Chapter 13

Management of Mechanical Ventilation During Extracorporeal Membrane Oxygenation

David Stahl MD and Victor Davila MD

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/64248

Abstract

This chapter explores the best practices of mechanical ventilation during extracorporeal membrane oxygenation (ECMO) through a detailed discussion of the physiologic theory and clinical evidence. Future areas of study and unanswered questions about mechanical ventilation during ECMO are also delineated.

Keywords: mechanical ventilation, venovenous extracorporeal membrane oxygenation, venoarterial extracorporeal membrane oxygenation, ECMO, lung protective ventilation, positive end expiratory pressure

1. Introduction

Extracorporeal membrane oxygenation (ECMO) has been used as rescue therapy for hypoxemic, hypercarbic, and cardiogenic respiratory failure for decades, despite high complication rates [1, 2]. Venovenous (VV) ECMO was implemented internationally to great success during the recent H1N1 pandemic, and continues to be used as a last hope in refractory hypoxemia [3, 4]. Venoarterial (VA) ECMO is often employed when respiratory failure is secondary following hemodynamic collapse (most commonly cardiogenic in origin).

In a global effort to improve both the application and outcomes of VV and VA ECMO, all aspects of ECMO patients' care have been called into question. In this chapter, we explore both the theory and data behind specific mechanical ventilation (MV) strategies used in patients receiving ECMO to better understand current practice and propose areas of future study.

2. Ventilator associated lung injury

The landmark studies of lung protective ventilation in acute respiratory distress syndrome (ARDS) were published nearly 20 years ago, but the goal of lung protective ventilation remains to avoid ventilator associated lung injury (VALI) while permitting healing from the initial pathologic state [5, 6]. VALI is commonly described as a series of related injurious phenomena.

Barotrauma was the first, distinct aspect of VALI to be described. It can be defined as alveolar injury resulting from elevated transpulmonary pressures [7, 8]. Volutrauma is a related process where overdistension of alveolar volume results in lung injury [7, 8]. Barotrauma and volutrauma are both clinical explanations to approximate the physiologic principles of lung stress and strain using commonly measured variables including tidal volume, plateau pressure and positive end expiratory pressure (PEEP) [9]. MV strategies commonly aim to prevent barotrauma or volutrauma by limiting plateau airway pressures to ≤30 cm H_2O or tidal volumes to ≤6 ml/kg predicted body weight (PBW) [5].

Atelectrauma, conversely, occurs when low (or negative) end-expiratory transpulmonary pressures result in cyclic opening and closing of alveoli, generating disruptive forces on the basement membrane, resulting in lung injury [7, 10]. PEEP is commonly used to prevent atelectrauma by minimizing alveolar closure at the end of exhalation. Mechanical activation of the lung creates a biological reaction (e.g., neutrophil recruitment, cytokine release) known as biotrauma [8, 10–12]. Evidence of biotrauma may serve as a surrogate marker of the response to mechanical ventilation, and is often employed as an outcome measure when comparing MV strategies.

3. Mechanical ventilation strategies during venovenous extracorporeal membrane oxygenation

Guidelines for MV during ECMO are sparse. The Extracorporeal Life Support Organization 25 (ELSO) has published guidelines that include pressure assist-control ventilation (PCV) with low inflation 26 pressures (10 cm H2O), higher PEEP (15 cm H2O), low respiratory rate (5 bpm), and FiO2 of 0.5 27 or less [13]. The European Network of Mechanical Ventilation had similar guidelines in a 2009 response to the H1N1 pandemic recommending tidal volumes to obtain a plateau pressure of 20–25 cm H_2O, PEEP above 10 cm H_2O and with a respiratory rate of 6–20 cycles per minute and an FiO_2 between 0.3 and 0.5 [14]. However, in practice, there is significant variation in the mode of mechanical ventilation used in patients receiving ECMO [15, 16].

In the past 20 years, significant progress has been made in identifying the specific mechanical ventilation strategies that benefit patients with ARDS and acute respiratory failure [5, 17–20]. However, during this time, little progress has been made on the optimal method of mechanical ventilation in ECMO patients [14]. While volume assist-control ventilation (VCV) remains the most common mode of MV in ARDS, an observational study of current practice demonstrated

http://dx.doi.org/10.5772/64248

pressure controlled modes of ventilation to be the most common mode of MV during ECMO [16, 21]. In many circumstances, ECMO may even facilitate ultraprotective MV, loosely defined as ventilation with tidal volumes below 4 ml/kg PBW. Although surrogate outcomes such as inflammatory markers may be improved by using this strategy, clinical benefit has not been demonstrated [22–24].

Experts continue to advocate for particular variations of VCV, PCV, or airway pressure release ventilation (APRV) predominantly based on physiologic 7 rationale and surrogate outcome studies demonstrating the avoidance of VALI [13]. However, there is a growing body of clinical evidence to guide the use of MV during ECMO [25, 26].

3.1. Lung rest: prevention of barotrauma or volutrauma

In a 2014 survey of ELSO centers, the majority (77%) reported "lung rest" to be the primary goal of mechanical ventilation during ECMO [15]. Although the definition of lung rest was not prespecified, one can assume that an intended goal was to limit both tidal volume and inspiratory airway pressures in that 81% of participants used tidal volumes ≤6 ml/kg PBW, including 34% who used ultraprotective tidal volumes ≤4 ml/kg PBW [15].

Initial studies of very low tidal volume ventilation in lung-injured rats demonstrated that tidal volumes of 3 ml/kg decreased pulmonary edema formation and improved pulmonary epithelial fluid clearance even when compared to 6 ml/kg [27]. Decreased levels of pulmonary inflammatory markers have also been found in humans ventilated with very low tidal volumes [22, 28]. These findings parallel a *post hoc* analysis of five large ARDS trials, which demonstrated a continuous mortality benefit to very low tidal volumes even when plateau pressures were less than 30 cm H_2O [29]. Case reports of tidal volumes as low as 1.9 ml/kg PBW have also shown positive outcomes [30]. However, prospective studies have failed to show a mortality benefit to ultralow tidal volume ventilation [24]. The Xtravent study compared very low tidal volume ventilation (~3 ml/kg PBW) plus $ECCO_2R$, to conventional low tidal volume ventilation (~6 ml/kg PBW) without $ECCO_2R$ in 79 patients with ARDS and did not find a difference in ventilator-free days or mortality at 60 days [24]. There was, however, an improvement in ventilator-free days in the more hypoxemic subgroup ($PaO_2/FiO_2 \leq 150$) [24].

Although it is generally accepted that limiting tidal volumes and plateau pressures with controlled ventilation modes should minimize VALI in the population requiring VV ECMO, preferences for volume control vs. pressure control ventilation vary significantly [4, 16, 25]. Advocates of volume control ventilation cite the ease of setting and studying a pre-specified tidal volume, as well as the added benefit of preventing large tidal volumes as lung compliance improves. However, VCV requires manually checking plateau pressures to analyze the compliance of the respiratory system. PCV has the benefit prespecifying a maximal inspiratory pressure and of being able to visually observe improving lung compliance by noting the change in tidal volume for a given driving pressure.

The most likely reason for the abundant use of PCV during ECMO is its use during the CESAR trial, the largest and most widely accepted comparison of ECMO to conventional ventilation in patients with potentially reversible respiratory failure [25]. In the CESAR trial, PCV settings

included a peak inspiratory pressure of 20–25 cm H_2O, PEEP of 10–15 cm H_2O, respiratory rate of 10 bpm, and FiO_2 of 0.3. Similar settings were used in 54% of ECMO patients in a recent observational study in three major centers [16]. Only 10% of patients received a volume controlled mode of ventilation again suggesting the widespread acceptance of the CESAR trial and the ESLO guidelines [16]. However, it remains unclear how these potential risks and benefits of VCV versus PCV translate into clinical outcomes.

The disadvantage to lung protective ventilation is primarily hypercarbia (and subsequent effects of increase $PaCO_2$) that can often be mitigated by ECMO or $ECCO_2R$. Right ventricular (RV) heart function must be considered in this setting as pulmonary vascular resistance and right ventricular stroke work index is likely to increase significantly even with relatively small (10 mm Hg) increases in $PaCO_2$ [31]. Lung recruitment may result in decreased hypoxemic pulmonary vasoconstriction and increased available pulmonary vasculature which may offset some of the increase in pulmonary vascular resistance seen with hypercarbia [32]. Alternative therapies for refractory hypoxemia including aerosolized prostacyclin may also mitigate hypercarbia-induced pulmonary hypertension, but prospective studies have failed to demonstrate a mortality benefit [33].

Finally at the extremes of ultralow tidal volume ventilation (nearing or below physiologic dead space), high levels of PEEP are required to maintain convective ventilation and prevent small airway closure and progressive atelectasis as seen during apneic oxygenation [34, 35].

3.2. Lung recruitment: prevention of atelectrauma

Lung recruitment does not exist in a vacuum, isolated from lung protection. Some strategies designed to maximize lung rest may exacerbate atelectrauma, other strategies selected to prevent atelectrauma may worsen alveolar overdistension. Ideally, these strategies can be combined to balance lung rest with lung recruitment. For example, most studies of ultralow tidal volume ventilation use relatively high amounts of PEEP to prevent atelectasis and ventilation/perfusion mismatch [7, 22, 24].

The goal of lung recruitment is to prevent atelectrauma by maintaining open all available lung units. The primary strategy to accomplish this is through the use of PEEP. The optimal PEEP for acute respiratory failure remains unknown [17–20, 36]. Even less data exists about the optimal PEEP for patients receiving ECMO. One retrospective observational study demonstrated an increase in mortality for lower PEEP during the first 7 days of ECMO [16]. It is notable that "lower PEEP" in this study was <12 cm H_2O which would include all patients at the ELSO guideline-recommended PEEP of 10 cm H_2O [16]. The SOLVE ARDS study is currently enrolling to compare PEEP set for optimal lung compliance versus zero PEEP (ZEEP), in patients receiving ECMO [37].

One alternative strategy to maintain an open lung is the regular use of recruitment maneuvers [18, 38]. Recruitment maneuvers have not been systematically studied in the ECMO population. Data on their use in acute respiratory failure is conflicting. When incorporated into a multifaceted open lung strategy, recruitment maneuvers failed to show mortality benefit when compared to conventional low tidal volume ventilation [18]. The lack of benefit of recruitment

http://dx.doi.org/10.5772/64248

maneuvers is often attributed to the bundling of many lung protective strategies in one intervention or to studies being underpowered to detect significant differences in outcomes [39]. Neither a systematic review nor the Cochrane meta-analysis demonstrated a mortality benefit to recruitment maneuvers [39, 40].

One downside of recruitment maneuvers relates to the heterogeneity of the lung in the setting of ARDS that may result in simultaneous alveolar overdistension and atelectasis during lung recruitment, particularly if PEEP is not adjusted or re-optimized following recruitment [41]. Alveolar overdistension may also be caused by excess use of PEEP with manifold negative consequences including decrease in venous return, decrease in cardiac index and increase in RV afterload [42].

Some centers have advocated the use of airway pressure release ventilation (APRV) during ECMO to augment lung recruitment. APRV is a "time-triggered, time-cycled, bi-level, pressure-regulated ventilation mode that allows a patient's spontaneous breathing pattern to be superimposed upon the mechanical ventilation pattern" [43]. Functionally, the patient is held at an inspiratory pressure level ($PEEP_{High}$) and with short "releases" to $PEEP_{Low}$ (typically less than 1.5 s) while able to breathe spontaneously throughout. Oxygenation is typically improved by increasing airway pressure (both $PEEP_{High}$ and $PEEP_{Low}$) or FiO_2, while ventilation is achieved through the number and duration of "releases" as well as by spontaneous ventilation. When the mode is adjusted so that the time spent at $PEEP_{High}$ is equal to, or less than $PEEP_{Low}$ the mode is often referred to as bilevel, bipap, or biphasic positive airway pressure.

Advocates of APRV assert that higher mean airway pressures improve both lung recruitment (decreasing microstrain) and functional residual capacity (FRC) (improving lung compliance) [43, 44]. They also add that facilitating spontaneous ventilation improves *V*/*Q* matching by increasing ventilation near the diaphragm in well-perfused areas, and may enhance venous return and cardiac output [43–46]. Alternatively, these benefits may simply reflect improved lung recruitment due to higher mean airway pressures, as similar beneficial effects are seen during lung protective ventilation with higher PEEP [44]. Furthermore, permissive hypercarbia during APRV either results in an increased work of breathing for the patient, or undesirably high release volumes, which likely offsets the benefits of lung recruitment by increasing tidal strain [43]. Given the lack of large trials comparing the use of APRV to conventional lung protective ventilation, the benefit of using APRV during ECMO remains theoretical at best. The in-progress EOLIA trial does permit APRV and subgroup analyses may delineate the role of APRV in the future management of MV during ECMO [26].

3.3. Additional concerns

In adults with acute respiratory failure undergoing MV, high plateau pressures due to decreased respiratory system compliance often trigger clinicians to limit tidal volumes (or driving pressures) and PEEP. In a subset of patients, however, the decrease in respiratory system compliance reflects a decrease in chest wall compliance rather than lung compliance. In these patients attempts to measure surrogates of pleural pressure such as esophageal manometry may facilitate further optimization of MV [47, 48]. Future studies, including the currently enrolling EPVent2 may help elucidate the benefits of esophageal pressure monitor-

ing in the management of MV in patients with acute respiratory failure [49]. Specifically, esophageal manometry may help select patients who can avoid VV ECMO, and those in whom atypical MV settings should be considered even during ECMO.

A high fraction of inspired oxygen increases shunt by increasing absorption atelectasis [50, 51]. In most settings, ECMO facilitates weaning of ventilator FiO_2 to ≤0.5. However, during ECMO weaning, ventilator FiO_2 is often increased. Given that ECMO weaning is a priority for 84% of ELSO centers surveyed, future studies should examine the optimal timing of ECMO weaning, including the necessary changes to MV to facilitate ECMO weaning and the negative effects of premature weaning [15].

4. Mechanical ventilation strategies during venoarterial extracorporeal membrane oxygenation

The lung protective principles described are generally applicable to all patients on ECMO. For VA ECMO patients, however, the cardiovascular effects of mechanical ventilation can be especially relevant. RV dysfunction is a predictor of poor outcomes and increased mortality for patients with left ventricular assist devices (LVADs) [52]. These devices are often the bridge/destination therapy for patients requiring VA ECMO [52]. Also, because VA ECMO may limit blood flow through the lungs, the optimal amount of alveolar ventilation may be different compared with patients requiring VV ECMO [53].

4.1. Lung volume and right ventricular afterload

The primary measurement of RV afterload is pulmonary vascular resistance (PVR) [54]. PVR is comprised of the resistance imparted by (1) alveolar vessels and (2) parenchymal vessels. PVR is altered significantly by increasing lung volumes and is minimized when the lung is at functional residual capacity (FRC). As lung volumes increase and alveoli become distended, alveolar pressure exceeds pulmonary arteriolar pressure, leading to vascular compression, and increased PVR. However, that same increase in lung volume also increases the radial traction on parenchymal lung vessels and improves their geometry; decreasing the contribution of parenchymal vessels to PVR [54]. Thus, generally, as lung volume increases, the contribution of alveolar vasculature to total PVR increases, while the contribution of parenchymal vasculature decreases. The net effect is a balance between these two phenomena in which PVR is relatively stable at normal lung volumes [54].

In normal individuals, PVR is optimized (at its lowest point) when the lung is at FRC [54]. It is important to note that lung volumes slightly below FRC may be more deleterious to PVR than lung volumes slightly above FRC. As alveolar units collapse, decreased oxygenation leads to hypoxic vasoconstriction, which further increases PVR above the expected increase from parenchymal lung vessels. Thus, one approach to decreasing RV afterload using MV would be ventilation with relatively low tidal volumes at or slightly above FRC. This would optimize pulmonary mechanics to decrease PVR while also minimizing volutrauma to the susceptible segments of the lung.

http://dx.doi.org/10.5772/64248

4.2. PEEP and venoarterial extracorporeal membrane oxygenation

In the ideal physiologic scenario during VA ECMO, PEEP would be optimized to maintain FRC thus optimizing PVR, and minimizing the negative effects on RV preload (unless clinically desired). However, little is known clinically about the optimal PEEP in the setting of VA ECMO.

The use of PEEP to maintain FRC is clinically challenging. Helium dilution and other traditional methods of determining FRC are highly impractical in the clinical setting. While techniques involving nitrogen washout or partial CO_2 rebreathing have been proposed, and may be automated on some ventilators, they have not been widely adopted [55, 56]. Thus, "optimal" PEEP is often determined by the PEEP that maximizes oxygenation, improves lung compliance, or decreases lung stress [57]. Optimal PEEP has rarely been studied in the presence of ECMO, and is often extrapolated from studies of ARDS. For example, in animal studies of ARDS, optimal PEEP is often cited as the point at which thoracopulmonary dynamic and static compliance is maximized, which correlates with the PEEP value immediately above that at which FRC begins to decrease [58, 59]. In these studies, PEEP was incrementally decreased to determine the point at which respiratory system compliance decreased—thereby approximating the minimal amount of "open lung" PEEP required to maintain FRC. There is mixed evidence on whether optimal PEEP should be determined using this methodology [60, 61]. Others argue that incremental PEEP combined with dynamic compliance monitoring allows for the simultaneous evaluation of recruitment and compliance [61]. More recent studies using computed tomography-guided optimal PEEP have reported that lung recruitability and the amount of PEEP required to maintain alveolar recruitment are independent and therefore the optimal PEEP may not be related to lung recruitability [62].

PEEP, when it contributes to total intrathoracic pressure, affects venous return to the heart [63]. As PEEP increases above resting pleural pressure, intrathoracic pressure increases; decreasing venous return to the right heart and therefore decreasing RV preload [64]. These effects are often seen as negative, but in the correct setting may be beneficial [64, 65]. For example, patients with afterload-dependent left ventricular (LV) heart failure, including many patients on VA ECMO, may benefit from the decreased RV preload associated with the addition of PEEP, particularly if PEEP is helping to minimize PVR [64, 66]. Conversely, patients with a preload dependent cardiac output (CO) could potentially benefit from lower levels of positive pressure ventilation and PEEP. In this patient population, if PEEP is required, careful attention should be paid to minimizing the effects on cardiac preload.

Many argue that in the ARDS patient, true optimal PEEP does not exist, maintaining that it is not clinically realistic to expect all of the beneficial effects of PEEP to converge on a particular value for a given patient [67]. A similar argument could be extended to patients on ECMO. As such, given a lack of direct evidence, it remains in the hands of the clinician to determine which parameters are most important to optimize for their individual patients.

4.3. Inhaled pulmonary vasodilators and right ventricular function

RV dysfunction is common in patients receiving both VV and VA ECMO. In patients with moderate-to-severe ARDS (likely candidates for VV ECMO), the prevalence of RV dysfunction is approximately 20%. RV dysfunction is more common in patients with pneumonia, those with high driving pressures (≥18 cm H_2O), low PaO_2/F_iO_2 ratio (<150 mmHg), and high $PaCO_2$ (≥48 mmHg); patients who would also be more likely to meet criteria for VV ECMO [68]. Similarly, in LVAD patients (a cohort related to VA ECMO patients), RV dysfunction may be seen in up to 40% of cases [69].

While inhaled pulmonary vasodilators have long served as adjuvant therapies for patients with increased PVR receiving LVADs [69], the data supporting their use in ARDS and VV ECMO is less clear [70]. Inhaled nitric oxide (iNO) is commonly used in pediatric patients with persistent pulmonary hypertension [71], and adults with LVADs [69]. It may temporarily improve oxygenation in patients with acute respiratory failure [72, 73], but has not been shown to improve mortality [70], comes with substantial cost (**Table 1**) and at doses above 20 ppm has an escalating side effect profile [72, 74]. Inhaled aerosolized prostacyclin (iAP) has also been used in the treatment of pulmonary hypertension [75], as well as refractory hypoxemia [72]. Similar to iNO, no mortality benefit has been demonstrated for its noncardiac use [33], and drug delivery depends on delivery setup [74]. However, the cost savings compared with iNO may be as large as 17-fold [76]. Controlled studies on the use of inhaled vasodilators specifically on ECMO patients are currently lacking.

Medication	Administration methods	Dosing	Cost per day
Inhaled aerosolized prostacyclin	Nebulization	5–50 ng/kg/min (can be fixed or weight-based and delivered drug will vary according to setup)	$100–900
Inhaled nitric oxide	Direct gas delivery (diluted with nitrogen and oxygen)	5–20 ppm (range 1–80 ppm)	$2000–5000

Table 1. Inhaled vasodilators dosing and cost [75, 76].

Although inhaled nitric oxide and prostacyclins are well-established therapies for patients with RV dysfunction, associated with increased transpulmonary gradients, there are other agents that may be beneficial. Milrinone, a type III phosphodiesterase inhibitor, typically used intravenously as an inotrope with systemic vasodilatory effects, has been used successfully as inhaled pulmonary vasodilator [77, 78]. The use of inhaled sodium nitroprusside has also been reported [79]. Despite a lack of firm scientific evidence, these agents are often used as adjuvants in patients with RV dysfunction on ECMO (given a plausible physiologic benefit and lack of evidence of harm) and may be considered in patients with elevated transpulmonary gradients refractory to the MV maneuvers described.

4.4. Venoarterial extracorporeal membrane oxygenation and ventilation of the lungs

Protective and ultraprotective MV settings can lead to hypercarbia. In patients on VV ECMO, this concern is mitigated significantly because of the ECMO circuit's ability to effectively clear CO_2. In the patient on VA ECMO, however, alveolar hypoventilation may be a therapeutic tool.

Patients on VA ECMO have a unique physiology where the pulmonary circulation (Q_p) is unlinked from, and is necessarily lower than, the systemic circulation (Q_s) because a significant amount of the total CO (Q_T) is shunted through the VA ECMO circuit (Q_{ecmo}). This decoupling of the pulmonary circulation from total cardiac output may lead to unusual ventilation and perfusion conditions in the lung. In patients on VA ECMO, the decrease in Q_p can be expected to decrease pulmonary arterial pressures (P_{pa}). This decrease in pulmonary perfusion should increase areas of relative dead space if ventilation is held constant. However, in the lung injured patient, pulmonary perfusion is likely to be heterogeneous worsening V/Q matching and increasing both shunt and dead space. This decreased Q_p and P_{pa} requires some additional considerations when selecting a ventilation strategy for patients on VA ECMO.

Patients on VA ECMO with "normal" alveolar ventilation but a relatively low flow through the pulmonary vascular system (low Q_p) may be at risk for significant localized pulmonary hypocapnia and alkalosis. In a rat lung model, hypocapnia, independently of pH, directly impaired alveolar fluid reabsorption [80]. Hypocapnia also has direct bronchoconstricting effects, demonstrated to decrease lung compliance in small studies of human subjects [81]. Although both impaired alveolar fluid reabsorption and bronchoconstriction have been noted to be reversible with a return to normocapnia, there is increasing evidence that hypocapnia is not innocuous and may exert directly harmful effects to the lungs [53]. Conversely, there is animal data to suggest that therapeutic hypercapnia may attenuate pulmonary inflammation and reduce free radical injury; there is also some support for the therapeutic use of hypercapnea [82, 83]. These positive effects need to be balanced against the increase in PVR and RV afterload that can be caused by hypercarbia. Therefore, while lung protective ventilation is recommended in patients receiving ECMO, the benefit of avoiding localized hypocarbia may make ultraprotective ventilation more enticing. Future studies into the therapeutic benefit of hypercapnia in these patients will be needed to offset the downsides of increased RV afterload.

4.5. Venoarterial extracorporeal membrane oxygenation and arterial blood gas measurements

Arterial blood gas measurements are not normally representative of pulmonary function for patients on VA ECMO. For patients who are on VV ECMO, oxygenated blood from the ECMO circuit is mixed with deoxygenated venous blood prior to entering the right ventricle. Therefore, the patient's lungs increase the oxygen content and clear CO_2 for all of the blood entering the patient's arterial circulation equally. If the ECMO flow is increased on VV ECMO, the oxygen content of all of the patient's blood is increased. Similarly, when native pulmonary CO_2 clearance improves all of the patient's arterial blood will reflect these changes.

For patients on VA ECMO, oxygenated blood from the ECMO circuit is returned to the patient distal to their native pulmonary circulation. Depending the patient's native cardiac output (Q_p), this effectively "isolates" the lung from interrogation via arterial blood gases. It is not unusual, for example, for a patient on VA ECMO to have Q_p equal to 20% of Q_s (with the other 80% coming from Q_{ecmo}). Pulmonary function would then accounts for, at most, 20% of the oxygen content found in the peripheral arterial blood. However, even this estimate may be misleading, as ECMO blood may not mix uniformly with blood ejected from the native heart at the site where it is sampled by as arterial blood gas. As a result, arterial blood gas analysis in a patient on VA ECMO may provide more information about the patient's native cardiac function then native pulmonary function. In other words, the arterial blood gas reflects the patient's native cardiac output (Q_p) relative to Q_{ecmo} more than the effects of pulmonary oxygenation or ventilation. Consequently, making decisions about MV based on arterial blood gas analyses in patients on VA ECMO should be done cautiously.

Ironically, when cardiac output improves in patients on VA ECMO it is normal to find a worsening PaO_2 on arterial blood gas measurement. While this should not occur in patients with satisfactory lung function, as Q_p increases in a patient with poor native lung function (and represents and increasingly higher percentage of Q_s) a lack of oxygenation from the native lung would be unmasked. At that point, it may become necessary to either escalate MV settings or transition to veno-venoarterial ECMO. Conversely, when arterial blood gases indicate a very high PaO_2 (approximating the PaO_2 found in the arterial limb of the ECMO circuit), it may indicate worsening cardiac function rather than improving lung function.

5. Conclusion

The primary goal of mechanical ventilation in patients on ECMO should be optimization of respiratory variables to permit healing from the pathologic state. Much of the data used to establish guidelines for mechanical ventilation strategies in ECMO patients is derived from studies of patients with ARDS. Similar to ARDS, the prevention of VALI remains of central importance to pulmonary recovery for patients on ECMO. Furthermore, by mitigating hypercarbia, ECMO may lift some of the previously encountered limits on MV permitting ultraprotective ventilation to be used.

Hemodynamic effects of MV are important considerations for patients on ECMO. Many patients on both VV and VA ECMO for ARDS have significant RV compromise and may benefit from optimized RV preload and afterload by closely attending to intrathoracic pressures and pulmonary lung volumes [84].

Finally, it is important to consider the possibility that patients on ECMO may not require invasive MV support at all. There has been at least one case report of a patient undergoing VA ECMO support without the need for mechanical ventilation and only minimal analgosedation [85]. Although additional data will need to be obtained before definitive guidelines can help improve the quality of MV during ECMO, it is important to consider that, for some patients, the best strategy for mechanical ventilation is to remove it entirely.

Author details

David Stahl MD* and Victor Davila MD

*Address all correspondence to: david.stahl@osumc.edu

Department of Anesthesiology, The Ohio State University, Columbus, OH, USA

References

[1] Morris, A.H., et al., *Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome.* Am J Respir Crit Care Med, 1994. 149(2 Pt 1): p. 295–305.

[2] Zapol, W.M., et al., *Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study.* JAMA, 1979. 242(20): p. 2193–6.

[3] Davies, A., et al., *Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome.* JAMA, 2009. 302(17): p. 1888–95.

[4] Brodie, D. and M. Bacchetta, *Extracorporeal membrane oxygenation for ARDS in adults.* N Engl J Med, 2011. 365(20): p. 1905–14.

[5] The Acute Respiratory Distress Syndrome Network. N Engl J Med, 2000. 342(18): p. 1301–8. http://www.nejm.org/doi/full/10.1056/NEJM200005043421801#t=article.

[6] Amato, M.B., et al., *Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome.* N Engl J Med, 1998. 338(6): p. 347–54.

[7] Kuchnicka, K. and D. Maciejewski, *Ventilator-associated lung injury.* Anaesthesiol Intensive Ther, 2013. 45(3): p. 164–70.

[8] Oeckler, R.A. and R.D. Hubmayr, *Ventilator-associated lung injury: a search for better therapeutic targets.* Eur Respir J, 2007. 30(6): p. 1216–26.

[9] Chiumello, D., et al., *Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome.* Am J Respir Crit Care Med, 2008. 178(4): p. 346–55.

[10] Gattinoni, L., et al., *Ventilator-induced lung injury: the anatomical and physiological framework.* Crit Care Med, 2010. 38(10 Suppl): p. S539–48.

[11] Whitehead, T. and A.S. Slutsky, *The pulmonary physician in critical care * 7: ventilator induced lung injury.* Thorax, 2002. 57(7): p. 635–42.

[12] Uhlig, S., *Ventilation-induced lung injury and mechanotransduction: stretching it too far?* Am J Physiol Lung Cell Mol Physiol, 2002. 282(5): p. L892–6.

[13] *Extracorporeal Life Support Organization (ESLO) Guidelines for Adult Respiratory Failure v1.3*. December 2013; Available from: http://www.elso.org/Portals/0/IGD/Archive/

FileManager/989d4d4d14cusersshyerdocumentselsoguidelinesforadultrespiratoryfailure1.3.pdf.

[14] Schmidt, M., et al., *Mechanical ventilation during extracorporeal membrane oxygenation.* Crit Care, 2014. 18(1): p. 203.

[15] Marhong, J.D., et al., *Mechanical ventilation during extracorporeal membrane oxygenation. An international survey.* Ann Am Thorac Soc, 2014. 11(6): p. 956–61.

[16] Schmidt, M., et al., *Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study.* Crit Care Med, 2015. 43(3): p. 654–64.

[17] Brower, R.G., et al., *Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome.* N Engl J Med, 2004. 351(4): p. 327–36.

[18] Meade, M.O., et al., *Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.* JAMA, 2008. 299(6): p. 637–45.

[19] Mercat, A., et al., *Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial.* JAMA, 2008. 299(6): p. 646–55.

[20] Briel, M., et al., *Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis.* JAMA, 2010. 303(9): p. 865–73.

[21] Esteban, A., et al., *Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study.* JAMA, 2002. 287(3): p. 345–55.

[22] Terragni, P.P., et al., *Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal.* Anesthesiology, 2009. 111(4): p. 826–35.

[23] Terragni, P.P., et al., *Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome.* Am J Respir Crit Care Med, 2007. 175(2): p. 160–6.

[24] Bein, T., et al., *Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO_2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study.* Intensive Care Med, 2013. 39(5): p. 847–56.

[25] Peek, G.J., 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.* Lancet, 2009. 374(9698): p. 1351–63.

[26] *Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) Study Protocol NCT01470703.*

[27] Frank, J.A., et al., *Low tidal volume reduces epithelial and endothelial injury in acid-injured rat lungs.* Am J Respir Crit Care Med, 2002. 165(2): p. 242–9.

[28] Bein, T., et al., *Pumpless extracorporeal removal of carbon dioxide combined with ventilation using low tidal volume and high positive end-expiratory pressure in a patient with severe acute respiratory distress syndrome.* Anaesthesia, 2009. 64(2): p. 195–8.

[29] Hager, D.N., et al., *Tidal volume reduction in patients with acute lung injury when plateau pressures are not high.* Am J Respir Crit Care Med, 2005. 172(10): p. 1241–5.

[30] Mauri, T., et al., *Long-term extracorporeal membrane oxygenation with minimal ventilatory support: a new paradigm for severe ARDS?* Minerva Anestesiol, 2012. 78(3): p. 385–9.

[31] Viitanen, A., M. Salmenpera, and J. Heinonen, *Right ventricular response to hypercarbia after cardiac surgery.* Anesthesiology, 1990. 73(3): p. 393–400.

[32] Maung, A.A. and L.J. Kaplan, *Airway pressure release ventilation in acute respiratory distress syndrome.* Crit Care Clin, 2011. 27(3): p. 501–9.

[33] Afshari, A., et al., *Aerosolized prostacyclin for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).* Cochrane Database Syst Rev, 2010(8): p. Cd007733.

[34] Nielsen, N.D., et al., *Apneic oxygenation combined with extracorporeal arteriovenous carbon dioxide removal provides sufficient gas exchange in experimental lung injury.* Asaio J, 2008. 54(4): p. 401–5.

[35] Kallet, R.H., et al., *Lung collapse during low tidal volume ventilation in acute respiratory distress syndrome.* Respir Care, 2001. 46(1): p. 49–52.

[36] Santa Cruz, R., et al., *High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome.* Cochrane Database Syst Rev, 2013. 6: p. Cd009098.

[37] *Strategies for Optimal Lung Ventilation in ECMO for ARDS: The SOLVE ARDS Study (SOLVE ARDS) Study Protocol NCT01990456.*

[38] Gattinoni, L., et al., *Lung recruitment in patients with the acute respiratory distress syndrome.* N Engl J Med, 2006. 354(17): p. 1775–86.

[39] Hodgson, C., et al., *Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation.* Cochrane Database Syst Rev, 2009(2): p. Cd006667.

[40] Fan, E., et al., *Recruitment maneuvers for acute lung injury: a systematic review.* Am J Respir Crit Care Med, 2008. 178(11): p. 1156–63.

[41] Grasso, S., et al., *Inhomogeneity of lung parenchyma during the open lung strategy: a computed tomography scan study.* Am J Respir Crit Care Med, 2009. 180(5): p. 415–23.

[42] Toth, I., et al., *Hemodynamic and respiratory changes during lung recruitment and descending optimal positive end-expiratory pressure titration in patients with acute respiratory distress syndrome.* Crit Care Med, 2007. 35(3): p. 787–93.

[43] Kallet, R.H., *Patient-ventilator interaction during acute lung injury, and the role of spontaneous breathing: part 2: airway pressure release ventilation.* Respir Care, 2011. 56(2): p. 190–203; discussion 203–6.

[44] Kollisch-Singule, M., et al., *Mechanical breath profile of airway pressure release ventilation: the effect on alveolar recruitment and microstrain in acute lung injury.* JAMA Surg, 2014. 149(11): p. 1138–45.

[45] Putensen, C., et al., *Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome.* Am J Respir Crit Care Med, 1999. 159(4 Pt 1): p. 1241–8.

[46] Yoshida, T., et al., *The impact of spontaneous ventilation on distribution of lung aeration in patients with acute respiratory distress syndrome: airway pressure release ventilation versus pressure support ventilation.* Anesth Analg, 2009. 109(6): p. 1892–900.

[47] Grasso, S., et al., *ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure.* Intensive Care Med, 2012. 38(3): p. 395–403.

[48] Talmor, D., et al., *Mechanical ventilation guided by esophageal pressure in acute lung injury.* N Engl J Med, 2008. 359(20): p. 2095–104.

[49] [cited 2016 February 29]; EPVent 2- A Phase II Study of Mechanical Ventilation Directed by Transpulmonary Pressures (EPVent2) Study Protocol NCT01681225]. Available from: https://clinicaltrials.gov/ct2/show/NCT01681225.

[50] Aboab, J., et al., *Effect of inspired oxygen fraction on alveolar derecruitment in acute respiratory distress syndrome.* Intensive Care Med, 2006. 32(12): p. 1979–86.

[51] Santos, C., et al., *Pulmonary gas exchange response to oxygen breathing in acute lung injury.* Am J Respir Crit Care Med, 2000. 161(1): p. 26–31.

[52] Meineri, M., A.E. Van Rensburg, and A. Vegas, *Right ventricular failure after LVAD implantation: prevention and treatment.* Best Pract Res Clin Anaesthesiol, 2012. 26(2): p. 217–29.

[53] Laffey, J.G., D. Engelberts, and B.P. Kavanagh, *Injurious effects of hypocapnic alkalosis in the isolated lung.* Am J Respir Crit Care Med, 2000. 162(2 Pt 1): p. 399–405.

[54] Shekerdemian, L. and D. Bohn, *Cardiovascular effects of mechanical ventilation.* Arch Dis Child, 1999. 80(5): p. 475–80.

[55] Brewer, L.M., et al., *Measurement of functional residual capacity by modified multiple breath nitrogen washout for spontaneously breathing and mechanically ventilated patients.* Br J Anaesth, 2011. 107(5): p. 796–805.

[56] Brewer, L.M., D.G. Haryadi, and J.A. Orr, *Measurement of functional residual capacity of the lung by partial CO_2 rebreathing method during acute lung injury in animals.* Respir Care, 2007. 52(11): p. 1480–9.

[57] Chiumello, D., et al., *Bedside selection of positive end-expiratory pressure in mild, moderate, and severe acute respiratory distress syndrome.* Crit Care Med, 2014. 42(2): p. 252–64.

[58] Lambermont, B., et al., *Comparison of functional residual capacity and static compliance of the respiratory system during a positive end-expiratory pressure (PEEP) ramp procedure in an experimental model of acute respiratory distress syndrome.* Crit Care, 2008. 12(4): p. R91.

[59] Suarez-Sipmann, F., et al., *Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study.* Crit Care Med, 2007. 35(1): p. 214–21.

[60] Hickling, K.G., *Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs.* Am J Respir Crit Care Med, 2001. 163(1): p. 69–78.

[61] Stahl, C.A., et al., *Dynamic versus static respiratory mechanics in acute lung injury and acute respiratory distress syndrome.* Crit Care Med, 2006. 34(8): p. 2090–8.

[62] Cressoni, M., et al., *Compressive forces and computed tomography-derived positive end-expiratory pressure in acute respiratory distress syndrome.* Anesthesiology, 2014. 121(3): p. 572–81.

[63] Stahl, D.L., et al., *Case scenario: power of positive end-expiratory pressure: use of esophageal manometry to illustrate pulmonary physiology in an obese patient.* Anesthesiology, 2014. 121(6): p. 1320–6.

[64] Duke, G.J., *Cardiovascular effects of mechanical ventilation.* Crit Care Resusc, 1999. 1(4): p. 388–99.

[65] Jardin, F. and A. Vieillard-Baron, *Is there a safe plateau pressure in ARDS? The right heart only knows.* Intensive Care Med, 2007. 33(3): p. 444–7.

[66] Wiesen, J., et al., *State of the evidence: mechanical ventilation with PEEP in patients with cardiogenic shock.* Heart, 2013. 99(24): p. 1812–7.

[67] Gattinoni, L., E. Carlesso, and M. Cressoni, *Selecting the 'right' positive end-expiratory pressure level.* Curr Opin Crit Care, 2015. 21(1): p. 50–7.

[68] Mekontso Dessap, A., et al., *Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact.* Intensive Care Med, 2015.

[69] Argenziano, M., et al., *Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension.* Ann Thorac Surg, 1998. 65(2): p. 340–5.

[70] Adhikari, N.K., et al., *Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis.* Crit Care Med, 2014. 42(2): p. 404–12.

[71] Roberts, J.D., Jr., et al., *Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group.* N Engl J Med, 1997. 336(9): p. 605–10.

[72] Liu, L.L., et al., *Special article: rescue therapies for acute hypoxemic respiratory failure.* Anesth Analg, 2010. 111(3): p. 693–702.

[73] Ichinose, F., J.D. Roberts, Jr., and W.M. Zapol, *Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential.* Circulation, 2004. 109(25): p. 3106–11.

[74] Dzierba, A.L., et al., *A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome.* Pharmacotherapy, 2014. 34(3): p. 279–90.

[75] Hill, N.S., I.R. Preston, and K.E. Roberts, *Inhaled therapies for pulmonary hypertension.* Respir Care, 2015. 60(6): p. 794–802; discussion 802–5.

[76] Torbic, H., et al., *Inhaled epoprostenol vs inhaled nitric oxide for refractory hypoxemia in critically ill patients.* J Crit Care, 2013. 28(5): p. 844–8.

[77] Lamarche, Y., et al., *Preliminary experience with inhaled milrinone in cardiac surgery.* Eur J Cardiothorac Surg, 2007. 31(6): p. 1081–7.

[78] Laflamme, M., et al., *Preliminary experience with combined inhaled milrinone and prostacyclin in cardiac surgical patients with pulmonary hypertension.* J Cardiothorac Vasc Anesth, 2015. 29(1): p. 38–45.

[79] Pasero, D., et al., *Inhaled nitric oxide versus sodium nitroprusside for preoperative evaluation of pulmonary hypertension in heart transplant candidates.* Transplant Proc, 2013. 45(7): p. 2746–9.

[80] Myrianthefs, P.M., et al., *Hypocapnic but not metabolic alkalosis impairs alveolar fluid reabsorption.* Am J Respir Crit Care Med, 2005. 171(11): p. 1267–71.

[81] Cutillo, A., et al., *Effect of hypocapnia on pulmonary mechanics in normal subjects and in patients with chronic obstructive lung disease.* Am Rev Respir Dis, 1974. 110(1): p. 25–33.

[82] Laffey, J.G., et al., *Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion.* Am J Respir Crit Care Med, 2000. 162(6): p. 2287–94.

[83] Ni Chonghaile, M., B. Higgins, and J.G. Laffey, *Permissive hypercapnia: role in protective lung ventilatory strategies.* Curr Opin Crit Care, 2005. 11(1): p. 56–62.

[84] Repesse, X., C. Charron, and A. Vieillard-Baron, *Acute cor pulmonale in ARDS: rationale for protecting the right ventricle.* Chest, 2015. 147(1): p. 259–65.

[85] van Houte, J., et al., *Non-intubated recovery from refractory cardiogenic shock on percutaneous VA-extracorporeal membrane oxygenation.* Neth Heart J, 2015. 23(7–8): p. 386–8.