mean airway pressure as opposed to CV can be effectively used to recruit the lung using higher airway pressures. This may reduce volutrauma and atelectrauma; however, the risks of barotrauma on HFOV are not well understood. The biologic plausibility of HFOV makes it likely that patients with symmetrical lung injury with less compliant lungs and more hypercapnia may benefit most. Animal studies comparing HFOV with CV have demonstrated that HFOV leads to improved alveolar recruitment [53] and decreased lung inflammation [54]. However, there are uncertainties regarding the lung-protective properties of HFOV. Tidal volumes are neither measured nor monitored during HFOV, and in the absence of quantification of volume in conjunction with very high frequencies, the risk of volutrauma may be increased [55,56].

The results of recently published Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) [57] and Oscillation in ARDS (OSCAR) [58] trials that compared HFOV with LPV in patients with moderate-to-severe ARDS will significantly influence the choice of HFOV as a routine rescue option in these patients. Although the former showed increased in-hospital mortality with HFOV (47% vs 35 %), there was no 30-day mortality benefit seen in the latter. However, there were significant issues with the HFOV arm of OCILLATE and LPV arm of OSCAR. The OSCILLATE trial may have exaggerated the adverse outcomes by comparing an arguably injurious HFOV strategy (mean airway pressures up to 38 cm of water) with effective LPV in the control arm. Similarly, nonstandardized LPV in the OSCAR trial may have led to a higher mortality in the LPV group (41%), thereby underestimating the outcomes from HFOV. The answers may lie in another randomized trial that compares stringent LPV with a more conservative HFOV strategy, as used in the OSCAR trial. Although, these trials failed to demonstrate an outcome benefit with HFOV, they did highlight the importance of LPV with a 6% mortality difference (35% vs 41%) between the LPV arms of either studies. It should be noted that both these studies set out to investigate the use of HFOV when used as an early ARDS strategy rather than a rescue measure [59,60].

Before these randomized trials, much of the available evidence supporting HFOV in adults stemmed from small observational studies. The existing studies comparing HFOV with CV were limited by their conduct in the pre-LPV era and the heterogeneity in patient population. Most of them had shown that HFOV improved oxygenation but not mortality [61,62]. On the contrary, a recent meta-analysis that included 8 randomized control trials found that HFOV had favorable survival effect (RR, 0.77; 95% CI, 0.61-0.98) and reduced treatment failure (RR, 0.67; 95% CI, 0.46-0.99) [63].

The published experience with HFOV (n = 22) and VV ECMO (n = 68) during the H1N1 pandemic in Australia and New Zealand provides useful insights into the roles of HFOV and VV ECMO as rescue strategies for ARDS [64,65]. Only 3% of ICU patients with H1N1 received rescue HFOV as opposed to 9% who received ECMO. This disparity may reflect limited HFOV availability across study centers, variable severity of illness, contraindications for HFOV, or a selection bias. Patients who received ECMO were more severely ill, requiring higher airway pressures, and with lower Pa_{O_2}/F_{IO_2} ratios and higher lung injury scores compared with patients who received HFOV. Although, overall, survival rates were similar (HFOV 77% and ECMO 71%), this was not risk adjusted. Another small study reported similar survival rates for HFOV (75%) and ECMO (71%) in the management of H1N1-related ARDS [66]. However, such unmatched comparison of retrospective data has limitations and may not be interpreted as clinical equipoise. In addition, the results of OSCILLATE and OSCAR trials are likely to discourage the routine use of HFOV in ARDS.

In addition to lack of evidence, the use of HFOV in patients with suppurative lung pathology, bronchospasm, and asymmetrical lung injury is further limited by reduced ability to perform adequate pulmonary toilet and provide optimal humidification and asymmetrical distribution of airway pressures resulting in potential barotrauma. High-frequency oscillatory ventilation is also problematic in patients with hemodynamic instability [67], especially severe right ventricular dysfunction, which is not uncommon in patients with ARDS. As demonstrated in the OSCILLATE trial, maintaining higher mean airway pressure may also necessitate large-volume intravenous fluid administration and vasoactive agents for circulatory support, which may lead to adverse outcomes. Despite recent evidence suggesting benefit with NMBAs [46], clinicians may have concerns over the need for deep sedation and neuromuscular blockade for the duration of HFOV.

Another issue is the inability to clearly define failure of HFOV based on gas exchange criteria. This lack of clarity may therefore delay initiation of other rescue therapies such as VV ECMO. The safety and efficacy of prolonged HFOV are also uncertain. In the absence of clear consensus on the criteria for failure of HFOV and the lack of studies comparing HFOV and ECMO and with evidence of harm or no clear benefit in recent studies, HFOV is an unlikely to intermediate option between LPV and ECMO. More than 7 days of non–lung-protective CV is generally considered a relative contraindication for VV ECMO [68]. Whether similar conclusions can be drawn for HFOV is currently unclear.

High-frequency oscillatory ventilation may still have a role in a select subgroup of patients with ARDS in whom pulmonary compliance is more critically reduced as compared with oxygenation. Any attempts to resurrect HFOV should involve studies that (i) identify optimal HFOV technique and (ii) define the group of patients who benefit most. Until such data are available, clinicians may persist with LPV complimented by adjuncts described in earlier sections while waiting for more clarity on the use of VV ECMO in patients with ARDS.

4. Extracorporeal membrane oxygenation—leave the lungs alone?

Although HFOV represents a method of extreme low-VT ventilation, VV ECMO can potentially abolish the need for tidal ventilation. In fact, emerging data indicate that ultraprotective ventilation to limit plateau pressures may be required to improve outcomes during VV ECMO [69]. Although more invasive, by not relying on injured lungs for gas exchange, extracorporeal respiratory support techniques such as VV ECMO and ECCOR add another dimension for ARDS management. Extracorporeal membrane oxygenation for adult respiratory failure was reported in 1972, where it was successfully used in an adult patient with ARDS after major trauma [70]. After this success, a multicenter randomized controlled trial was conducted by the National Institute of Health in United States, where ECMO was compared with CV [71]. The results of this trial were disappointing, with very high mortality rates in both the ECMO and CV groups. Continued refinement of ECMO techniques in selected patients with severe ARDS is promising [72] and has resulted in further improvement in outcomes. The conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) study conducted outside the influenza pandemic found that an ECMO-based protocol improved survival without severe disability [68]. Mortality or severe disability at 6 months after randomization was lower for the 90 patients randomized to receive ECMO (37% vs 53%; $P = .03$). Of these patients, 22 did not receive ECMO and a most of them improved with LPV, making an argument for timely referral of eligible patients with ARDS to an ECMO specialist center. This study is also criticized for lack of standardization of LPV in the control group.

However, analysis of the highly variable global clinical data [65,69,73-76] collected during the 2009 H1N1 pandemic continues to provide interesting insights into the role of VV ECMO. The overall reported mortality from ARDS during the pandemic was 14% to 41%. The mortality in patients treated with rescue ECMO was 0% to 39%. Analysis of the data collected during the pandemic also suggests improved survival upon referral of patients to a specialist ECMO center [76]. The recently published propensity score–matched (1:1) cohort analysis [69] of the French re'seau europe'en derecherche en ventilation artificielle (REVA) registry data of patients admitted with H1N1 (2009-2011) reported no differences in mortality when patients treated with LPV were compared with those treated with ECMO (40% vs 50%; $P = .44$). Such statistical conclusions are yet to be reproduced in well-designed randomized trials, and such comparisons are limited by the inherent selection bias. Interestingly, in unmatched younger patients (mean [SD] age, 38 [13] years) who were more severely hypoxic and treated with ECMO, the mortality was much lower (22% vs 50%). However, it should also be noted that the previously reported mortality for young patients (15-19 years of age) with ARDS who were managed conventionally is as low as 24% [6]. This may indicate that ECMO, as a rescue strategy, is reserved for young patients who fail LPV despite the evidence-based adjuncts such as NMBAs and prone ventilation.

In this setting, the current best status of rescue VVECMO when compared with LPV is one of "equipoise," pending ongoing studies (ECMO to rescue Lung Injury in severe ARDS (EOLIA); ClinicalTrial.gov Identifier NCT 01470703). The pragmatically designed EOLIA trial is currently investigating the use of ECMO, instituted early after the diagnosis of ARDS not evolving favorably after 3 to 6 hours of optimal ventilatory management, and maximum medical treatment may provide more definitive answers on the role of ECMO as a rescue therapy in ARDS. This may, in essence, be a comparison between benefits of continuation of LPV with various adjuncts against risks of ECMO. However, the trial design allows for the use of a variety of adjuncts such as prone ventilation, HFOV, and NO; allows crossover to ECMO arm; and, at this stage, does not have long-term functional end points as an outcome measure, all of which may add to the complexities of interpreting the study results.

4.1. Selecting the right patient

Venovenous ECMO represents a significant escalation of support rather than a mere substitution for LPV, and careful patient selection is key to its success. Not all patients with a potentially reversible cause of respiratory failure and severe gas exchange abnormalities while on LPV require ECMO. Other less invasive adjuncts (such as RM, NMBAs, and prone ventilation) may be used to assess for improvements in gas exchange and lung compliance. As per the Extracorporeal Life Support Organisation, ECMO is indicated when this risk exceeds 80%, that is, when Pao_2/Fio_2 is less than 80 or Fio_2 greater than 90% and Murray score is 3 to 4 [77]. Based on the results of the CESAR trial [68], a Murray score of at least 3 or a pH less than 7.2 with uncompensated hypercapnia may be used as a criterion for consideration of ECMO. More conservative criteria proposed by the French REVA Group [78] appear most appropriate for the current level of evidence for use of ECMO. They recommend ECMO in patients with refractory and persistent hypoxemia

defined by Pa_{O_2}/F_{IO_2} less than 50 mm Hg, despite high PEEP (10-20 cm H_2O) and high F_{IO_2} (>80%) ventilation or a plateau pressure of 35 cm H_2O or higher, despite VT reduction to 4 mL/kg. In the absence of robust evidence for ECMO and emerging evidence for prone ventilation, it may be prudent to consider failure of a trial of prone ventilation as an additional entry criterion. Significant comorbidities and multiple-organ failure (Sequential Organ Failure Assessment Score >15) have been proposed as contraindications for ECMO [78]. Mechanical ventilation for more than 7 days, major immunosuppression, and recent central nervous system hemorrhage have been shown to be associated with suboptimal outcomes [77].

However, these criteria may not always identify a true need for ECMO because in the CESAR trial, about 20% of patients who met these criteria were successfully managed with CV. Rarely, VV ECMO may not suffice in a patient with severe cardiorespiratory failure who is in extremis and may necessitate advanced extracorporeal life support with venoarterial ECMO [79]. Although outcomes in such patients are likely to be poor, such decisions at best are to be made on a case-by-case basis.

4.2. Should ECMO be the last resort?

Some may argue that, despite the contemporary use of VV ECMO as a recue therapy in ARDS, outcomes (55% survival to discharge) in the subgroup of patients with refractory hypoxemia and who fail LPV are still favorable [80] and may justify its ongoing use in select patients. On the contrary, its invasive nature, lack of conclusive evidence and familiarity, the risk of potential complications [81-83], and the increased costs may influence clinicians to persist with LPV or occasionally opt for HFOV. A recent study [84] reported comparable outcomes with VV ECMO and CV at 1 year when assessed for lung function and morphology, health-related quality of life, and psychologic impairment. Long-term survivors of VV ECMO have been shown to have similar physical health but decreased mental health, general health, vitality, and social function compared with other ARDS survivors and poor return to work [85]. Future studies comparing LPV vs ECMO should not only identify the patient groups that benefit most but also ensure long-term follow-up to provide data on functional outcomes.

Units with well-established ECMO programs may have a lower threshold for ECMO. Extracorporeal membrane oxygenation also necessitates high-risk transfers to specialized centers, when retrieval on ECMO is not possible. Despite some suggestion of it being cost-effective, running the service in several nearby centers outside a pandemic may lead to inadequate exposure, infrequent training opportunities, and questionable cost effectiveness. The actual requirement for ECMO outside the influenza pandemics [86] itself is expected to be low (1-2 cases per million population annually). Centralizing ECMO services to ICUs with established venoarterial ECMO programs may improve results and cost effectiveness. Pending further evidence, ECMO may have to be considered and early referrals be made to an ECMO-equipped center in patients with severe ARDS, where no contraindications exist. This, by itself, may improve outcomes, as demonstrated in the CESAR study [68].

5. Conclusions

Lung-protective ventilation is generally successful in most patients with ARDS. Some patients may not respond to LPV despite being complimented with adjuncts such as NMBAs, prone ventilation, and recruitment maneuvers and will require rescue therapies. It is unlikely that one rescue therapy will suffice in all forms of severe ARDS, and more studies are needed, not only to determine their true efficacy but also to assess whether one rescue therapy may work best in an individual patient based on the cause and progression of ARDS. High-frequency oscillatory ventilation may no longer be considered a routine rescue therapy for ARDS. Venovenous ECMO may be reserved for young patients who fail LPV, and minimizing plateau pressures while on ECMO may further improve outcomes. The roles for LPV, HFOV, and ECMO have to be better defined in future studies to enable clinicians to make evidence-based decisions.

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