AJRCCM Articles in Press. Published on 14-November-2019 as 10.1164/rccm.201907-1283CI

Mechanical Ventilation for ARDS During Extracorporeal Life Support: Research and Practice

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AJRCCM Articles in Press. Published on 14-November-2019 as 10.1164/rccm.201907-1283CI

Author contributions: All authors provided substantial contributions to the conception or design of the work. DA and DB drafted the work, all authors revised it critically for important intellectual content. All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sources of support: none

Running header: Mechanical ventilation for ARDS during ECLS

Descriptor number: 4.2 ALI/ARDS: Diagnosis & Clinical Issues

Total word count: 4491

Take Home Message
The goal of invasive mechanical ventilation during ECLS for ARDS should be to decrease the intensity of ventilation with the aim of reducing VILI and maximizing the potential benefit of ECLS. The EOLIA ventilator protocol during ECLS provides a default minimum standard for such ventilation. Future studies should focus on more precisely delineating the best strategies for optimizing invasive mechanical ventilation during ECLS for ARDS.

Conflicts of Interests
MS has received lectures fees from Getinge, Xenios and Dräger, outside the submitted work. EF reports personal fees from ALung Technologies Inc., personal fees from MC3 Cardiopulmonary, outside the submitted work. ECG is supported by an Early Career Investigator Award from the Canadian Institutes of Health Research (AR7-162822); research support in the form of equipment from Timpel and Getinge and personal fees from Getinge, outside the submitted work. JJMcN reports grants from Northern Ireland Health and Social Care Research and Development Agency and NIHR HTA, with in-kind support from ALung Technologies, Inc, for a clinical trial of ECCO2R, outside the submitted work. AC reports grants and personal fees from Maquet, grants and personal fees from Baxter, outside the submitted work. NDF reports personal fees from Sedana Medical, personal fees from Baxter, personal fees from Getinge, outside the submitted work. DFM has received funding from the NIHR HTA and Northern Ireland Health and Social Care Research and Development Agency with in-kind support from ALung Technologies, Inc for a clinical trial of ECCO2R, outside the submitted work; personal fees from consultancy for Peptinnovate, Bayer, GlaxoSMithKline, Boehringer Ingelheim, outside the submitted work; grants from NIHR and other funders as an investigator for clinical trials in ARDS, outside the submitted work; patent US8962032 for a novel treatment for ARDS issued to his institution, outside the submitted work. AP receives consulting fees from Xenios, Maquet, Baxter, outside the submitted work. AM reports personal fees from Faron Pharmaceuticals, personal fees from Air Liquide Medical Systems, grants and personal fees from Fisher and Paykel, grants and personal fees from Covidien, personal fees from Pfizer, personal fees from Resmed, personal fees from Drager, outside the submitted work. VP reports one-time travel fees and an honorarium from Xenios Medical, outside the submitted work. LB reports grants from Medtronic-Covidien, non-financial support from Air Liquide, grants and non-financial support from Fisher and Paykel, non-financial support from General Electric, non-financial support from

Philips, non-financial support from Sentec, outside the submitted work. DB reports fees to his university from ALung Technologies, personal fees from Baxter and anticipated fees from BREETHE and Xenios, and an unpaid association with Hemovent, outside the submitted work. DA, TP, JRB, NP, MEW, MQ, JF, CL Hodgson, CL Hough, TM, VMR, KR, and KS have no disclosures to report.

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Abstract

Ventilator-induced lung injury remains a key contributor to the morbidity and mortality of the acute respiratory distress syndrome. Efforts to minimize this injury are typically limited by the need to preserve adequate gas exchange. In the most severe forms of the syndrome, extracorporeal life support is increasingly being deployed for severe hypoxemia or hypercapnic acidosis refractory to conventional ventilator management strategies. Data from a recent randomized controlled trial, a post-hoc analysis of that trial, a meta-analysis, and a large, international, multicenter observational study, all suggest that extracorporeal life support, when combined with lower tidal volumes and airway pressures than the current standard of care, may improve outcomes compared with conventional management in patients with the most severe forms of the acute respiratory distress syndrome. These findings raise important questions not only about the optimal ventilator strategies for patients receiving extracorporeal support, but how various mechanisms of lung injury in the acute respiratory distress syndrome may potentially be mitigated by ultra-lung-protective ventilation strategies when gas exchange is sufficiently managed with the extracorporeal circuit. Additional studies are needed to more precisely delineate the best strategies for optimizing invasive mechanical ventilation in this patient population.

Total word count for abstract: 192

Outline

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Key points

- Ventilator-induced lung injury is a major contributor to morbidity and mortality in ARDS, driven in large part by injurious mechanical forces
- ECLS can supplement or supplant native lung gas exchange in ARDS, allowing for reductions in the mechanical forces contributing to ventilator-induced lung injury
- Conventional management strategies (standard of care lung-protective ventilation, prone positioning, PEEP titration, conservative fluid balance, and perhaps neuromuscular blockade) should be optimized prior to consideration of ECLS
- The ventilation strategies employed in the EOLIA trial are a reasonable default standard of care for invasive mechanical ventilation in patients with ARDS receiving ECMO, although we suggest targeting respiratory rates of 10 (the lower range in EOLIA) or less
- Excess work of breathing may promote lung injury in ARDS and should be avoided, whether or not ECLS is used
- More data are needed to determine the ventilator parameters that are associated with improved short- and long-term outcomes

Introduction

Extracorporeal life support (ECLS) can support gas exchange in patients with the acute respiratory distress syndrome (ARDS) whose oxygenation or ventilation cannot be maintained adequately with best practice conventional mechanical ventilation and adjunctive therapies, including prone positioning (1). ECLS enables the use of lower tidal volumes and airway pressures in patients whose gas exchange could otherwise be maintained only at the expense of injurious mechanical ventilation strategies (1-3). Ventilator-induced lung injury (VILI) is a key contributor to morbidity and mortality in ARDS (4) particularly among those considered for ECLS. Therefore adopting lung-protective ventilator strategies beyond the current standard of care concomitantly with the application of ECLS in these patients, appears to be key to realizing the potential benefit of this strategy. The objectives of this review are to summarize the current understanding of the role ECLS may play in minimizing VILI; suggest best practice mechanical ventilation strategies during ECLS given the existing data; describe the interplay between ECLS, gas exchange, and ventilator parameters; and, lastly, identify the areas of research that are needed to better inform the optimal management of mechanical ventilation and spontaneous breathing efforts during ECLS. The suggestions put forth in this narrative review reflect consensus expert opinions of clinicians and researchers with expertise in mechanical ventilation, ARDS, and ECLS that originated from a roundtable discussion at the 4th Annual International ECMO Network Scientific Meeting in Rome, Italy in 2018 (https://www.internationalecmonetwork.org/conferences).

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Conventional approaches to minimizing VILI

The main focus of mechanical ventilation in ARDS is to provide adequate gas exchange while limiting injury to the organs (4), the contributors to which include barotrauma, volutrauma, atelectrauma, ergotrauma, myotrauma, and biotrauma (Figure 1) (5-9). Lung injury may be further exacerbated by spontaneous breathing efforts and patient-ventilator dyssynchrony with a consequent increase in transpulmonary pressures (10-12). Tidal volume, plateau airway pressure, driving pressure, respiratory rate, inspiratory flow, and excessive positive end-expiratory pressure (PEEP) have all been implicated as contributors to VILI to varying degrees (4, 9, 13), though it remains unclear which of these parameters are most important in reducing injury. Driving pressure appears to be the ventilation variable that correlates most strongly with mortality (14), though a causal relationship between driving pressure and outcome has not been firmly established (14-17). Many of these factors have been incorporated into mathematical equations reflecting the amount of energy transferred from the ventilator to the respiratory system, referred to as 'mechanical power' (13).

Volume- and pressure-limited ventilation (tidal volume of 4-8 mL/kg predicted body weight, frequently referred to as "6 ml/kg" because that is the initial goal after stabilization, and plateau airway pressure of 30 cm H_2O or less) and prone positioning have demonstrated survival benefits in ARDS (18-20), and have been recommended in recent clinical practice guidelines (21). Additional strategies, including high levels of PEEP, and, to a lesser degree, recruitment maneuvers may likewise be beneficial, although the efficacy of these approaches have been called into question given the results of a randomized controlled trial that found increased mortality in patients who received a lung recruitment and titrated PEEP strategy (16, 22, 23). Although the *Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome*

(ROSE) trial did not demonstrate a benefit from the addition of a fixed-dose, 48-hour infusion of neuromuscular blockade in patients with ARDS and a PaO_2:FIO_2 <150 mm Hg (24), the use of neuromuscular blockade may nonetheless be considered on an individualized basis, particularly in the setting of ventilator dyssynchrony (e.g. double-triggering), which may increase the propensity for VILI, or as needed for the implementation of prone positioning (25-28). Although not specifically addressed in this narrative review, a restrictive fluid management strategy may have additional benefits in ARDS (29).

Rationale for ultra-lung-protective ventilation

Data supporting ultra-lung-protective ventilation

Both preclinical and human data suggest VILI continues to occur during ARDS despite adherence to best practices conventional ventilator management (30-32). Animal models have highlighted the injurious effects of cyclic alveolar stretch, particularly at high tidal volumes or in the context of hyperoxemia (33-35). Frank *et al*. demonstrated that lung injury in a rat model of ARDS decreased when tidal volume was lowered from 12 mL/kg to 6 mL/kg, but lung injury appeared to be minimized even further when tidal volume was lowered to 3 mL/kg (30). *Post hoc* analysis of the *Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome* (ARMA) trial suggests that there is a consistent correlation between lower tidal volumes, lower plateau airway pressures, and improved survival (31), and Needham and colleagues demonstrated that this relationship continues in a linear fashion below the traditional lung-protective tidal volume of 6 mL/kg (32).

Limitations in achieving ultra-lung-protective ventilation

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With no apparent lower limit to the mortality reduction associated with volume and pressure reductions during ARDS management (31, 32), it may be reasonable to conclude that tidal volumes and airway pressures should be reduced below the current standard of care in order to minimize VILI and maximize outcomes. If tidal volumes of 6 mL/kg (and corresponding plateau airway pressures of 30 cm H_2O or less) are considered 'lung-protective' (18), then perhaps even lower tidal volumes (i.e. <4 mL/kg) and airway pressures (e.g. <25 cm H_2O) should be referred to as 'ultra-lung-protective' ventilation. Respiratory rate, which from a VILI perspective may be viewed as the frequency with which the lung is exposed to injurious volumes and pressures, has likewise been proposed as a potential target for VILI reduction (13, 36, 37).

The main physiological barrier to achieving ultra-lung-protective ventilation in some patients with ARDS (particularly those with the most severe forms of ARDS) is the development of intolerable respiratory acidosis, which in turn often necessitates a high respiratory rate that may or may not be sufficient to mitigate the acidemia and may itself add to VILI. In fact, in order to maintain acceptable pH during the application of even traditional low tidal volumes (6.2-6.5 mL/kg) during the ARMA trial, respiratory rates were substantially higher (29-30 breaths per minute) than in the high tidal volume control group (16-20 breaths per minute) over the first 7 days of the study (18). The use of extracorporeal gas exchange offers an opportunity to achieve ultra-lung-protective ventilation, including reductions in respiratory rate, while mitigating the resultant respiratory acidosis. Of course, not all patients require ECLS to achieve ultra-lung-protective ventilation (38). However, without ECLS, this would be difficult to achieve in most patients with severe ARDS.

ECMO and $ECCO_2R$ in ARDS

Indications for ECMO and $ECCO_2R$

Venovenous extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$) are two related forms of ECLS that have the ability to support impairment in gas exchange (39). In both circumstances, venous blood is drained from a central vein via a cannula, pumped through a semipermeable membrane that permits diffusion of oxygen and carbon dioxide, and returned via a cannula to a central vein. ECMO, which uses high blood flow rates to both oxygenate the blood and remove carbon dioxide, may be considered in patients with severe ARDS with refractory hypoxemia or severe respiratory acidosis (1, 2). Because carbon dioxide removal is much more efficient than oxygenation, $ECCO_2R$ can be accomplished at relatively low blood flow rates, although this approach will not effectively improve oxygenation (Figure 2) (40, 41). Lower blood flow rates permit the use of smaller cannulae for $ECCO_2R$ than would be required for ECMO (42), which theoretically provides a safer risk profile when compared with ECMO from the perspective of cannula-associated complications. However, a need for higher levels of anticoagulation with $ECCO_2R$ as compared with ECMO given the lower blood flow rates (43), may be associated with higher -not lower- risks of complications (44, 45). The majority of $ECCO_2R$ is performed as venovenous but pumpless arteriovenous $ECCO_2R$ has also been reported, a method that introduces the additional risk of arterial cannulation and does not allow for the same degree of control of extracorporeal blood flow rates (46).

ECMO is supported by an increasing body of literature justifying various thresholds for its use in severe ARDS for the management of marked impairments in gas exchange (1, 26, 47, 48). There

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has been a steady rise in its use for these indications (49, 50). Identifying maximally protective ventilator management and gas exchange targets are essential to realizing the potential benefit of ECMO when it is employed in this context. In less severe ARDS, whether $ECCO_2R$ should be applied solely for the purpose of facilitating ultra-lung-protective ventilation is a subject of ongoing clinical investigation (Table E2) (40). More data is needed before one could recommend $ECCO_2R$ in less severe forms of ARDS for which ECMO itself is not otherwise indicated.

Ability of ECLS to facilitate ultra-lung-protective ventilation

In an experimental study, Grasso *et al*. demonstrated the feasibility and potential impact of using $ECCO_2R$ to achieve isolated reductions in respiratory rates (from 30.5 to 14.2 breaths per minute), with notable decreases in several inflammatory cytokines associated with VILI (36). Several prospective trials of ECLS in ARDS have demonstrated the feasibility of reducing various ventilator parameters while maintaining adequate gas exchange (36, 46, 51, 52). Most of these trials have employed $ECCO_2R$ but the results may be extrapolated to ECMO, which provides even greater gas exchange support. Terragni *et al*. used $ECCO_2R$ in ARDS patients to facilitate reductions in plateau airway pressures from 29.1 to 25.0 cm H_2O (and tidal volumes from 6.3 to 4.2 mL/kg) while correcting the resultant respiratory acidosis, with an associated reduction in pulmonary inflammatory cytokines (51). The Xtravent study randomized 79 patients with moderate to severe ARDS to standard mechanical ventilation or $ECCO_2R$-assisted ultra-lung-protective ventilation: it achieved very low tidal volumes (3.4 mL/kg), with marked reductions in driving pressure, and maintaining normal pH without an increase in respiratory rate (Table 1) (46).

A recent phase 2 international collaborative study of $ECCO_2R$ to facilitate ultra-lung-protective

ventilation was performed in 95 subjects with moderate ARDS. Reductions in tidal volumes from 6.0 mL/kg to 4.2 mL/kg, plateau airway pressures from 27.7 cm H_2O to 23.9 cm H_2O, and respiratory rates from 27.4 to 23.5 breaths per minute were achieved simultaneously, all while maintaining $PaCO_2$ and pH within pre-defined acceptable ranges (Table 1) (52). The reductions in tidal volumes and airway pressures led to a decrease in driving pressure from an average of 13.2 cm H_2O to 9.9 cm H_2O ($p=0.001$), while maintaining a similar level of PEEP.

In the context of clinical practice, retrospective studies, patient-level meta-analyses, and a prospective multicenter study of high-volume ECLS centers all corroborate the findings of the aforementioned feasibility studies, wherein ECLS initiation is typically accompanied by reductions in tidal volume, plateau airway pressure, driving pressure, respiratory rate, and FIO_2, with variable changes to PEEP and preservation of gas exchange (Table 1) (53-56). The LIFEGARDS international observational study enrolled 350 patients supported by ECLS across 23 intensive care units with experience in ECLS. An ultra-lung-protective ventilation strategy was largely applied: driving pressure was maintained ≤15 cm H_2O, correlating with a decrease in mechanical power from 26.1±12.7 pre-ECLS to 6.6±4.8 J/min during ECLS (56). Mechanical ventilation settings during the first 2 days of ECLS were not associated with mortality, in contrast with previous observations that suggested that decreased driving pressure and increased PEEP early in the course of ECLS were independently associated with reduced mortality (53, 54). This lack of association between early mechanical ventilation settings and outcomes indirectly suggests that once ultra-lung-protective ventilation, i.e., low driving pressure and very low power, has been efficiently implemented, the residual ventilation does not substantially influence outcome. A time-varying Cox model identified higher tidal volume and lower driving pressure over the duration of ECLS support, implying progressive improvement in static

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respiratory system compliance, as being independently associated with lower 6-month mortality.

Optimizing ventilator settings during ECLS for ARDS

There are no large, prospective clinical trials comparing different ventilator strategies during ECLS for ARDS, and thus no definitive standard of care exists. Available data, however, might offer valuable insights into what might be considered current best practices.

A pre-clinical swine study investigating the effect of mechanical ventilation strategies on lung injury in ARDS supported with ECMO, found that a ventilator strategy with very low airway pressures, tidal volumes, and respiratory rates (PEEP 10 cm H_2O, driving pressure 10 cm H_2O, tidal volume of approximately 2 mL/kg, respiratory rate of 5 breaths per minute) led to less histologic lung injury than so-called nonprotective (PEEP 5 cm H_2O, tidal volume 10 mL/kg, respiratory rate of 20) or conventional protective (PEEP 10 cm H_2O, tidal volume 6 mL/kg, respiratory rate of 20) approaches (57).

A recent single-center, randomized, crossover trial provides pilot data on the effect of ultra-lung-protective ventilation (maximum plateau airway pressure of 24 cm H_2O) with various combinations of PEEP (range 5-20 cm H_2O) and driving pressure (range 4-19 cm H_2O) on inflammatory cytokines in 16 patients receiving ECMO for severe ARDS (58). Compared to pre-ECMO standard of care conventional ventilation, strategies that combined higher PEEP with lower driving pressure demonstrated significant reductions in both plasma IL-6 and soluble receptor for advanced glycation end-products (sRAGE). Of note, driving pressures of 12 and 4 cm H_2O correlated with mean tidal volumes of 3.3 and 1.5 mL/kg, respectively, despite which pH and $PaCO_2$ levels were maintained within the normal range.

The most rigorous controlled data for major clinical outcomes with ECMO in severe ARDS comes from the EOLIA trial (1), which in combination with a *post hoc* Bayesian analysis (47) and a systematic review with meta-analysis (48), suggest improved mortality in those supported with ECMO compared with patients receiving best practice conventional management strategies. The ventilator strategy used in EOLIA during ECMO limited plateau airway pressure to a maximum of 24 cm H_2O in conjunction with PEEP ≥10 cm H_2O (corresponding to a driving pressure of 14 cm H_2O or less), respiratory rate of 10 to 30 breaths per minute, and FIO_2 of 0.3-0.5 (Table E1) (1). The subgroup of EOLIA with the greatest reduction in mortality consisted of those patients enrolled because of excessive ventilatory pressures and respiratory acidosis, rather than for hypoxemia, although randomization was not stratified by inclusion criteria. It seems reasonable to propose that ECMO-supported patients be managed with ventilator settings that do not exceed the parameters used in the EOLIA trial, or, alternatively, the CESAR trial, whose ECMO-facilitated ventilator settings were similar to those of EOLIA and whose data were included in the systematic review with meta-analysis (3, 48). Given the impact of tidal volume, driving pressure and possibly respiratory rate on VILI, and the relative ease with which these variables can be reduced during ECMO, it may be advantageous to target lower volumes, pressures and respiratory rates beyond those used in EOLIA (Table 3) but this remains unproven. It is similarly unclear what the optimal PEEP is for patients receiving ECLS, and may require individualization based on a given patient's alveolar recruitability, pleural pressure, and hemodynamics (59). In the absence of data to the contrary, again a PEEP of at least 10 cm H_2O may be reasonably proposed based on the favorable outcomes with the strategy used in EOLIA, with consideration for higher PEEP with morbid obesity. Beyond this, whether apneic

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oxygenation (i.e. optimized PEEP with no respiratory rate or driving pressure, so-called 'maximal lung rest') is better than tidal ventilation has yet to be determined.

While ultra-lung-protective ventilation appears to be both achievable and beneficial for patients receiving ECLS for ARDS, the optimal targets of these parameters, how best to individualize these settings, how long to stay within the limits of these targets, whether adjunctive therapies (e.g. prone positioning, neuromuscular blockade) may be of additional benefit, when to wean patients from extracorporeal support, and the impact of these strategies on long-term outcomes are all areas that require further investigation (Table 2) (21, 60-63). Ongoing and upcoming randomized controlled trials may provide further insight into several of these topics (Table E2). Prone positioning during ECLS, which is the subject of a multicenter trial in the planning phase, is one area of particular interest given that there is robust data for prone positioning during conventional ARDS management. However, the physiological effects of prone positioning may not necessarily be as impactful when ultra-lung-protective ventilation, and thus very low tidal volume, is applied, and there is added risk of ECLS cannula dislodgement during the maneuver itself. A study matching patients receiving prone positioning during ECMO for ARDS with those not receiving prone positioning suggested a benefit from being in the prone position. However, this practice remains investigational pending further evidence (64). Future trials of mechanical ventilation during ECLS for ARDS may benefit from enriching study populations with patients whose physiological parameters would suggest the greatest likelihood of detecting a response from the intervention (65).

Gas exchange targets during ECLS for ARDS

Recommendations

There are no evidence-based guidelines for the management of oxygenation, carbon dioxide, or pH in patients with ARDS supported with ECLS, and safe limits of hypoxemia and hypercapnia have not been firmly established. In the absence of data to the contrary, it is reasonable to use the gas exchange targets implemented in the EOLIA trial (PaO_2 65 to 90 mm Hg; $PaCO_2$ below 45 mm Hg) (1) as a default approach during ECLS until more specific data addressing these parameters are obtained. Previously established values from studies using conventional management strategies, including the ARMA approach, may also be appropriate (see Table E1 in the online data supplement) (18, 66).

Potential consequences of extremes in oxygen and carbon dioxide

Existing data have called attention to uncertainty about the tolerable lower and upper limits of oxygenation (67, 68), both of which may be relevant for patients receiving ECMO. Retrospective observational data of patients receiving venovenous ECMO for respiratory failure suggest increased mortality associated with both moderate hyperoxemia (PaO_2 101-300 mm Hg) and hypoxemia (PaO2 <60 mm Hg) 24 hours after ECMO initiation compared to near-normal oxygenation (PaO_2 60-100 mm Hg) (69). Other data suggest that the neurocognitive impact from prolonged hypoxemia (e.g. SpO_2 80% for up to 10 days) during ECLS for ARDS might be limited so long as tissue hypoxia (as assessed by blood lactate levels) is avoided (70, 71). However, such data must only be considered hypothesis generating for future studies.

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An association between hyperoxemia (PaO_2 >200 mm Hg) within the first 48 hours of ECLS initiation and increased mortality was also identified in a pediatric ECMO cohort, although this analysis was not limited to patients with respiratory failure and involved both venovenous and venoarterial ECLS (72). The same study reported an association between $PaCO_2$ <30 mm Hg within the first 48 hours of ECLS and an increased rate of neurological events (72). Of note, the rapidity with which carbon dioxide is reduced after ECLS initiation has been implicated in the development of neurological complications and is an area that warrants further study (73).

Special considerations for gas exchange during ECLS: Hypoxemia under ECMO

The degree to which ventilator settings can be reduced while targeting oxygenation and ventilation goals will depend predominantly on the amount of carbon dioxide removal and oxygenation achieved via the extracorporeal circuit, in addition to the tolerance for accepting deviations from pre-specified gas exchange targets. Certain physiological effects of ECLS on gas exchange may pose challenges to achieving these targets and warrant particular consideration.

In venovenous ECMO, extracorporeal gas exchange is provided in series with native gas exchange – well-oxygenated blood returned to the venous system from the ECMO circuit then passes through the native pulmonary circulation prior to reaching the systemic circulation. The contribution of ECMO to systemic oxygenation is dependent on the proportion of extracorporeal blood flow (Q_E) relative to systemic blood flow (Q_S); the greater the percentage of cardiac output passing through the circuit, the greater the contribution to systemic oxygenation (Figure 3) (39, 41). This configuration has certain physiological consequences that determine whether mechanical ventilation is still required for gas exchange. Delivery of blood with high oxygen content to the pulmonary vasculature will attenuate the hypoxemic vasoconstriction associated

with regions of the lung with low ventilation-perfusion ratios, which in turn may reduce right ventricular afterload and improve right ventricular function (74). However, in cases where there is residual native lung function, the consequent pulmonary vasodilation may also increase the shunt fraction through the native lung, potentially diminishing the benefit derived from ECMO in terms of oxygenation (75).

High ECMO blood flow rates relative to native cardiac output (Q_E/Q_S) -- which in turn requires larger ECMO cannulae -- along with minimization of recirculation (oxygenated blood taken back up by the extracorporeal circuit without having passed through the systemic circulation) may therefore be necessary to provide sufficient gas exchange to achieve additional lung-protective ventilation (42, 76). Methods to reduce recirculation to maximize systemic oxygenation have been described elsewhere (76).

Special considerations for gas exchange during ECLS: Hypoxemia under ECCO2R

By contrast, $ECCO_2R$ does not contribute meaningfully to oxygenation and may in fact exacerbate hypoxemia, requiring increases in PEEP and FIO_2. There are two major mechanisms by which $ECCO_2R$ may lead to hypoxemia. If $ECCO_2R$ is used to achieve a decreased tidal volume, the lower tidal volume will lead to a decrease in tidal recruitment and mean airway pressure resulting in worsened atelectasis and an increase in shunt fraction. This could be offset by an increase in PEEP to recruit lung units and increase oxygenation.

The second mechanism of hypoxemia is more complex and pertains to the reduction in native lung alveolar ventilation in response to the addition of $ECCO_2R$, if maintaining a constant partial pressure of carbon dioxide in arterial blood ($PaCO_2$) (77, 78). Assume that carbon dioxide elimination is 200 mL/min through alveolar ventilation, and that $ECCO_2R$ is able to remove 100

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mL/min. If maintaining steady state $PaCO_2$, the addition of $ECCO_2R$ will cause native lung alveolar ventilation to be reduced by half (from 200 mL/min to 100 mL/min), resulting in a marked reduction in the partial pressure of oxygen in the alveoli (PAO_2), and, by extension, the partial pressure of oxygen in arterial blood (PaO_2). These changes are reflected in the alveolar gas equation:

$$PAO_2 = (P_{atm} - P_{H_2O}) \times FIO_2 - PaCO_2/RER$$

where RER (respiratory exchange ratio) represents the relationship between carbon dioxide elimination (VCO_2) and oxygen uptake (VO_2) within the lung. RER is defined as VCO_2/VO_2. In the presence of $ECCO_2R$, VCO_2 within the alveolar gas equation is now equal to native lung VCO_2 (VCO_2NL) minus VCO_2 accomplished by the $ECCO_2R$ membrane (referred to as VCO_2ML):

$$PAO_2 = (P_{atm} - P_{H_2O}) \times FIO_2 - PaCO_2/[(VCO_2NL-VCO_2ML)/VO_2]$$

Assuming a typical RER of 0.8 (VCO_2NL = 200 ml/min, VO_2 = 250 ml/min), an extracorporeal circuit with a VCO_2ML of 100 mL/min will lead to a halving of the RER (0.4, i.e. (200-100)/250, assuming that the oxygen added to the circulation by the extracorporeal circuit is negligible). According to the alveolar gas equation, this decrease in RER would lead to a marked decrease in PAO_2, which can be "corrected" by increasing FIO_2 (77, 78). Such an effect on PAO_2 may also be mitigated by targeting a lower $PaCO_2$, rather than maintaining it at the pre-$ECCO_2R$ level, thereby reducing $PaCO_2$ in proportion to the RER.

Additional areas for research

The role of spontaneous breathing

Up to this point, the discussion on optimal ventilator management during ECLS for ARDS has focused on the application of controlled mechanical ventilation with limits on airway pressures, tidal volumes, and respiratory rates. Whether the allowance of spontaneous breathing, with or without ventilator support, during ECLS affords net benefit or harm likely depends, in part, on the patient's respiratory pattern, patient-ventilator dyssynchrony, pendelluft, the phase and duration of ARDS, and biological predisposition to mechanical injury (79). Vigorous spontaneous breathing with excessive tidal volumes and minute ventilation can lead to worsened lung injury through excessive transpulmonary pressure and transmural pulmonary vascular pressure, so-called patient self-inflicted lung injury (P-SILI) (10, 11, 79, 80). One cannot, therefore, simply assume that patients breathing spontaneously are protected from worsening lung injury, especially when the patient's drive to breath is substantial.

The use of deep sedation (with or without neuromuscular blockade) during invasive mechanical ventilation may diminish patient-ventilator dyssynchrony and allow for full control of invasive mechanical ventilation (12), yet such an approach exposes patients to greater risk of diaphragmatic atrophy and adverse effects of increased doses of these drugs (e.g. delirium, inability to participate in physical therapy, delayed transition to spontaneous breathing, liberation from invasive mechanical ventilation) (7). In addition, increased sedation can actually lead to worsening of some types of patient-ventilator dyssynchrony (e.g. reverse triggering) (81, 82). Allowing for patient inspiratory effort during invasive mechanical ventilation may reduce the risks of sedative and neuromuscular blocking agents and allow for greater preservation of

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respiratory and peripheral muscle strength (83, 84), but in some patients may increase the risk of lung injury (12). How best to identify the optimal balance between minimizing sedation and avoiding VILI is unclear.

Extracorporeal support offers a potential means of controlling respiratory drive in select spontaneously breathing patients, and has been demonstrated with variable success in ARDS patients (85, 86). Titrating carbon dioxide removal to achieve an acceptable respiratory drive offers an opportunity to maintain safe spontaneous breathing – i.e. patient respiratory efforts that do not lead to unsafe dynamic stress and strain within the lung. This would alleviate the need for sedation and paralysis, permit the maintenance of respiratory effort to minimize diaphragm atrophy and avoid the neurocognitive sequelae of heavy sedation. The feasibility of such regulation may also depend on the extent to which respiratory drive is subject to chemoreflex control, which in turn may depend on the duration and severity of ARDS. Such control, if feasible, opens the possibility of endotracheal extubation during extracorporeal support, which in turn would eliminate VILI altogether. Whether an initial strategy of ECLS and extubation (or avoidance of intubation) for ARDS is more favorable than controlled mechanical ventilation (with or without ECLS) has yet to be determined.

Weaning from mechanical support

For patients receiving both mechanical ventilation and ECLS who are recovering from ARDS and ready to wean from device support, whether to first decannulate or extubate depends on individual patient circumstances and clinical judgment, as there are no high quality data to guide decision-making. Those suffering from or at higher risk of developing ECLS complications (e.g. bleeding, hemolysis, infection) may benefit from decannulation before extubation, whereas

others at greater risk of ventilator-associated complications (e.g. patients with pneumothorax) or who require substantial amounts of sedation solely to maintain ventilator synchrony may benefit from a strategy that favors endotracheal extubation first.

Conclusion

The overall goal of invasive mechanical ventilation during ECLS for ARDS should be to decrease its intensity with the aim of reducing VILI and maximizing the potential benefit of ECLS. Precisely how particular ventilator variables should be adjusted has yet to be determined. In the interim, the EOLIA ventilator protocol during ECMO is a reasonable new minimum standard. Future studies should focus on more precisely delineating the best strategies for optimizing invasive mechanical ventilation during ECLS for ARDS.

Acknowledgements

We would like to thank Arthur S. Slutsky for his invaluable contributions to the conceptualization of this work. We would also like to thank Thomas Bein, Alois Philipp, and David Hajage for supplying primary data from clinical trials used in the construction of Table 1.

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Figure legends

Figure 1. Potential effects of ECLS on VILI. Panel A. Invasive mechanical ventilation may cause VILI through multiple mechanisms, including atelectrauma, barotrauma, volutrauma, myotrauma, and biotrauma. Panel B. The addition of ECLS allows for reductions in many of the contributors to VILI, through decreases tidal volume, respiratory rate, driving pressure, and plateau airway pressure, while maintaining adequate gas exchange. The effect on certain parameters, such as myotrauma, will depend on the patient's respiratory effort and synchrony between the patient and ventilator. ECLS may help reduce myotrauma by minimizing excess respiratory drive. ECLS extracorporeal life support; VILI ventilator-induced lung injury; V_T tidal volume; P_{plat} plateau airway pressure; RR respiratory rate; ΔP driving pressure; TNF-a tumor necrosis factor alpha; IL-6 interleukin 6; IL-8 interleukin 8; IL-1B interleukin 1 beta. Illustration created by Savannah Soenen.

Figure 2. Mathematical model demonstrating the relationship between ECLS blood flow, cardiac output, oxygen delivery, and carbon dioxide removal through the membrane lung. Maximal rates of carbon dioxide removal can be achieved at relatively low blood flow rates compared to those needed for oxygen delivery. Panel A: Rates of carbon dioxide removal and oxygen delivery at a cardiac output of 5 L/min. Near-total carbon dioxide removal is achieved at an ECLS blood flow rate of approximately 3 L/min. Panel B: Rates of carbon dioxide removal (VCO_2ML) and oxygen delivery (VO_2ML) through the membrane lung at a cardiac output of 8 L/min. Near-total carbon dioxide removal is achieved at an ECLS blood flow rate of approximately 5 L/min. This model assumes a sweep gas flow rate of 10 L/min, fraction of inspired oxygen (FIO_2) of 1.0, fraction of delivered oxygen to the membrane lung (FDO_2) of 1.0, total carbon dioxide production of 200 mL/min, total oxygen consumption of 250 mL/min, partial pressure of carbon

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dioxide ($PaCO_2$) maintained at 40 mmHg, hemoglobin of 10 g/dL, and recirculation of 15%. Graphs derived from www.ecmomodel.unimi.it courtesy of Alberto Zanella and Antonio Pesenti based on a previously published mathematical model (40).

Figure 3. Mathematical model demonstrating the relationship between ECLS blood flow, cardiac output, and arterial oxygen saturation. An increase in the ECLS blood flow-to-cardiac output ratio (Q_E/Q_S) leads to an increase in arterial oxygen saturation. This model assumes a shunt fraction of 100%, fraction of delivered oxygen to the membrane lung of 1.0, hemoglobin of 10 g/dL, and recirculation of 15%. Shaded blue bar: potential target arterial oxygen saturation during ECLS support. CO cardiac output. Graphs derived from www.ecmomodel.unimi.it courtesy of Antonio Pesenti based on a previously published mathematical model (40).

Table 1. Ventilatory parameters before and after ECLS initiation in studies of ECLS for ARDS

	Retrospective studies						Prospective studies							
	Schmidt (54)		Marhong (55)		Serpa Neto (53)		Xtravent (46)		EOLIA (1)		SUPERNOVA (52)		LIFEGARDS (56)	
	Pre	Post*	Pre	Post†	Pre	Post†	Pre	Post†	Pre	Post†	Pre	Post†	Pre	Post‡
V_T (mL/kg PBW)	6.3	3.9	6.1	3.9	6.0	4.0	5.9	3.4	6.0	3.4	6.0	4.2	6.4	3.7
RR (bpm)	22.0	15.0	-	-	21.9	17.8	22.4	22.2	30.4	23.1	27.4	23.5	26	14
MV_E (L/min)	8.8	3.6	-	-	9.1	5.0	9.9	5.8	-	-	10.2	5.9	10.2	3.5
PEEP (cmH_2O)	13.0	12.0	14.0	12.0	13.7	12.9	16.1	17.1	11.7	11.2	13.6	14	12	11
P_{plat} (cmH_2O)	32.2	26.4	32	25.5	31.1	26.2	29.0	25.1	29.8	24.4	27.7	23.9	32	24
ΔP (cmH_2O)	19	13.7	18	13.5	17.7	13.7	12.9	8.0	17.8	13.2	13.2	9.9	20	14
Crs (mL/cmH_2O)	23.2	19.9	22.7	19.4	26.8	23.2	34.4	32.2	25.0	20.1	-	-	24	19
FIO_2	0.96	0.60	0.99	0.40	0.90	0.69	0.62	0.54	0.96	0.50	-	-	1.0	0.5
$PaCO_2$ (mmHg)	66.0	40.5	-	-	58.3	40.3	57.3	53.9	57	38	48	46.7	68	42
pH	7.24	7.41	-	-	7.27	7.39	7.34	7.38	7.24	7.37	7.34	7.39	7.24	7.4
PaO_2:FIO_2 (mmHg)	67.0	-	61.0	-	72.6	152.5	152	154.5	73	-	168	168	71	-
Q_E (L/min)	-	4.5	-	3.0	-	4.3	-	1.3	-	5.0	-	0.4	-	4.2

ECLS extracorporeal life support; V_T Tidal volume; PBW predicted body weight; RR respiratory rate; MV_E minute ventilation; PEEP positive end-expiratory pressure; P_{plat} plateau airway pressure; ΔP driving pressure; Crs respiratory system compliance; FIO_2 fraction of inspired oxygen; $PaCO_2$ arterial partial pressure of carbon dioxide; PaO_2 arterial partial pressure of oxygen; Q_E extracorporeal blood flow rate

*average over days 1-3 of ECLS

†at 24hrs of ECLS

‡within first 2 days of ECLS

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Table 2. Suggested areas of future research for ECLS in ARDS

Ventilator settings

Which ventilator parameters are most predictive of outcomes in ARDS?

How should PEEP be titrated, and is there a role for recruitment maneuvers during ECLS?

Adjunctive therapies

Is there a role for neuromuscular blockade during ECLS?

Is there a role for prone positioning during ECLS?

Gas exchange targets during ECLS

What are optimal oxygen, carbon dioxide, and pH targets during ECLS support?
- What is the impact of hyperoxemia during ECLS?
- What is the consequence, if any, of rapid changes in carbon dioxide?

Spontaneous breathing

Which factors influence respiratory drive in ARDS patients receiving ECLS?

Should we allow for spontaneous breathing during ECLS?
- If so, does the timing matter, relative to the onset of ARDS?

Should mechanical ventilation be maintained during ECLS?
- If so, which should be weaned first, ECLS or mechanical ventilation?

Can ECLS facilitate a lung and diaphragm-protective ventilation strategy?
- How can we determine which patients require ECLS for this strategy?

ARDS acute respiratory distress syndrome; $ECCO_2R$ extracorporeal carbon dioxide removal; ECLS extracorporeal life support; PEEP positive end-expiratory pressure

Table 3. Suggested initial mechanical ventilation targets during ECLS for ARDS

Parameter	Target	Notes
Plateau pressure (P_{Plat})[1]	≤ 24 cm H_2O, may choose to go lower, if feasible	
Driving pressure (**ΔP**)[1]	≤ 14 cm H_2O	
Tidal volume	Adjust for goal P_{Plat}	Typically ≤ 4ml/kg PBW, often much lower
Respiratory rate[2]	≤ 10 breaths per minute	Typically only achieved when sedation, with or without NMBAs, is being used. Consider increased sweep flow to achieve, when appropriate
PEEP[1]	≥ 10 cm H_2O	See text for circumstances that may warrant particularly high levels of PEEP
FIO_2[1]	0.3 to 0.5	Higher FIO_2 may be necessary if ECLS is inadequate at achieving acceptable levels of oxygenation Adequate oxygen delivery is the primary goal, not a particular SaO_2

[1]These recommended targets are based on the ventilator protocol of the intervention arm of the EOLIA trial
[2]The recommendation for respiratory rate below the lower limit of the EOLIA protocol is based on the presumption that lower respiratory rates are both more protective and achievable during ECLS
ARDS acute respiratory distress syndrome; ECLS extracorporeal life support; EOLIA *Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome*; FIO_2 fraction of inspired oxygen; NMBAs neuromuscular blocking agents; **ΔP** driving pressure; PBW predicted body weight; PEEP positive end-expiratory pressure; P_{Plat} plateau airway pressure; SpO_2 arterial oxygen saturation

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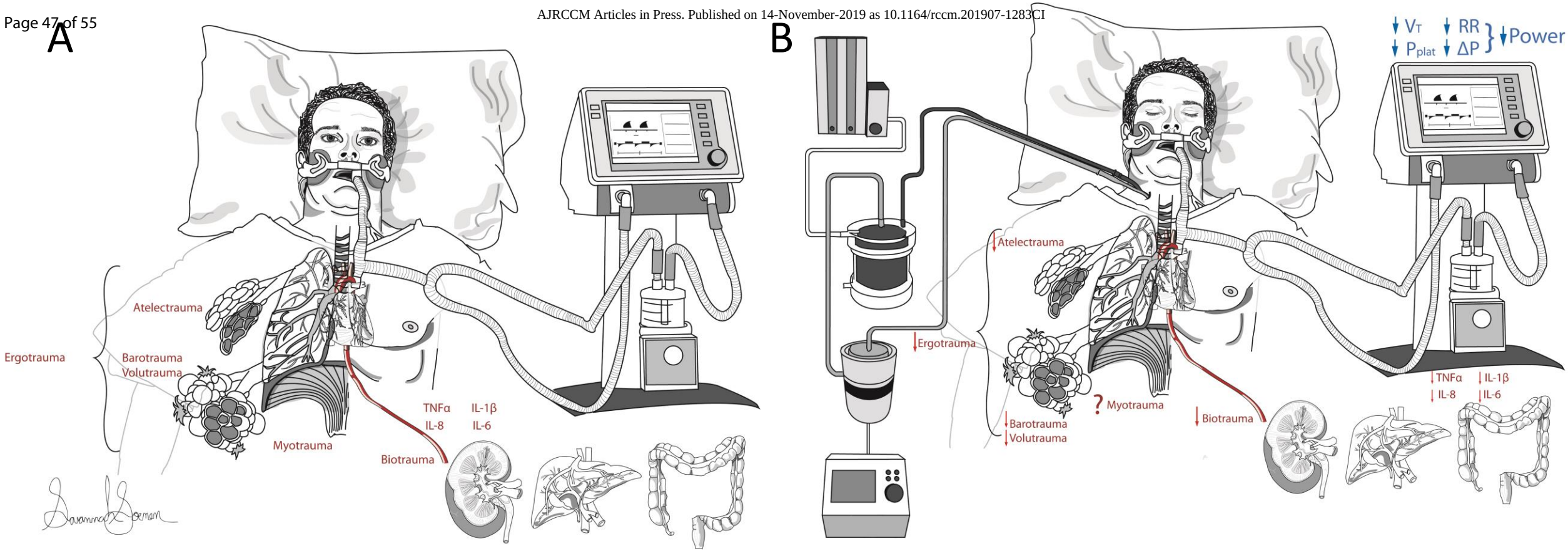

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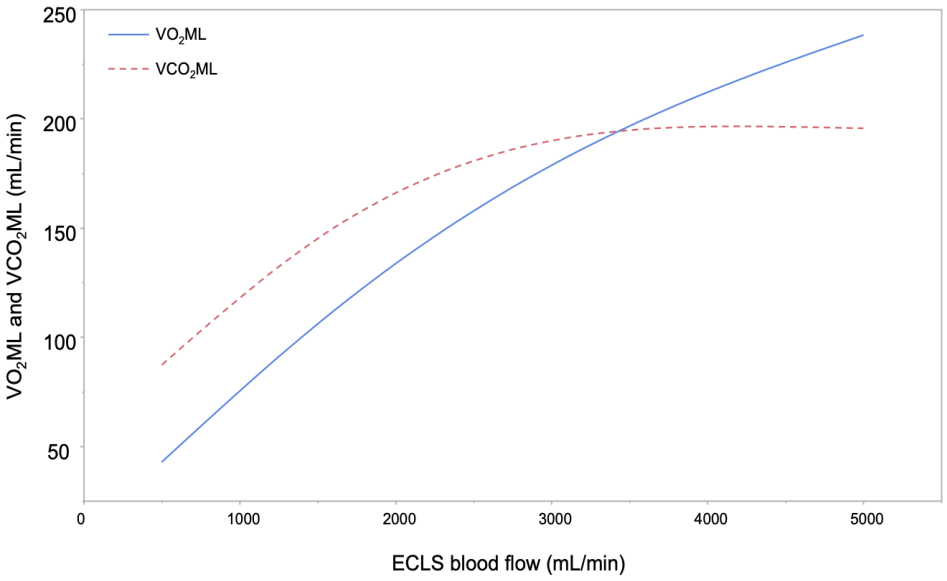

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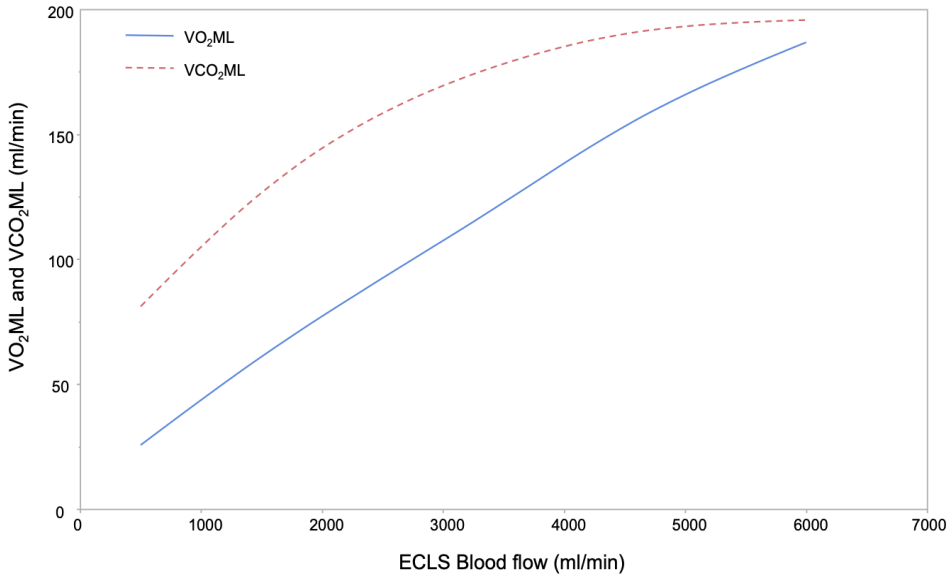

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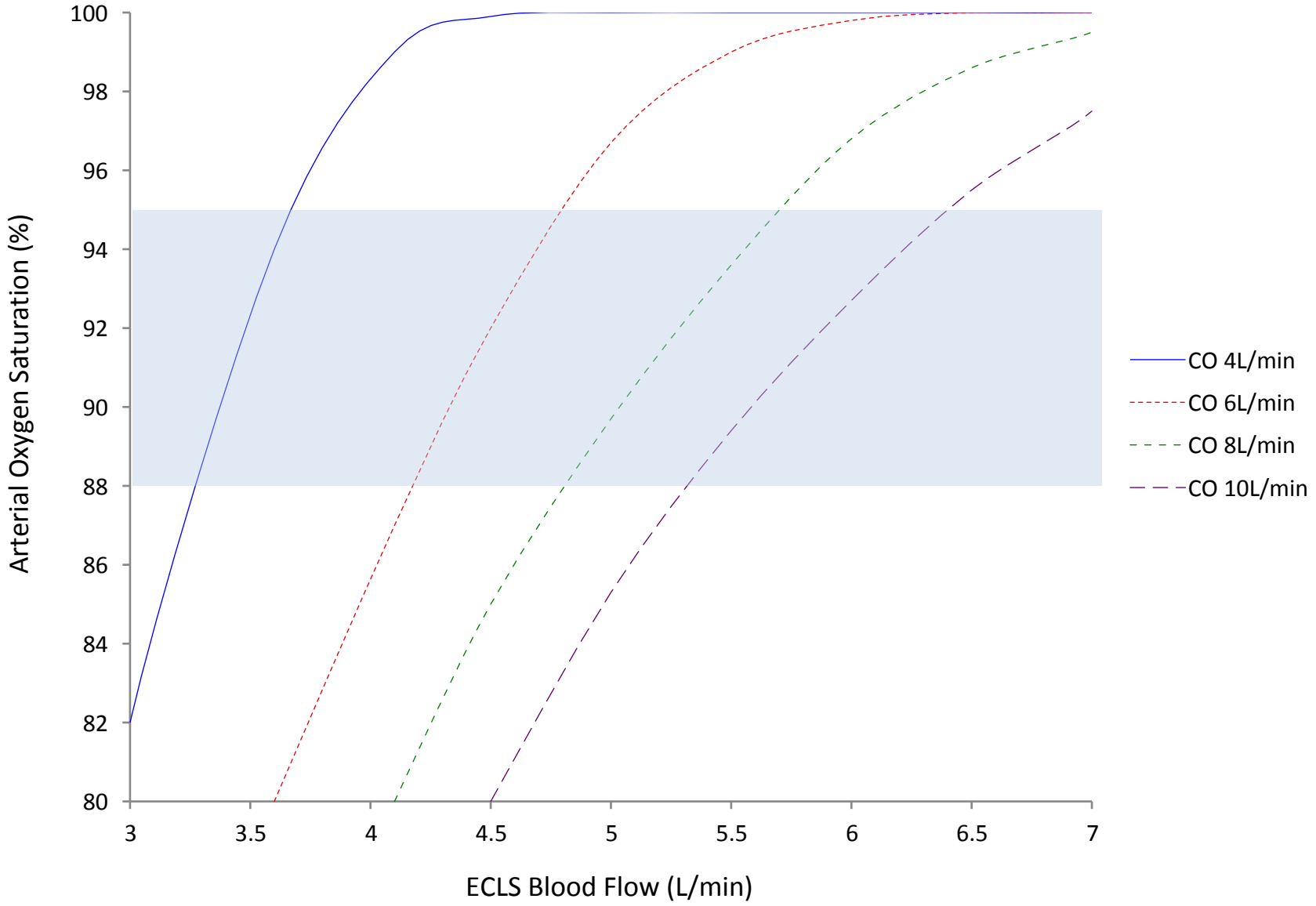

Mechanical Ventilation for ARDS During Extracorporeal Life Support: Research and Practice

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Online Data Supplement

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Table E1. Comparison of ventilator parameters and gas exchange goals between the intervention arms of the ARMA and EOLIA trials

	ARMA	EOLIA*	
Inclusion criteria	ARDS† (any severity)	ARDS† with any of the following: PaO_2:FIO_2 < 50 mmHg for > 3 hours‡,§ PaO_2:FIO_2 < 80 mmHg for > 6 hours‡,§ pH < 7.25 with $PaCO_2$ ≥ 60 mmHg for > 6 hours‡,§,ll	
Ventilatory Mode	Any	V-AC	"APRV"**
V_T and P_{plat} goals	V_T (8 mL/kg PBW or less) for P_{plat} ≤ 30 cmH_2O	V_T for P_{plat} ≤ 24 cmH_2O	P_{high} ≤ 24 cmH_2O
Respiratory Rate (breaths/min)	≤ 35	10-30	
FIO_2	0.3-1.0	0.3-0.5	
PEEP (cmH_2O)	5 – 24††	≥ 10	
Oxygenation goal	PaO_2 55-80 mmHg SaO_2 88-95%	PaO_2 65-90 mmHg SaO_2 > 90%	
pH or $PaCO_2$ goals	pH 7.30-7.45	$PaCO_2$ < 45 mmHg	

*The ventilator parameters and gas exchange goals described were applied to patients receiving ECMO in the EOLIA trial. Both volume-assist control and APRV were acceptable ventilator modes

†As defined by the American-European Consensus Conference Definition

‡Despite optimized conventional V_T 6 mL/kg PBW, PEEP ≥ 10 cm H_2O, and FIO_2 ≥ 0.8

4§Neuromuscular blockade and prone positioning strongly encouraged

llWith respiratory rate increased to 35 breaths per minute and mechanical ventilation settings adjusted to keep a plateau airway pressure of ≤32 cm of water

**This mode was not traditional APRV (airway pressure release ventilation), but rather a non-synchronized form of bilevel positive airway pressure with a maximum pressure of 24 cmH_2O, a minimum PEEP of 10 cmH_2O and a respiratory rate of 10-30. An inspiratory-to-expiratory ratio of 1:2 was recommended

††Increases in PEEP up to 34 cm H_2O were permitted

APRV airway pressure release ventilation; ARDS acute respiratory distress syndrome; ARMA *Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome*; EOLIA *Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome*; FIO_2 fraction of inspired oxygen; $PaCO_2$ partial pressure of carbon dioxide in arterial blood; PaO_2 partial pressure of oxygen in arterial blood; PEEP positive end-expiratory pressure; P_{high} airway pressure during inspiratory phase of APRV; P_{plat} plateau airway pressure; SaO_2 oxygen saturation in arterial blood; V-AC volume-assist control ventilation; V_T tidal volume

Table E2. Ongoing studies of mechanical ventilation strategies during ECLS in ARDS

Title	Study design	Brief description	Primary outcome
pRotective vEntilation With Veno-venouS Lung assisT in Respiratory Failure (REST); NCT 02654327	Multicenter randomized controlled trial	Standard of care lung-protective ventilation versus $ECCO_2R$ + ultra lung-protective ventilation	90-day mortality
Strategies for Optimal Lung Ventilation in ECMO for ARDS: The SOLVE ARDS Study; NCT01990456	Single-center non-randomized crossover study	Varying tidal ventilation and PEEP strategies	Serum cytokines and physiologic parameters
Low Frequency, Ultra-low Tidal Volume Ventilation in Patients with ARDS and VV-ECMO; NCT03764319	Single-center randomized controlled trial	ECMO + standard of care lung-protective ventilation versus ECMO + ultra-protective settings	Ventilator-free days at day 28 of ECMO
Ultra-protective Pulmonary Ventilation Supported by Low Flow Extracorporeal Carbon Dioxide Removal (ECCO2R) and Prone Positioning for ARDS; a Pilot Study; NCT02252094	Single-center randomized controlled trial	Standard of care lung-protective mechanical ventilation versus $ECCO_2R$ + ultra lung-protective ventilation	Ability to achieve plateau pressure ≤ 25 cmH2O in the $ECCO_2R$ arm
Enhanced Lung Protective Ventilation With Extracorporeal CO2 Removal During Acute Respiratory Distress Syndrome; NCT03525691	Single-center randomized crossover trial	Standard of care lung-protective ventilation versus ECCO2R + two different ultra lung-protective ventilation strategies	Change in $PaCO_2$ after initiation of $ECCO_2R$

ARDS acute respiratory distress syndrome; $ECCO_2R$ extracorporeal carbon dioxide removal; ECMO extracorporeal membrane oxygenation; $PaCO_2$ partial pressure of carbon dioxide in arterial blood; PEEP positive end-expiratory pressure; VV venovenous

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Descriptions of studies listed in Table 1

Schmidt M, Stewart C, Bailey M, Nieszkowska A, Kelly J, Murphy L, Pilcher D, Cooper DJ, Scheinkestel C, Pellegrino V, Forrest P, Combes A, Hodgson C. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study. *Crit Care Med* 2015; 43: 654-664.

Study design: Retrospective observational study.
Patients: 168 patients receiving venovenous ECMO for ARDS at 3 high-volume ECMO centers.
Methods: Analysis of association between mechanical ventilation settings and ICU mortality.
Main results: Higher PEEP during the first 3 days of ECMO was found to be associated with lower ICU mortality in multivariate analysis.

Marhong JD, Munshi L, Detsky M, Telesnicki T, Fan E. Mechanical ventilation during extracorporeal life support (ECLS): a systematic review. *Intensive Care Med* 2015; 41: 994-1003.

Study design: Systematic review.
Patients: 2,042 patients receiving ECLS (all forms) for ARDS.
Methods: Analysis of change in mechanical ventilation settings after the initiation of ECLS.
Main results: Tidal volume, plateau airway pressure, PEEP, and FIO_2 are commonly reduced after initiation of ECLS.

Serpa Neto A, Schmidt M, Azevedo LC, Bein T, Brochard L, Beutel G, Combes A, Costa EL, Hodgson C, Lindskov C, Lubnow M, Lueck C, Michaels AJ, Paiva JA, Park M, Pesenti A, Pham T, Quintel M, Marco Ranieri V, Ried M, Roncon-Albuquerque R, Jr., Slutsky AS, Takeda S, Terragni PP, Vejen M, Weber-Carstens S, Welte T, Gama de Abreu M, Pelosi P, Schultz MJ, Re VARN, the PNI. Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis : Mechanical ventilation during ECMO. *Intensive Care Med* 2016; 42: 1672-1684.

Study design: Individual patient data meta-analysis.
Patients: 545 patients receiving venovenous ECMO for refractory hypoxemia in the setting of ARDS.
Methods: Analysis of relationship between ventilator settings within the first 3 days of ECMO and in-hospital mortality.
Main results: Initiation of ECMO was associated with significant decreases in tidal volume, PEEP, plateau airway pressure, driving pressure, respiratory rate, and minute ventilation, although only driving pressure was independently associated with mortality.

Xtravent: Bein T, Weber-Carstens S, Goldmann A, Muller T, Staudinger T, Brederlau J, Muellenbach R, Dembinski R, Graf BM, Wewalka M, Philipp A, Wernecke KD, Lubnow M, Slutsky AS. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med* 2013; 39: 847-856.

Study design: Randomized, controlled trial.
Patients: 79 patients with moderate to severe ARDS.
Methods: Randomization to conventional low tidal volume ventilation (6 mL/kg) or very low tidal volume ventilation (3 mL/kg) plus $ECCO_2R$. Primary outcome was ventilator-free days (VFDs) at 28 and 60 days.
Main results: No overall difference in VFDs, although a significant difference in VFDs at 60 days was seen among those with PaO_2:FIO_2 ≤150 mmHg in post hoc analysis.

EOLIA: Combes A, Hajage D, Capellier G, Demoule A, Lavoue S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A, Eolia Trial Group R, Ecmonet. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2018; 378: 1965-1975.

Study design: Randomized, controlled trial.
Patients: 249 patients with severe ARDS who met one of the following inclusion criteria after optimization of conventional management (e.g. low tidal volume ventilation, neuromuscular blockade, prone positioning): PaO_2:FIO_2 < 50 mm Hg for > 3 hours; PaO_2:FIO_2 < 80 mm Hg for > 6 hours; or arterial blood pH < 7.25 with a $PaCO_2$ ≥ 60 mm Hg for > 6 hours.
Methods: Randomization to ongoing conventional treatment or venovenous ECMO. Primary endpoint was 60-day mortality.
Main results: No statistically significant difference in 60-day mortality (ECMO group 35%, control group 46%, relative risk, 0.76; 95% confidence interval [CI], 0.55 to 1.04; p=0.09). Thirty-five patients (28%) crossed over from control to ECMO for refractory hypoxemia, with an associated mortality of 57%.

SUPERNOVA: Combes A, Fanelli V, Pham T, Ranieri VM, European Society of Intensive Care Medicine Trials G, the "Strategy of Ultra-Protective lung ventilation with Extracorporeal CORfN-OmtsAi. Feasibility and safety of extracorporeal CO2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. *Intensive Care Med* 2019; 45: 592-600.

Study design: Prospective multicenter phase 2 study.
*Patient*s: 95 patients with moderate ARDS.
Methods: Initiation of $ECCO_2R$ to target ultra-lung-protective ventilation (tidal volume of 4 mL/kg and plateau airway pressure of ≤ 25 cmH2O, respectively. The primary endpoint

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was the proportion of patients achieving ultra-lung-protective ventilation with $PaCO_2$ being maintained within 20% of baseline and arterial pH > 7.30.
Main results: 78% and 82% of patients achieved ultra-lung-protective ventilation by 8 and 24 hours, respectively. ECCO2R-related adverse events were reported in 39% of patients.

LIFEGARDS: Schmidt M, Pham T, Arcadipane A, Agerstrand C, Ohshimo S, Pellegrino V, Vuylsteke A, Guervilly C, McGuinness S, Pierard S, Breeding J, Stewart C, Ching SSW, Camuso JM, Stephens RS, King B, Herr D, Schultz MJ, Neuville M, Zogheib E, Mira JP, Roze H, Pierrot M, Tobin A, Hodgson C, Chevret S, Brodie D, Combes A, International EN, the LSG. Mechanical Ventilation Management during ECMO for ARDS: An International Multicenter Prospective Cohort. ***Am J Respir Crit Care Med*** **2019.**

Study design: Prospective cohort study.
Patients: 350 patients receiving venovenous ECMO for severe ARDS.
Interventions: Analysis of the association between mechanical ventilation practices and 6-month outcomes.
Main results: Ultra-lung-protective ventilation, as practiced through reductions in tidal volume, plateau airway pressure, driving pressure, and respiratory rate, is commonly applied to patients receiving venovenous ECMO for severe ARDS at medium to high-volume ECMO centers. No association was found between ventilator settings during the first 2 days of ECMO and survival. Higher tidal volume and lower driving pressures over the duration of ECMO (likely reflecting gradual improvement in static compliance) were associated with better outcomes.