Review Article

Mechanical Ventilation during Extracorporeal Membrane Oxygenation in Patients with Acute Severe Respiratory Failure

Zhongheng Zhang,1 Wan-Jie Gu,2 Kun Chen,3 and Hongying Ni3

1Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310016, China
2Department of Anesthesiology, Nanjing Drum Tower Hospital, Medical College of Nanjing University, Nanjing 210008, China
3Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Zhejiang, China

Correspondence should be addressed to Zhongheng Zhang; zh_zhang1984@hotmail.com

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Conventionally, a substantial number of patients with acute respiratory failure require mechanical ventilation (MV) to avert catastrophe of hypoxemia and hypercapnia. However, mechanical ventilation per se can cause lung injury, accelerating the disease progression. Extracorporeal membrane oxygenation (ECMO) provides an alternative to rescue patients with severe respiratory failure that conventional mechanical ventilation fails to maintain adequate gas exchange. The physiology behind ECMO and its interaction with MV were reviewed. Next, we discussed the timing of ECMO initiation based on the risks and benefits of ECMO. During the running of ECMO, the protective ventilation strategy can be employed without worrying about catastrophic hypoxemia and carbon dioxide retention. There is a large body of evidence showing that protective ventilation with low tidal volume, high positive end-expiratory pressure, and prone positioning can provide benefits on mortality outcome. More recently, there is an increasing popularity on the use of awake and spontaneous breathing for patients undergoing ECMO, which is thought to be beneficial in terms of rehabilitation.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is an important technique for the treatment of severe respiratory failure, providing opportunity for lung recovery or transplantation [1, 2]. Hill and colleagues first described ECMO support for cases of severe respiratory failure four decades ago [3]. Since then, a large number of observational studies and randomized trials have been performed [4, 5]. In common practice, ECMO is indicated when conventional mechanical ventilation fails to improve arterial oxygenation and/or eliminate carbon dioxide [6]. Another indication is the circulatory and/or cardiac failure. However, ECMO has not been well established (e.g., in the framework of evidence based medicine) for its effectiveness in the treatment severe respiratory failure, especially in some particular situations such as immune-compromised patients [7]. While there is uncertainty on the effectiveness of ECMO versus mechanical ventilation on mortality outcome, ECMO is still widely used for patients with refractory respiratory failure.

Because ECMO is expansive, is technically challenging, and bears catastrophic complications, it is not considered as a first line therapy for patients with respiratory failure [8]. A typical therapeutic protocol of severe acute respiratory distress syndrome (ARDS) is shown in Figure 1 [9]. The first line therapy (step 1) for severe ARDS is mechanical ventilation with a variety of modes [10–13]. Protective ventilation is typically employed. If the patient responds poorly to the initial MV setting, the strategy is to initiate VV-ECMO with the therapeutic target to maintain SaO2 and serum pH. Weaning off the ECMO is considered when the blood and gas flow are decreased to 2 L/min and 21%, respectively [9]. During ECMO running, mechanical ventilation is still in use. As a result, respiratory support of such patients comprises the native lung and artificial lung. The mechanical ventilation setting in patients undergoing ECMO is an area
of active research. There is controversy on the optimal degree of mechanical ventilation support. While ultra-protective ventilation provides enough lung rest, lung recruitment may accelerate lung recovery [14]. In the present review we summarize the current evidence on mechanical ventilation during ECMO.

2. Physiology behind ECMO

Because this review primarily focuses on mechanical ventilation during ECMO, we first need to understand some physiological changes during ECMO. Venovenous extracorporeal membrane oxygenation (VV-ECMO) is commonly used for the management of patients with respiratory failure and stable hemodynamics. The venous blood with low oxygen saturation (SvO2) is typically drained from superior vena cava, inferior vena cava, and/or large vein such as femoral or subclavian vein. It passes through the oxygenator [15] and then returns to the patient in or near the right atrium [16]. The returned blood with high oxygen content is mixed with systemic venous blood and enters into right heart. The mixed venous blood is further oxygenated in the native lung. However, due to low mechanical ventilation setting, such oxygenation is always negligible. Mechanical ventilation in this regard is more to keep the lung open than to provide oxygen [16]. However, native lung function is not always negligible; this may be the case for native lung CO2 removal. Respiratory drive cannot be fully controlled by extracorporeal CO2 removal, especially in acute hypoxemic patients.

Because ECMO is able to provide oxygen and remove carbon dioxide, the respiratory drive and effort can be controlled. A few animal studies showed that carbon dioxide removal by ECMO was able to induce apnea [17, 18]. In human study, when gas flow (e.g., control of carbon dioxide) dropped from 100% to 0%, pressure generated in the first 100 ms of inspiration against an occluded airway increased from 0.9 ± 0.5 to 2.8 ± 2.7 cmH2O (p < 0.001); the maximal inspiratory muscles pressure increased from 4.5 ± 3.1 to 8.5 ± 6.3 cmH2O. The authors concluded that carbon dioxide removal had significant impact on spontaneous breathing effort [19].

An important feature of VV-ECMO is its mild hemodynamic effect on circulation. This is of particular importance for hemodynamically unstable patients with acute respiratory failure (ARF). In animal models, Shen and colleagues found that although there were mild changes in ultrastructure and function of cardiomyocyte and mitochondria, the global...
hemodynamics were stable [20]. Also, there is evidence that the installation of VV-ECMO decreases heart rate, but mean arterial pressure is not significantly affected [21]. Given the favorable hemodynamic features of VV-ECMO, it can be used for patients with hemodynamically unstable patients. However, if a patient shows ARF in combination with refractory shock, venaarterial ECMO (VA-ECMO) should be recommended for use.

3. Timing of ECMO Initiation: Indications from Ventilation Parameters

Because mechanical ventilation typically precedes ECMO and mechanical ventilation parameters provide important information for the initiation of ECMO, in this section, we discuss when to start ECMO for severe respiratory failure.

The principle to start ECMO is when conventional mechanical ventilation cannot provide enough oxygenation and/or carbon dioxide elimination or ventilator setting is too high that can cause significant lung injury. Another condition is that the duration of mechanical ventilation is not too long that the underlying pathology is reversible. The timing of ECMO is usually based on the severity of ARDS, as represented by severe hypoxemia despite high PEEP (PaO$_2$/FiO$_2$ < 80 mmHg) and uncompensated hypercapnia (pH < 7.2) [22]. There is evidence that early initiation of ECMO (1.9 ± 1.4 days after onset of severe ARDS defined by Berlin definition) improves survival in trauma patients [23]. However, this study is limited by small sample size and the use of historical control. A large randomized controlled trial conducted by Peek and colleagues was probably the cornerstone in exploring the indications of ECMO for ARDS patients [24]. In the study, ARDS patients with Murray score > 3.0 or pH < 7.20 were randomized to receive either ECMO or conventional mechanical ventilation. The 6-month survival was 63% in the ECMO group versus 47% in the control group (p = 0.03). With the success of this trial, the criteria were adopted by Italian ECMO network. Use of the criteria in ARDS patients caused by influenza A (H1N1) virus showed a survival discharge rate of 68% [25]. In a well-matched cohort, early VV-ECMO was associated with lower mortality in patients with severe hypoxemic respiratory failure [26]. A threshold of plateau pressure is commonly used to avoid lung injury during mechanical ventilation. However, plateau pressure is generated by elastances of the lung and chest wall. It is the transpulmonary pressure that is introduced into clinical practice. The following paragraphs examine the use of protective ventilation in patients undergoing ECMO.

Four Protective Ventilation in ECMO

It is well understood that conventional ventilation mode can cause ventilator induced lung injury (VILI). The underlying mechanisms of VILI include alveolar overdistension (volutrauma), alveolar instability leading to alveolar collapse and reopening with each breath (atelectrauma), and the secondary inflammation caused by these mechanical injuries which is known as biotrauma [33]. Volutrauma is caused by ventilation at high tidal volumes. The effect of ventilation volumes on injury is independent of the peak airway pressure. Rat models have shown that, at the same peak airway pressure (45 cmH$_2$O), those ventilated with low tidal volumes developed less severe permeability and pulmonary edema [34]. In clinical practice, ventilation at high airway pressure is observed to cause lung injury manifested as pneumothorax or subcutaneous emphysema. However, since the high airway pressures per se do not cause VILI unless they are associated with high lung volumes, the term barotrauma is a misnomer [35]. To ameliorate the VILI, the concept of protective MV is introduced into clinical practice. The following paragraphs examine the use of protective ventilation in patients undergoing ECMO.

Protective ventilation with low tidal volume has long been known as a major component of ventilation strategy for both injured and healthy lung [10, 36, 37]. A landmark study on low tidal volume ventilation was conducted nearly two decades ago [38]. The study showed that patients who received protective ventilation versus conventional group had significantly lower 28-day mortality rate (38% versus 71%; p < 0.001). A recent network meta-analysis showed that ventilation with low tidal volume plus prone position was associated with reduced risk of death (hazards ratio: 0.62; 95% CI: 0.42–0.98) [39]. However, some studies failed to identify a beneficial effect on mortality [40, 41] or the effect size is much less than that in Amato's study [42]. While the benefit of low tidal volume ventilation is to reduce lung injury, it may cause carbon dioxide retention and hypoxemia due to reduced ventilation. In other words, the balance between lung rest and working is difficult to determine. Patient population with severe ARDS is actually an extremely heterogeneous group that one size does not fit all, and the relative importance...
of lung rest versus metabolic demand can be different across the population. During VV-ECMO, mechanical ventilation is still required due to reasons that (1) ECMO blood flow rate is usually not enough and in hyperdynamic status a substantial proportion of blood still passed via native lung, not having gone through the artificial lung first; (2) lung should be mildly ventilated and kept open. Complete collapse of the lung may delay its recovery. There is evidence that a sufficient PEEP level is beneficial [43].

The major obstacle for performing low tidal volume ventilation is carbon dioxide retention, worsened oxygenation, and intrapulmonary shunt [44]. When tidal volume reduces below 6 mL/kg, arterial PaCO₂ level increased remarkably and the pH value dropped below 7.2. Such a procedure for lung rest is performed at the cost of metabolic disturbances and tissue hypoxia. Fortunately, ECMO can provide an opportunity for the lung to rest while maintaining tissue oxygen supply and carbon dioxide elimination. With extracorporeal carbon dioxide removal, Ranieri and colleagues showed that tidal volume < 6 mL/kg enhanced lung protection with respect to acid-base homeostasis, cytokine secretion, and pulmonary morphology [45]. Thus, it is wise to rest the lung in severe ARDS patients who are also supported with ECMO. In an international survey on ventilator setting during ECMO, 77% of ECMO centers reported “lung rest” as the primary goal of mechanical ventilation; a tidal volume of 6 mL/kg or less was targeted in 76% centers [46]. Although there is a lack of randomized controlled trial in this topic, there is a large body of observational evidence supporting the notion that protective ventilation is associated with better outcome [47]. In Schmidt et al’s study, protective ventilation was routinely used in high-volume ECMO centers. Higher positive end-expiratory pressure levels during the first 3 days of ECMO support were associated with lower mortality (odds ratio, 0.75; 95% CI, 0.64–0.88; \( p = 0.0006 \)) [43]. With multivariable regression model, it was found that each one cmH₂O increase in plateau pressure was associated with a 14.4% decrease in the odds of achieving hospital survival (95% CI = 1.75% to 25.4%, \( p = 0.027 \)). Conversely, each one cmH₂O increase in PEEP was associated with a 36.2% decrease in the odds of 30-day survival (95% CI = 10.8% to 54.4%, \( p = 0.009 \)) [48]. Pandemic influenza A is a tragedy for human being, but it provides a good opportunity for exploring mechanical ventilator setting in ECMO patients [49]. Survivors had significantly lower plateau pressure during ECMO than nonsurvivors (25 ± 3 versus 29 ± 5 cmH₂O; \( p < 0.01 \)). The result remained unchanged even after multivariable adjustment (OR: 1.33; 95% CI: 1.14–1.59; \( p < 0.01 \)). More recently, some authors also explored the use of ultra-protective ventilation (i.e., tidal volume reduced to 4 mL/kg predicted body weight while PEEP was increased to target a plateau pressure between 23 and 25 cmH₂O) with the help of low-flow extracorporeal carbon dioxide removal (ECCO₂R) in moderate ARDS [50].

Another component of protective ventilation is low respiratory rate [51]. The rationale of this procedure is to rest the lung by reducing its motion. The lungs were ventilated 3 to 5 times per minute, with peak airway pressure limited to 35 to 45 cmH₂O. A continuous oxygen flow was provided. Carbon dioxide elimination was performed by extracorporeal method [51].

Closed-loop ventilation represents another novel protective ventilation mode [52]. It automatically adjusts some settings according to physiological target made by physicians, making it possible to select an individualized ventilator setting [53]. IntelliVent-ASV™ is an extension and development of adaptive support ventilation (ASV) that automatically adjusts ventilation settings such as minute volume, tidal volume (VT), and respiratory rate (RR), to reach a target end-tidal CO₂ (PETCO₂) in passively breathing patients and a target RR in actively breathing patients. Furthermore, inspiratory fraction of oxygen (FiO₂) and positive end-expiratory pressure (PEEP) are adjusted automatically to reach a target pulse oximetry (SpO₂). Although the closed-loop ventilation mode has been shown to be safe and effective in patients with ARDS, its use in patients undergoing ECMO has not been fully investigated [54, 55]. In a case series involving six patients, Karagiannidis and colleagues reported that closed-loop ventilation mode responded rapidly to decreased ECMO sweep gas flow. It concluded that the combination of neurally adjusted ventilatory assist (NAVA) and ECMO might permit a closed-loop ventilation with automated protective ventilation [56].

5. Recruitment Maneuvers

Recruitment maneuver is the indispensable component of protective ventilation, and there are a variety of methods to perform recruitment maneuver. In this section, we aimed to describe some commonly used recruitment maneuvers. Grasso and colleagues proposed the titration of PEEP according to stress index. Stress index (\( b \)) can be estimated based on airway pressure and inspiratory time by the following equation:

\[
\text{Airway pressure} = a \cdot \text{Inspiratory time}^b + c,
\]

where the coefficient \( b \) is the stress index describing the shape of the airway opening pressure (Pao) corresponding to the period of constant-flow inflation. For \( b < 1 \), the Pao curve presents a downward concavity, suggesting a continuous decrease in elastance during constant-flow inflation. For \( b > 1 \), the curve presents an upward concavity suggesting a continuous increase in elastance. PEEP level was titrated to target a stress index between 0.9 and 1.1 [57]. Specifically, PEEP was decreased if the stress index was higher than 1.1 and was increased if the stress index was lower than 0.9. PEEP is not changed if the stress index was between 0.9 and 1.1 [58].

Talmor and colleagues proposed to set PEEP levels in reference to the esophageal pressure. Patients underwent heavy sedation and paralysis. Recruitment maneuver was performed by increasing airway pressure to 40 cmH₂O for 30 seconds. Thereafter, PEEP was set to achieve a transpulmonary pressure of 0 to 10 cmH₂O at end expiration, according to a sliding scale based on the PaO₂ and the FiO₂ (Table 1) [59]. Ventilator setting was adjusted in one column at a time.
to keep the partial pressure of arterial oxygen (PaO₂) between 55 and 120 mmHg. Alternatively, the oxygen saturation, as measured by pulse oximeter, was kept between 88 and 98% by using the ventilator settings in one column at a time. The PEEP was set at such a level that transpulmonary pressure during end-expiratory occlusion (PLexp) stays between 0 and 10 cmH₂O and keeps transpulmonary pressure during end-inspiratory occlusion at less than 25 cmH₂O.

| FiO₂ | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 |
|------|-----|-----|-----|-----|-----|-----|-----|
| Plexp| 0   | 2   | 4   | 6   | 8   | 10  | 10  |

Predicted body weight

\[ \text{Predicted body weight} = 50 \times (\text{centimeters of height} - 152.4) + 0.91 \]  

In the EXPRESS trial, “open-lung approach” was employed to treat patients with severe ARDS [60]. The ventilator procedures included pressure-control mode, targeting tidal volume of 6 mL/kg of predicted body weight, and plateau airway pressures less than 40 cmH₂O. The recruitment maneuver included a 40-second breath-hold at an airway pressure of 40 cmH₂O and an FiO₂ of 1.0. Oxygenation was maintained in a target range as described previously using a slide scale of PEEP/FiO₂ combinations (Table 2) [42].

6. Prone Positioning of Patients during ECMO

Prone position is an alternative or rescue therapy for patients with severe ARDS. Prone positioning may help to reduce collapse of dorsal lung segments with subsequent avoidance of alveolar overdistension of ventral lung segments. The aim is to homogenize transpulmonary pressure and reduce intrapulmonary shunt. In patients with severe ARDS, prone positioning has been proven to be beneficial in some clinical outcomes such as mortality (relative risk [RR]: 0.9; 95% CI: 0.82–0.98) [61], ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (63.0 ± 66.8 versus 44.6 ± 68.2, \( p = 0.02 \)) [62], and ventilator-associated pneumonia (1.66 versus 2.14 episodes per 100 patients-days of intubation; \( p = 0.045 \)) [63]. The well-known PROSEVA study is the largest multicenter study investigating the effect of prone positioning on mortality outcome. The study confirmed that early application of prolonged prone positioning sessions significantly decreased 28-day (16.0% versus 32.8%; \( p < 0.001 \)) and 90-day mortality (23.6% versus 41.0%; \( p < 0.001 \)) in patients with severe ARDS [64].

Prone positioning can be successfully performed during ECMO, and it is associated with improved respiratory parameters. In 17 subjects undergoing VV-ECMO who also failed at least one weaning attempt, prolonged prone positioning (24 hours) was performed [65]. Respiratory system compliance increased from 18 (12–36) to 32 (15–36) mL/cmH₂O (\( p < 0.0001 \)) and the PaO₂/FiO₂ ratio increased from III (84–128) to 173 (120–203) mmHg (\( p < 0.0001 \)). Similar findings were reported in several case series and observational cohort studies [66–69]. Indications of prone positioning during ECMO include difficult-to-wean, severe hypoxia (PaO₂/FiO₂ < 70) and injurious ventilator setting with plateau pressure exceeding 32 cmH₂O [70].

One challenging issue in performing prone positioning is the potential risk of turning the patient. Thus, some authors propose that ECMO may be a relative contraindication of prone positioning [67]. Reported adverse effects include cannula malfunction, inadvertent extubation, bed sore, and dislodged arterial and central venous lines [71]. Cannula and chest tube site bleedings were also noted in some studies [72, 73]. A standard turning procedure should be protocolized in specialized centers to avoid these potentially detrimental events. There is evidence that prone positioning during ECMO is safe if performed properly [74, 75].

7. Spontaneous Breathing during ECMO

Spontaneous breathing is usually not allowed during early phase of severe ARDS, mostly because these critically ill patients require protective ventilation (e.g., low tidal volume, high positive end-expiratory pressure, and recruitment maneuver) [76]. To perform protective ventilation, patients usually require deep sedation and paralysis. In ACURASYS (ARDS et Curarisation Systématique) trial, the use of neuromuscular blocking agents to suppress spontaneous breathing was found to be beneficial on clinical important outcomes such as ICU-free days and mortality (hazard ratio at 90 days: 0.68; 95% CI: 0.48–0.98). The effect was statistically significant in severe ARDS (90-day mortality: 30.8% versus 44.6%, \( p = 0.04 \)) [77]. Similar results have been reported in other studies [78–82]. However, adverse effects of deep sedation and paralysis, including bradycardia, ICU-acquired paresis, ventilator-associated pneumonia, are still important concerns. To avoid potential adverse effects of deep sedation and paralysis, some pioneering centers start to use ECMO as the first line therapy, rather than rescue therapy after MV failure. Thus, there is accumulating evidence on the use of ECMO in awake, spontaneously breathing patients [83–85]. In patients waiting for lung transplantation, those underwent ECMO with spontaneous breathing demonstrated improved survival when compared to other bridging strategies [84].

ECMO may provide an alternative to deliver protective ventilation. As previously mentioned, carbon dioxide removal is able to control spontaneous breathing effort. With more carbon dioxide removal by increasing gas and blood flow, apnea can be induced in animals [17, 18]. Similar results

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Table 1: Sliding scale of esophageal pressure-guided titration of PEEP. The table was adapted from [59]. Ventilator setting is adjusted in one column at a time to keep the partial pressure of arterial oxygen (PaO₂) between 55 and 120 mmHg. Alternatively, the oxygen saturation, as measured by pulse oximeter, is kept between 88 and 98% by using the ventilator settings in one column at a time. The positive end-expiratory pressure (PEEP) is set at such a level that transpulmonary pressure during end-expiratory occlusion (PLexp) stays between 0 and 10 cmH₂O and keeps transpulmonary pressure during end-inspiratory occlusion at less than 25 cmH₂O.
have been found in human studies [19, 86]. In late phase of severe ARDS, spontaneous breathing can be allowed to prevent adverse impact of long-term controlled ventilation. For example, respiratory muscle atrophy is common in patients with prolonged mechanical ventilation, and the adverse effect can occur at as few as 18 hours after mechanical ventilation [87]. Restoration of respiratory muscle activity is helpful to decrease or prevent such disuse myopathy [88]. Another benefit of spontaneous breathing is its systemic and preportal organ blood flow. In an animal study, Hering and coworkers showed that the stomach blood flow increased from 0.13 ± 0.01 to 0.29 ± 0.05 mL/g/min with spontaneous breathing. Similar trends were found in other visceral organs [89]. It is well known that visceral organ perfusion is an important determinant of clinical outcomes in the critically ill. In a case series of six participants, Karagiannidis and colleagues found that patients could immediately regulate PaCO2 towards a physiological range. Tidal volume was increased from 2–5 mL/kg to 8 mL/kg with inactivated ECMO, and inspiratory pressure increased from 19–29 cmH2O to 21–45 cmH2O [56].

Spontaneous breathing in severe ARDS animals undergoing ECMO support was associated with improved oxygenation and intrapulmonary shunt and redistributed ventilation towards dorsal areas, as compared to those with controlled ventilation [44]. The mechanical ventilation mode allowing for spontaneous breathing can be assisted mode, continuous positive airway pressure plus pressure support, and neural adjusted mechanical ventilation.

Furthermore, allowing spontaneous breathing during ECMO may be beneficial in terms of early rehabilitation, because these patients require less sedation and paralysis. It is possible to perform early rehabilitation for this group of patients. In a study involving 100 ECMO patients, investigators found that 35% (35/100 patients receiving ECMO) could participate in early mobilization and that 51% (18/35) were able to walk [90]. Thus, early mobilization is considered safe and feasible. There is evidence that patients receiving physical training can have much shorter duration of ICU stay [91].

In aggregate, spontaneous breathing is not allowed at early phase of severe ARDS, aiming to perform protective ventilation. With ECMO support, there is no worrisome on hypoxemia and hypercapnia and protective ventilation can be easily delivered. At recovery phase of severe ARDS, it may be wise to lower the ECMO sweep gas and blood flows, allowing recovery of spontaneous breathing. The recovery can be very quick.

### 8. Weaning

Some authors proposed that weaning VV-ECMO should start with ventilator weaning. The procedure may begin when the patient was able to maintain adequate gas exchange with decreasing ECMO and sweep flow and minimal ventilator setting. Patients can be weaned from mechanical ventilation while still on ECMO therapy. The use of single-site, dual lumen catheter in the internal jugular vein allows extubated patients to be ambulatory while being connected to the ECMO circuit. Such a strategy requires a good teamwork among nurses, physicians, and other medical workers [92]. Thereafter, when the FiO2 is weaned on ECMO, the flow rate can be decreased below 2.5 L/min. Decannulation can be considered when the patient is treated at lowest FiO2 and ECMO flow.

Other authors prefer the use of a lung-protective MV approach and later decide to prioritize weaning VV-ECMO over MV [47]. In an international survey involving 141 individual responses, Marhong and colleagues reported that the majority of centers prioritized weaning VV-ECMO over mechanical ventilation [46]. The weaning protocol can be performed as recommended by extracorporeal life support organization (ELSO) guidelines (https://www.elso.org): ECMO flows are decreased in steps to a minimum of 1 L/min while maintaining sweep at 100%. Alternatively, the flows are decreased to 2 L/min and then the sweep FiO2 is decreased. Both approaches should aim to maintain SaO2 greater than 95%. When SaO2 is stable on this setting, the sweep can be clamped on ventilator settings of pressure support ventilation (PSV) or continuous positive airway pressure (CPAP) of 20 cmH2O. If SaO2 > 95% and PaCO2 < 50 mmHg can be maintained for 60 minutes, ECMO can be weaned.

### 9. Conclusions

Although MV is commonly employed to avert catastrophic hypoxemia and hypercapnia in patients with severe ARDS, MV per se can cause lung injury and accelerate the disease progression. Extracorporeal membrane oxygenation (ECMO) provides an alternative to rescue patients with severe respiratory failure that MV fails to maintain adequate gas exchange. The timing of ECMO initiation based on the risks and benefits of ECMO has been widely investigated. In the running of ECMO, the protective ventilation strategy can be employed without worrying about catastrophic hypoxemia and carbon dioxide retention. There is a large body of evidence showing that protective ventilation with low tidal volume, high PEEP, and prone positioning can provide benefits on mortality outcome. More recently, there is an increasing popularity on the use of awake and spontaneous breathing for patients undergoing ECMO. Lastly, we discussed ECMO weaning. The majority of centers prioritized weaning VV-ECMO over mechanical ventilation, while others preferred to wean MV first.

### Competing Interests

There is no conflict of interest.
References

[1] G. Makdisi and I.-W. Wang, "Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology," Journal of Thoracic Disease, vol. 7, no. 7, pp. E166–E176, 2015.

[2] J. A. Hayanga, J. K. Aboagye, H. K. Hayanga, J. D. Luketic, and J. D'Cunha, "Extracorporeal membrane oxygenation as a bridge to lung re-transplantation: is there a role?" The Journal of Heart and Lung Transplantation, vol. 35, no. 7, pp. 901–905, 2016.

[3] J. D. Hill, T. G. O'Brien, J. J. Murray et al., "Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung," New England Journal of Medicine, vol. 286, no. 12, pp. 629–634, 1972.

[4] M. Schmidt, M. Bailey, J. Sheldrake et al., "Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The respiratory extracorporeal membrane oxygenation survival prediction (RESP) score," American Journal of Respiratory and Critical Care Medicine, vol. 189, no. 11, pp. 1374–1382, 2014.

[5] C. Karagiannidis, D. Brodie, S. Strassmann et al., "Extracorporeal membrane oxygenation: evolving epidemiology and mortality," Intensive Care Medicine, vol. 42, no. 5, pp. 889–896, 2016.

[6] E. C. Goligher, N. D. Ferguson, and L. J. Brochard, "Clinical challenges in mechanical ventilation," The Lancet, vol. 387, no. 10030, pp. 1856–1866, 2016.

[7] M. V. Diuvert, K. A. Cawcutt, G. J. Scheers, and L. M. Baddour, "Use of extracorporeal membrane oxygenation for the treatment of influenza-induced acute respiratory distress syndrome in immunocompromised adults," The American Journal of the Medical Sciences, vol. 352, no. 1, pp. 81–85, 2016.

[8] R. M. Sweeney and D. F. McAuley, "Acute respiratory distress syndrome," The Lancet, vol. 388, no. 10058, pp. 2416–2430, 2016.

[9] M.-Y. Wu, C.-C. Huang, T.-I. Wu, C.-L. Wang, and P.-J. Lin, "Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome in adults: prognostic factors for outcomes," Medicine, vol. 95, no. 8, Article ID e2870, 2016.

[10] Y. Yu, C. Zhu, X. Qian, Y. Gao, and Z. Zhang, "Adult patient with pulmonary agenesis: focusing on one-lung ventilation during general anesthesia," Journal of Thoracic Disease, vol. 8, no. 1, pp. E124–E129, 2016.

[11] M. R. Tucci, E. L. Costa, M. A. Nakamura, and C. C. Morais, "Noninvasive ventilation for acute respiratory distress syndrome: the importance of ventilator settings," Journal of Thoracic Disease, vol. 8, no. 9, pp. E982–E986, 2016.

[12] C. Hodgson, E. C. Goligher, M. E. Young et al., "Recruitment manoeuvres for adults with acute respiratory distress syndrome receiving mechanical ventilation," The Cochrane Database of Systematic Reviews, vol. 11, Article ID CD006667, 2016.

[13] J. Li, H. Xu, M. Li, and J. Chen, "Effect of setting high APRV guided by expiratory inflection point of pressure-volume curve on oxygen delivery in canine models of severe acute respiratory distress syndrome," Experimental and Therapeutic Medicine, vol. 12, no. 3, pp. 1445–1449, 2016.

[14] G. Foti and A. Pesenti, "To recruit or not recruit, this is ...," Critical Care Medicine, vol. 43, no. 3, pp. 719–720, 2015.

[15] R. H. Bartlett, "Physiology of gas exchange during ECMO for respiratory failure," Journal of Intensive Care Medicine, In press.

[16] A. Sen, H. E. Callisen, C. M. Alward et al., "Adult venovenous extracorporeal membrane oxygenation for severe respiratory failure: current status and future perspectives," Annals of Cardiothoracic Surgery, vol. 5, no. 3, pp. 258–269, 2016.

[17] T. Kolobow, L. Gattinoni, and T. A. J. E. Tomlinson and Pierce, "Control of breathing using an extracorporeal membrane lung," Anesthesiology, vol. 63, no. 2, pp. 138–141, 1977.

[18] T. Langer, V. Vecchi, S. M. Belenkiy et al., "Extracorporeal gas exchange and spontaneous breathing for the treatment of acute respiratory distress syndrome: an alternative to mechanical ventilation?" Critical Care Medicine, vol. 42, no. 3, pp. e211–e220, 2014.

[19] T. Mauri, G. Grasselli, G. Suriano et al., "Control of respiratory drive and effort in extracorporeal membrane oxygenation patients recovering from severe acute respiratory distress syndrome," Anesthesiology, vol. 125, no. 1, pp. 159–167, 2016.

[20] J. Shen, W. Yu, J. Shi et al., "Effect of venovenous extracorporeal membrane oxygenation on the heart in a healthy piglet model," Journal of Cardiothoracic Surgery, vol. 8, no. 1, article 163, 2013.

[21] J. Golej, H. Kahlbacher, G. Schöffmann et al., "The immediate haemodynamic response to the initiation of extracorporeal membrane oxygenation in a piglet model of infant hypoxic respiratory failure," Perfusion, vol. 17, no. 6, pp. 421–426, 2002.

[22] T. Aokage, K. Palmér, S. Ichiba, and S. Takeda, "Extracorporeal membrane oxygenation for acute respiratory distress syndrome," Journal of Intensive Care, vol. 3, no. 1, article 17, 2015.

[23] P. L. Bosarge, L. A. Raff, G. McGwin et al., "Early initiation of extracorporeal membrane oxygenation improves survival in adult trauma patients with severe adult respiratory distress syndrome," Journal of Trauma and Acute Care Surgery, vol. 81, no. 2, pp. 236–243, 2016.

[24] G. J. Peek, M. Mugford, R. Tiruvoipati et al., "Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial," The Lancet, vol. 374, no. 9698, pp. 1351–1363, 2009.

[25] N. Patroniti, A. Zangrillo, F. Papпалардо et al., "The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks," Intensive Care Medicine, vol. 37, no. 9, pp. 1447–1457, 2011.

[26] H. D. Kanji, J. McCallum, M. Norena et al., "Early veno-venous extracorporeal membrane oxygenation is associated with lower mortality in patients who have severe hypoxemic respiratory failure: A retrospective multicenter cohort study," Journal of Critical Care, vol. 33, pp. 169–173, 2016.

[27] S. Grasso, P. Terragni, A. Birocco et al., "ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure," Intensive Care Medicine, vol. 38, no. 3, pp. 395–403, 2012.

[28] Y. Cheng, M. Wu, Y. Chang, C. Huang, and P. Lin, "Developing a simple preinterventional score to predict hospital mortality in adult venovenous extracorporeal membrane oxygenation: a pilot study," Medicine, vol. 95, no. 30, Article ID e4380, 2016.

[29] C.-H. Hsin, M.-Y. Wu, C.-C. Huang, K.-C. Kao, and P.-J. Lin, "Venovenous extracorporeal membrane oxygenation in adult respiratory failure: scores for mortality prediction," Medicine, vol. 95, no. 25, Article ID e3989, 2016.

[30] X. Liu, Y. Xu, R. Zhang et al., "Survival Predictors for Severe ARDS Patients Treated with Extracorporeal Membrane Oxygenation: A Retrospective Study in China," PLOS ONE, vol. 11, no. 6, Article ID e0158061, 2016.

[31] M. Li, L. Yi, X. Huang et al., "Factors affecting the outcome of pulmonary-acute respiratory distress syndrome patients..."
treated with veno-venous extracorporeal membrane oxygenation,” Zhonghua Yi Xue Za Zhi, vol. 96, no. 10, pp. 781–786, 2016.

[32] J. H. Song, W. K. Woo, S. H. Song et al., “Outcome of veno-venous extracorporeal membrane oxygenation use in acute respiratory distress syndrome after cardiac surgery with cardiopulmonary bypass,” Journal of Thoracic Disease, vol. 8, no. 7, pp. 1804–1813, 2016.

[33] G. F. Nieman, J. Satalin, P. Andrews, N. M. Habashi, and L. A. Gatto, "Lung stress, strain, and energy load: engineering concepts to understand the mechanism of ventilator-induced lung injury (VILI)," Intensive Care Medicine Experimental, vol. 4, article no. 16, 2016.

[34] D. Dreyfuss, P. Soler, G. Basset, and G. Saumon, "High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure," American Review of Respiratory Disease, vol. 137, no. 5, pp. 1159–1164, 1988.

[35] G. F. Curley, J. G. Laffey, H. Zhang, and A. S. Slutsky, "Biotrauma and ventilator-induced lung injury: clinical implications," Chest, vol. 150, no. 5, pp. 1109–1117, 2016.

[36] Z. Zhang, X. Hu, X. Zhang et al., "Lung protective ventilation in patients undergoing major surgery: a systematic review incorporating a Bayesian approach," BMJ Open, vol. 5, no. 9, Article ID e007473, 2015.

[37] W.-J. Gu, F. Wang, and J.-C. Liu, "Effect of lung-protective ventilation with lower tidal volumes on clinical outcomes among patients undergoing surgery: a meta-analysis of randomized controlled trials," CMAJ, vol. 187, no. 3, pp. E101–E109, 2015.

[38] M. B. P. Amato, C. S. V. Barbas, D. M. Medeiros et al., "Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome," New England Journal of Medicine, vol. 338, no. 6, pp. 347–354, 1998.

[39] C. Wang, X. Wang, C. Chi et al., "Lung ventilation strategies for acute respiratory distress syndrome: a systematic review and network meta-analysis," Scientific Reports, vol. 6, Article ID 22855, 2016.

[40] R. G. Brower, C. B. Shanhoitz, H. E. Fessler et al., "Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients," Critical Care Medicine, vol. 27, no. 8, pp. 1492–1498, 1999.

[41] L. Brochar, F. Roudot-Thoraval, E. Roupie et al., "Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome," American Journal of Respiratory and Critical Care Medicine, vol. 158, no. 6, pp. 1831–1838, 1998.

[42] Network TARDS, "Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network," The New England Journal of Medicine, vol. 342, no. 18, pp. 1301–1308, 2000.

[43] M. Schmidt, C. Stewart, M. Bailey et al., "Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study," Critical Care Medicine, vol. 43, no. 3, pp. 654–664, 2015.

[44] A. Güldner, T. Kiss, T. Bluth et al., "Effects of ultraprotective ventilation, extracorporeal carbon dioxide removal, and spontaneous breathing on lung morphofunction and inflammation in experimental severe acute respiratory distress syndrome," Anesthesiology, vol. 122, no. 3, pp. 631–646, 2015.

[45] V. M. Ranieri, P. P. Terragni, L. Del Sorbo et al., “Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal,” Anesthesiology, vol. III, no. 4, pp. 826–835, 2009.

[46] J. D. Marhong, T. Telesnicki, L. Munshi, L. Del Sorbo, M. Detsky, and E. Fan, "Mechanical ventilation during extracorporeal membrane oxygenation. An international survey," Annals of the American Thoracic Society, vol. II, no. 6, pp. 956–961, 2014.

[47] E. Fan, L. Gattinoni, A. Combes et al., "Venoextracorporeal membrane oxygenation for acute respiratory failure: a clinical review from an international group of experts," Intensive Care Medicine, vol. 42, no. 5, pp. 607–612, 2016.

[48] A. M. Modrykamien, O. O. Hernandez, Y. Im et al., "Mechanical ventilation in patients with the acute respiratory distress syndrome and treated with extracorporeal membrane oxygenation," ASAIO Journal, vol. 62, no. 5, 2016.

[49] T. Pham, A. Combes, H. Roze et al., "Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis," American Journal of Respiratory and Critical Care Medicine, vol. 187, no. 3, pp. 276–282, 2013.

[50] V. Fanelli, M. V. Ranieri, J. Mancebo et al., "Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome," Critical Care, vol. 20, no. 1, article 36, 2016.

[51] L. Gattinoni, A. Pesenti, D. Mascheroni et al., "Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure," Journal of the American Medical Association, vol. 256, no. 7, pp. 881–886, 1986.

[52] R. L. Chatburn and E. Mireles-Cabodevilla, "Closed-loop control of mechanical ventilation: description and classification of targeting schemes," Respiratory Care, vol. 56, no. 1, pp. 85–102, 2011.

[53] J.-M. Arnal, A. Garnero, D. Novonti et al., "Feasibility study on full closed-loop control ventilation (IntelliVent-ASV™) in ICU patients with acute respiratory failure: a prospective observational comparative study," Critical Care, vol. 17, no. 5, article R196, 2013.

[54] J.-M. Arnal, M. Wysocki, C. Nafati et al., "Automatic selection of breathing pattern using adaptive support ventilation," Intensive Care Medicine, vol. 34, no. 1, pp. 75–81, 2008.

[55] N. Clavieras, M. Wysocki, Y. Coisel et al., "Prospective randomized crossover study of a new closed-loop control system versus pressure support during weaning from mechanical ventilation," Anesthesiology, vol. 119, no. 3, pp. 631–641, 2013.

[56] C. Karagiannidis, M. Lubnow, A. Philipp et al., "Autoregulation of ventilation with neurally adjusted ventilatory assist on extracorporeal lung support," Intensive Care Medicine, vol. 36, no. 12, pp. 2038–2044, 2010.

[57] S. Grasso, P. Terragni, L. Mascia et al., "Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury," Critical Care Medicine, vol. 32, no. 4, pp. 1018–1027, 2004.

[58] S. Grasso, T. Stripoli, M. De Michele et al., "ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure," American Journal of Respiratory and Critical Care Medicine, vol. 176, no. 8, pp. 761–767, 2007.

[59] D. Talmor, T. Sarge, A. Malhotra et al., "Mechanical ventilation guided by esophageal pressure in acute lung injury," New England Journal of Medicine, vol. 359, no. 20, pp. 2095–2104, 2008.
[60] M. O. Meade, D. J. Cook, G. H. Guyatt et al., “Ventilation strategy using low tidal volumes, recruitment manoeuvres, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial,” *JAMA*, vol. 299, no. 6, pp. 637–645, 2008.

[61] S. Y. Park, H. J. Kim, K. H. Yoo et al., “The efficacy and safety of prone positioning in adults with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials,” *Journal of Thoracic Disease*, vol. 7, no. 3, pp. 356–367, 2015.

[62] L. G. Gattinoni, G. Tognoni, A. Pesenti et al., “Effect of prone positioning on the survival of patients with acute respiratory failure,” *New England Journal of Medicine*, vol. 345, no. 8, pp. 568–573, 2001.

[63] C. Guérin, S. Gaillard, S. Lemasson et al., “Effects of systematic prone positioning in hyperoxic acute respiratory failure: a randomized controlled trial,” *The Journal of the American Medical Association*, vol. 292, no. 19, pp. 2379–2387, 2004.

[64] C. Guérin, J. Reignier, J.-C. Richard et al., “Prone positioning in severe acute respiratory distress syndrome,” *New England Journal of Medicine*, vol. 368, no. 23, pp. 2159–2168, 2013.

[65] A. Kimmoun, S. Roche, C. Bridey et al., “Prolonged prone positioning under VV-ECMO is safe and improves oxygenation and respiratory compliance,” *Annals of Intensive Care*, vol. 5, no. 1, article 35, 2015.

[66] V. Kipping, S. Weber-Carstens, C. Lojewski et al., “Prone position during ECMO is safe and improves oxygenation,” *International Journal of Artificial Organs*, vol. 36, no. II, pp. 821–832, 2013.

[67] J. Littmate, C. Sucker, J. Easo, L. Wigger, and O. Dapunt, “Prone and ECMO—a contradiction per se?” *Perfusion*, vol. 27, no. 1, pp. 78–82, 2012.

[68] Y. Masuda, H. Tatsumi, H. Imaizumi et al., “Effect of prone positioning on cannula function and impaired oxygenation during extracorporeal circulation,” *Journal of Artificial Organs*, vol. 17, no. 1, pp. 106–109, 2014.

[69] M. Kredel, L. Bischof, T. E. Wurmb, N. Roewer, and R. M. Muellenbach, “Combination of positioning therapy and venovenous extracorporeal membrane oxygenation in ARDS patients,” *Perfusion*, vol. 29, no. 2, pp. 171–177, 2014.

[70] C. Gueriville, S. Hraiech, V. Garibaldi et al., “Prone positioning during veno-venous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome in adults,” *Minerva Anestesiologica*, vol. 80, no. 3, pp. 307–313, 2014.

[71] J. Mancebo, R. Fernandez, L. Blanch et al., “A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome,” *American Journal of Respiratory and Critical Care Medicine*, vol. 173, no. II, pp. 1233–1239, 2006.

[72] R. E. Culbrett and L. T. Goodfellow, “Complications of prone positioning during extracorporeal membrane oxygenation for respiratory failure: a systematic review,” *Respiratory Care*, vol. 61, no. 2, pp. 249–254, 2016.

[73] L. C. Otterspoor, F. H. Smit, T. J. Van Laar, J. Keseciąglu, and D. Van Dijk, “Prolonged use of extracorporeal membrane oxygenation combined with prone positioning in patients with acute respiratory distress syndrome and invasive Aspergillosis,” *Perfusion*, vol. 27, no. 4, pp. 335–337, 2012.

[74] M. T. Voelker, N. Jahn, S. Bercker et al., “Prone positioning of patients during venovenous extracorporeal membrane oxygenation is safe and feasible,” *Der Anaesthesist*, vol. 65, no. 4, pp. 250–257, 2016.

[75] C. E. Goettler, J. P. Pryor, B. A. Hoey, J. K. Phillips, M. C. Balas, and M. B. Shapiro, “Prone positioning does not affect cannula function during extracorporeal membrane oxygenation or continuous renal replacement therapy,” *Critical Care*, vol. 6, no. 5, pp. 452–455, 2002.

[76] A. Güldner, P. Pelosi, and M. G. De Abreu, “Spontaneous breathing in mild and moderate versus severe acute respiratory distress syndrome,” *Current Opinion in Critical Care*, vol. 20, no. 1, pp. 69–76, 2014.

[77] L. Papazian, J.-M. Forel, A. Gacouin et al., “Neuromuscular blockers in early acute respiratory distress syndrome,” *The New England Journal of Medicine*, vol. 353, no. 12, pp. 1107–1116, 2010.

[78] G. Lyu, X. Wang, W. Jiang, T. Cai, and Y. Zhang, “[Clinical study of early use of neuromuscular blocking agents in patients with severe sepsis and acute respiratory distress syndrome],” *Zhonghua wei zhong bing ji jiu yi xue*, vol. 26, no. 5, pp. 325–329, 2014.

[79] A. S. Neto, V. G. M. Pereira, D. C. Espósito, M. C. T. Damasceno, and M. J. Schultz, “Neuromuscular blocking agents in patients with acute respiratory distress syndrome: a summary of the current evidence from three randomized controlled trials,” *Annals of Intensive Care*, vol. 2, no. 1, article 32, 2012.

[80] M. Gainniner, A. Roch, J.-M. Forel et al., “Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome,” *Critical Care Medicine*, vol. 32, no. 1, pp. 113–119, 2004.

[81] J.-M. Forel, A. Roch, V. Marin et al., “Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome,” *Critical Care Medicine*, vol. 34, no. 11, pp. 2749–2757, 2006.

[82] A.-T. Wang, J.-L. Gao, X.-L. Li, Y.-X. Leng, Z.-Y. Yao, and X. Zhu, “The effect of neuromuscular blocking agents on prognosis of patients with acute respiratory distress syndrome: a meta analysis,” *Chinese Critical Care Medicine*, vol. 25, no. 3, pp. 149–153, 2013.

[83] T. Langer, A. Santini, N. Bottino et al., “‘Awake’ extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering,” *Critical Care*, vol. 20, no. 1, article 150, 2016.

[84] M. A. Schechter, A. M. Ganapathi, B. R. Englum et al., “Spontaneously Breathing Extracorporeal Membrane Oxygenation Support Provides the Optimal Bridge to Lung Transplantation,” *Transplantation*, vol. 100, no. 12, pp. 2699–2704, 2016.

[85] H. J. Yeo, W. H. Cho, and D. Kim, “Awake extracorporeal membrane oxygenation in patients with severe postoperative acute respiratory distress syndrome,” *Journal of Thoracic Disease*, vol. 8, no. 1, pp. 37–42, 2016.

[86] R. Marcolin, D. Mascheroni, A. Pesenti, M. Bombino, and L. Gattinoni, “Ventilatory impact of partial extracorporeal CO2 removal (PECOR) in ARF patients,” *ASAIO transactions*, vol. 32, no. 1, pp. 508–510, 1986.

[87] S. K. Powers, A. N. Kavazis, and S. Levine, “Prolonged mechanical ventilation alters diaphragmatic structure and function,” *Critical Care Medicine*, vol. 37, no. 10, pp. S347–S353, 2009.

[88] S. Levine, T. Nguyen, N. Taylor et al., “Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans,” *The New England Journal of Medicine*, vol. 358, no. 13, pp. 1327–1335, 2008.

[89] R. Hering, J. C. Bolten, S. Kreyer et al., “Spontaneous breathing during airway pressure release ventilation in experimental lung injury: effects on hepatic blood flow,” *Intensive Care Medicine*, vol. 34, no. 3, pp. 523–527, 2008.

[90] D. Abrams, J. Javidfar, E. Farrand et al., “Early mobilization of patients receiving extracorporeal membrane oxygenation: A
Retrospective Cohort Study," *Critical Care*, vol. 18, no. 1, article R38, 2014.

[91] T. Fuehner, C. Kuehn, J. Hadem et al., "Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation," *American Journal of Respiratory and Critical Care Medicine*, vol. 185, no. 7, pp. 763–768, 2012.

[92] K. E. Williams, "Extracorporeal membrane oxygenation for acute respiratory distress syndrome in adults," *AACN Advanced Critical Care*, vol. 24, no. 2, pp. 149–158, 2013.