ANNALSATS Articles in Press. Published on 06-October-2017 as 10.1513/AnnalsATS.201704-345OT

Mechanical Ventilation in Adults with Acute Respiratory Distress Syndrome: Summary of the Experimental Evidence for the Clinical Practice Guideline

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Key Words: acute respiratory distress syndrome, mechanical ventilation, ventilator-induced lung injury, limited pressure and volume ventilation, prone position, high positive end expiratory pressure, recruitment maneuvers, high frequency oscillatory ventilation, extracorporeal life support.

Primary Source of Funding: ATS

Word Count: 4,719

Abstract

Rationale: The ATS/ESICM/SCCM guidelines on mechanical ventilation in adult patients with acute respiratory distress syndrome provide treatment recommendations derived from a thorough analysis of the clinical evidence on six clinical interventions. However, each of the recommendations contains areas of uncertainty and controversy, which may affect their appropriate clinical application.

Objectives: To provide a critical review of the experimental evidence surrounding the pathophysiology of ventilator-induced lung injury to help clinicians apply the clinical recommendations to individual patients.

Methods: Literature search and narrative review.

Results: A large number of experimental studies have been performed to better understand the pathophysiological effects of mechanical ventilation. These studies have formed the basis for the design of many clinical trials. Translational research has fundamentally advanced our understanding of the mechanisms of ventilator-induced lung injury, informing the design of interventions that improve survival in patients with acute respiratory distress syndrome.

Conclusions: Because daily management of patients with ARDS presents the challenge of competing considerations, clinicians should consider the mechanism of ventilator-induced lung injury, and the rationale for interventions designed to mitigate it, when applying evidence-based recommendations at the bedside.

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Since the first description of the acute respiratory distress syndrome (ARDS) 50 years ago(1), important advancements in the understanding of this life-threatening form of non-cardiogenic pulmonary edema have been made, resulting in remarkable improvements in the prognosis of patients with ARDS. Mortality from ARDS has decreased from greater than 60% in the 1970s to less than 30% in the most recent studies(2-5). This is largely attributable to the development of better supportive care and to improvements in the application of mechanical ventilation (MV)(6-8), which remains the mainstay of treatment for ARDS(9, 10).

Overall, the purpose of MV is to unload the respiratory muscles and provide adequate gas exchange, while allowing time for lung to recover from the primary injury(9). In the past few decades the recognition that MV can itself cause injury – ventilator-induced lung injury (VILI) – has led to a shift in the goals of MV(7). Whereas early on clinicians were titrating MV settings to achieve normal gas exchange, current supportive efforts are focused on the prevention of VILI (Figure), while maintaining gas exchange in a range compatible with life(11, 12).

The new guidelines for MV in adult patients with ARDS provide treatment recommendations derived from a thorough analysis of the clinical evidence on six interventions. Furthermore, the evidence supporting the ventilatory management of ARDS is complex—and the marked variability of response to treatment among ARDS patients is widely recognized. Therefore, a review of the experimental evidence underlying the recommendations for each of the interventions may provide clinicians with physiological insights (Figure) to help manage patients with ARDS, particularly in situations in which there are ongoing areas of uncertainty or controversy.

Ventilation with Lower Inspiratory Airway Pressure and Tidal Volume

The two main mechanisms of VILI are regional alveolar overdistension (volutrauma) resulting from pathological levels of stress and strain within the lung, and cyclic airway opening and closing with tidal ventilation (atelectrauma)(7, 13-15). Stress may be defined as the internal counterforce that reacts to an external load, and can be clinically estimated as transpulmonary pressure (P_L) - the distending pressure of the lung. Strain, the degree of deformation of an object relative to its original size, is related to the ratio between tidal volume and end-expiratory lung volume(15). Hence, for a given tidal volume (V_T), the loss of aerated lung in patients with ARDS due to alveolar consolidation, edema, and atelectasis ("baby lung")(16) increases the risk of excessive tidal strain, and hence alveolar overdistension. In addition, lung cell distension, disruption, and necrosis resulting from the application of excessive stress and strain may induce a pulmonary and systemic inflammatory response through a complex interplay between tissue deformation, mechano-transduction, inflammation, and edema(14).

Multiple lines of experimental and clinical evidence have demonstrated the association between VILI and outcomes in ARDS(14, 17). Therefore, current clinical practice relies on the application of MV strategies that limit end-inspiratory lung stretch or V_T with the goal of reducing VILI(12, 18). Indeed, as described in the systematic review and meta-analysis published in this issue of the journal(19), in patients with ARDS there was a trend toward lower mortality with protective ventilation, and a significant relationship between the degree of tidal volume reduction and mortality.

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However, the optimal reduction of airway pressure or V_T to avoid VILI and maximize survival is not known. In fact, airway plateau pressure (Pplat) and V_T have been shown not to be good surrogate for alveolar stress and strain(15). Indeed, small V_T at a high positive end-expiratory pressure (PEEP) may still lead to alveolar overdistention, and a very high Pplat may not indicate overdistension in a patient with a stiff chest wall(7). Nonetheless, the ARDSNet strategy of limiting V_T to 6 mL/kg predicted body weight (PBW) and Pplat to 30 cmH_2O improved survival(12), and these are now accepted lung-protective targets for ventilation in patients with ARDS. Moreover, an experimental study in healthy pigs demonstrated that MV settings providing a lung strain greater than 1.5-2 caused VILI and led to multi-organ failure(20).

In contrast, other data suggest the absence of clearly identifiable thresholds of stress or strain that can be applied in every patient to prevent VILI. For example, about a third of patients with ARDS have CT findings consistent with alveolar overdistension despite being ventilated with V_T of 6 ml/kg PBW and Pplat<30 cmH_2O (21). Furthermore, a post-hoc analysis of the ARMA trial showed that higher Pplat on day one was associated with higher mortality(22). In addition, a recent analysis of individual patient data from nine randomized controlled trials (RCTs) demonstrated that driving pressure (ΔP = Pplat - PEEP) was the ventilatory variable most strongly associated with mortality(18). ΔP is the ratio between V_T and respiratory system compliance (C_{RS}), and since C_{RS} can be considered a surrogate for the volume of the aerated lung, ΔP can be interpreted as a marker of lung strain.

Similar levels of stress and strain may cause different degrees of VILI according to regional lung structure. In particular, the inhomogeneous distribution of alveolar consolidations throughout the lung parenchyma may result in the localized development of harmful levels of

stress (23). These inhomogeneities can act as a "stress raisers" converting a safe level of P_L for a homogeneous lung into a locally injurious stress(24). Therefore, the risk of VILI is higher in patients with greater inhomogeneities; this may account for the association between inhomogeneities, disease severity, and mortality(23).

Spontaneous breathing may be beneficial (25), as it may improve lung ventilation/perfusion matching, improve cardiac function, prevent ventilator-induced diaphragm dysfunction, and lead to reduced sedation requirements and delirium. However, VILI can be generated in mechanically ventilated ARDS patients during spontaneous breathing due to high respiratory drive, excessive spontaneous inspiratory efforts, and uneven distribution of lung stress and strain resulting in regional lung injury (25). During spontaneous breathing in pressure-targeted or volume-limited modes, even protective MV settings (e.g., Pplat <30 cmH_2O) may result in injurious level of P_L due to inspiratory effort-induced reduction of pleural pressure(26).

Experimental studies in injured rabbit lung demonstrated that high spontaneous inspiratory efforts during MV exacerbate lung injury without modifying Pplat(27, 28). In addition, a recent study showed that in injured lungs, the negative pleural pressure generated by diaphragmatic contraction during spontaneous breathing is not uniformly transmitted to the lung, and is more negative in the dependent regions compared to the non-dependent ones(29). These local changes in P_L cause a pendelluft phenomenon (movement of air from nondependent to dependent regions without change in V_T), which can result in VILI by inducing unexpected local overdistension in the dependent lung. Consequently, in paralyzed animals comparable inflation of the dependent regions of the injured lung required a driving airway

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pressure 3-fold higher than that applied during spontaneous breathing(29). This maldistribution of P_L arises because the injured lung behaves more as a solid than as a liquid(25).

Experimental data also suggest that the marked increase in transvascular pulmonary pressure (difference between intravascular pressure and pressure outside the vessels) and blood flow due to negative pleural pressure during spontaneous breathing may exacerbate pulmonary edema in the injured lung(30, 31). Furthermore, strong spontaneous efforts can damage the diaphragm, potentially contributing to prolonged MV duration(32). Indeed, a large RCT demonstrated that in patients with moderate/severe ARDS, early administration of neuromuscular blocking agents improves 90-day survival(33). Finally, factors such as severity of lung injury may modify the effect of spontaneous breathing in ARDS, as spontaneous breathing may actually prevent VILI and improve lung function in mild ARDS(28). Therefore, except for early severe ARDS, it remains unclear whether prioritising lung-protection by reducing inspiratory drive and effort results in fewer adverse effects than facilitating minimal sedation and spontaneous breathing. Better monitoring of patient inspiratory effort level and P_L under MV may assist with clinical decision-making around these issues.

Prone Positioning

Since its introduction in the 1970s as a rescue maneuver for patients with refractory hypoxemia(34), a large body of clinical and experimental evidence has progressively demonstrated the benefits of ventilating ARDS patients in the prone position(5, 34-36). Ultimately, the results of the systematic review and meta-analysis published in this issue of the

journal demonstrated that prone positioning applied daily for at least 12 hours significantly reduces mortality among patients with severe ARDS(37).

Approximately two-thirds of ARDS patients that are placed in the prone position demonstrate improved oxygenation(5, 38) due to an increase in ventilation of well-perfused lung areas (35, 36). The shift from supine to prone position induces recruitment of the dorsal lung regions and collapse of the ventral ones(39), whereas the distribution of perfusion does not change, remaining higher in the dorsal areas(40), resulting in a decrease in pulmonary shunt fraction(41). This was elegantly demonstrated in an ovine lung injury model (42), using positron-emission tomography to measure regional distribution of pulmonary perfusion, aeration, and shunt in the supine and prone positions. Another interesting study in acutely injured lungs demonstrated that the regional distribution of ventilation-perfusion rations is more uniform in prone position(43). However, the survival advantage from prone positioning likely derives from beneficial effect of the prone position on VILI, rather than improvements in oxygenation(11).

Convincing experimental evidence demonstrated that MV in the prone position is less injurious than ventilation in the supine position(35, 36, 44-46). In a randomized physiologic study in 39 ARDS patients, MV in the prone position was associated with a reduced release of inflammatory mediators in the BAL compared to ventilation in the supine position(47). Moreover, studies using lung CT scans in ARDS patients consistently demonstrated reduced alveolar overdistension and increased lung recruitment in the prone position compared to supine position(44, 48). Prone positioning significantly reduces atelectrauma secondary to cyclic airway opening and closing, especially in patients with high recruitability receiving higher

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PEEP(44). Perhaps the most important explanation for the reduced risk of VILI in the prone position may not derive entirely from its effect on alveolar recruitment, but rather from a more uniform distribution of P_L across lung regions(35, 36, 45).

Prone positioning increases chest wall elastance in patients with ARDS due to the reduced excursion of the sternum in contact with a firm surface (35, 41). This change in the regional respiratory system mechanical properties affects pleural pressure. In supine humans, pleural pressure is not uniformly distributed: it is lower in non-dependent regions, resulting in a more positive P_L (49, 50). In a large animal model of pulmonary edema, turning the animal from the supine to the prone position reduced the gradient in pleural pressure from the non-dependent regions to the dependent regions(51). The overall effect is a more homogeneous distribution of P_L and regional strain (52).

In addition, the improvement in gas exchange induced by prone position may prevent the negative hemodynamic issues associated with higher PEEP and airway pressure application(53). Although left ventricular afterload may increase and splanchnic perfusion may decrease secondary to the increase of the abdominal pressure, these side effects have rarely been reported.

Future studies should focus on elucidating the beneficial mechanisms of the delivery of MV to ARDS patients in the prone position, and should clarify whether prone position-specific setting of PEEP and the optimization of alveolar recruitment may further reduce VILI.

High-Frequency Oscillatory Ventilation

High frequency oscillatory ventilation (HFOV) is a modality of MV characterized by the delivery of pressure oscillations at very high frequencies (3-15 Hz) around a relatively constant mean airway pressure (mPaw), resulting in very small P_L, often less than the anatomic dead space (1–3 mL/kg)(54-56). The application of elevated mPaw may maximize alveolar recruitment while the delivery of small V_T prevents tidal overdistension, thus overall reducing atelectrauma and tidal stress and strain(55).

Several experimental animal studies have shown that HFOV reduces VILI compared to other lung protective MV strategies, while maintaining adequate gas exchange and stable hemodynamics(55). However, the HFOV settings used in experimental animal studies are markedly different from those applied clinically(55, 57-61). In particular, the oscillation frequency is often set at 5 Hz or less in clinical practice (average 4.5 ±2.1 Hz)(58), whereas in experimental conditions are always greater than 6 Hz and often greater than 10 Hz, resulting in substantially lower delivered V_T. In addition, the average mPaw reported in clinical studies during the first hours of HFOV application is 28 ±6 cmH_2O, whereas in experimental studies is less than 20 cmH_2O in most reports(55, 58, 60).

Hence, it is challenging to translate these experimental findings into clinical practice, and it remains unclear whether HFOV can also reduce VILI in patients with ARDS(62). In a physiologic, randomized investigation in 39 patients with ARDS, HFOV was associated with a significant increase in BAL inflammatory mediators compared to conventional MV(47). Moreover, the meta-analysis of 6 RCTs published in this issue of the journal showed that HFOV

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compared to MV with low tidal volumes and high PEEP was not associated with a mortality benefit in patients with ARDS(63). However, a recent individual patient data meta-analysis showed that HFOV was associated with a decrease in mortality in patients with severe ARDS(60).

The reasons for the disconnect between the RCTs and the strong animal data, and early clinical trials that showed an advantage of HFOV over conventional MV remains unclear. There are multiple settings during application of HFOV including mPaw, oscillatory pressure amplitude, frequency of oscillations, bias flow, and inspiratory and expiratory time ratio. The complex interaction between these parameters and the patient may result in a very limited therapeutic range where HFOV provides lung protective MV without increasing the risk of VILI(54, 55).

Given these multiple settings there are two major possible reasons for the negative results, both related to the high mPaw used: HFOV increased VILI, and/or caused negative hemodynamic consequences. First, excessive levels of mPaw may lead to high alveolar stress and strain, whereas if the level is too low the occurrence of atelectasis increases the lung inhomogeneity and thus the risk of VILI, as demonstrated in a model of neonatal ARDS(64). In clinical practice, mPaw on HFOV is set according to oxygenation without a direct assessment of the effect on alveolar recruitment.

Second the high mPaw on HFOV may have compromised venous return and right ventricular function. In a study of 16 patients with ARDS, HFOV delivered with mPaw up to 15 cmH_2O higher (mean 33±3 cmH_2O) than the mean airway pressure during conventional MV was associated with significant worsening of right ventricular function, especially in patients in

whom HFOV did not result in increased alveolar recruitment, as measured by electrical impedance tomography (EIT)(65). Moreover, in a large RCT of ARDS patients, which showed a higher mortality in the HFOV group, vasoactive drugs were used in more patients and for a longer period of time in the HFOV group than in controls(66).

Studies applying advanced techniques to monitor V_T, lung recruitment, and overdistension during HFOV may guide the future research on this MV modality. For example, monitoring P_L during HFOV may permit safer titration of mPaw according to lung-distending pressures.

Higher Positive End-Expiratory Pressure

At its initial description, ARDS was found to respond at least in part to the application of PEEP, which was described as a "therapeutic trial of apparent value"(1). Loss of lung volume in ARDS contributes to VILI by a number of potential mechanisms including atelectrauma, impairment of surfactant function, and regional hypoxia due to alveolar collapse, edema and damage(7, 13, 15, 67). PEEP may reduce VILI by preventing collapse of small airways and maintaining lung recruitment during expiration(68-72).

In a seminal study(73), lung injury in rats due to MV with high airway pressures (30 or 45 cmH_2O) was significantly reduced by adding 10 cmH_2O of PEEP. In this model, PEEP had the important effects of reducing driving pressure and hence tidal ventilation, and preventing atelectrauma, thus highlighting the complex interaction between regional alveolar overdistension and lung volume in determining VILI(6-8, 74). This was further investigated in an

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ex-vivo non-perfused rat lung model in which low V_T were delivered with different levels of PEEP. The application of PEEP below the lower inflection point of the pressure-volume (P-V) curve markedly increased VILI compared to a strategy using PEEP greater than the inflection point (75).

The translation of these promising experimental results into clinical practice, however, remains a considerable challenge(68, 69, 76, 77). Three large RCTs(78-80) failed to demonstrate decreased mortality using higher PEEP compared with lower PEEP. In these clinical studies, higher PEEP was set based on lung mechanics or according to oxygenation following a PEEP-FiO_2 table. Moreover, the systematic review and meta-analysis published in this issue of the journal(81), demonstrated that higher PEEP was not associated with decreased mortality in unselected patients with ARDS, after excluding RCTs that did not use lower tidal volume ventilation in the control group. However, two other meta-analyses(82, 83) suggested that higher PEEP might have a positive effect in patients with moderate/severe ARDS, but could be potentially injurious in mild ARDS.

These negative results can potentially be explained by the heterogeneous response of patients with ARDS to PEEP(84). When effective, PEEP increases or maintains alveolar recruitment with consequent reduction of VILI, improvement in gas exchange and improvement of hemodynamics(85-88). Nonetheless, PEEP can also have detrimental effects causing excessive end-inspiratory alveolar overdistention with the consequent worsening of intrapulmonary shunt, dead space, and pulmonary vascular resistance(89-91). Therefore, the physiological response to PEEP, which has not been included in the design of these RCTs, may be the major determinant of its impact on outcome.

In a clinical investigation evaluating lung recruitability in 68 patients with ARDS by pulmonary CT scanning(84), the portion of recruitable lung was highly variable among patients. Importantly, patients with greater lung recruitablity had worse oxygenation, higher dead space, lower compliance, and higher mortality. These results suggest that higher PEEP may have a beneficial effect only in patients with severe ARDS due to their greater lung recruitability. Therefore, higher PEEP should ideally be applied only in highly recruitable patients, while lower PEEP should be avoided in patients with lower recruitability to prevent its injurious effects. Hence, the degree of lung recruitability may turn out to be a useful guide in setting PEEP in any individual patient(92).

This hypothesis has been investigated from a physiological perspective in several other studies. One study applied both lower and higher PEEP to 19 patients with ARDS, in whom lung recruitability was assessed performing quasi-static P-V curves at the different PEEP levels(93). In 9 patients, the increase from lower to higher PEEP resulted in more than 150 mL of lung recruitment and was associated with an increase in oxygenation and lung compliance. In the other 10 patients with low lung recruitablity, the increase in PEEP caused a reduction of lung compliance and did not improve oxygenation. A retrospective analysis of two large RCTs on higher versus lower PEEP in ARDS showed that patients with an improvement in oxygenation following an increase in PEEP had a lower mortality, suggesting that PEEP-induced lung recruitment might have a beneficial effect on survival(94).

In a study of 68 ARDS patients, CT scans were used to determine the effect of lung recruitability on alveolar strain and intratidal airway opening and closing when PEEP was increased from 5 to 15 cmH_2O(95). Higher PEEP levels significantly reduced the amount of lung

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tissue undergoing intratidal airway opening and closing only in patients with higher lung recruitability, which was independently associated with mortality. In contrast, higher PEEP induced a similar increase of alveolar strain in patients with high and low recruitability. These results demonstrate that in patients with high recruitability the protective effect of higher PEEP on airway opening and closing likely outweighs the risks of overdistension.

The use of esophageal manometry to estimate pleural pressure and titrate PEEP in order to maintain a positive end-expiratory P_L may allow individualization of MV to avoid VILI from tidal recruitment and tidal overdistension(96). In 61 ARDS patients, those randomized to esophageal pressure-guided PEEP had significantly better oxygenation and compliance up to 72 hours from randomization as compared to controls (i.e., ARDSNet PEEP-FiO_2 table).

Future investigations on the effect of PEEP on the interaction between lung volume and alveolar overdistension and the refinement of means to accurately assess lung recruitability and overdistension will further inform the design of new clinical trials to identify optimal PEEP titration strategies in patients with ARDS.

Lung Recruitment Maneuvers

Increasing alveolar recruitment in patients with ARDS has the potential of improving gas exchange and reducing the risk of VILI by reducing stress and strain and minimizing atelectrauma(15, 23, 84). These are the clinical goals of the “open-lung approach” in patients with ARDS (71). One strategy in the open-lung approach is the use of lung recruitment maneuver (RMs)(97). They are defined as intentional intermittent sustained elevations of high

airway pressure with the goal of improving gas exchange, increasing compliance and hence reducing VILI(98, 99).

To be efficacious a RM needs to reach elevated airway pressure resulting in P_L higher than the opening pressure of the collapsed alveoli. The opening pressure of most of the lung units in patients with ARDS is less than 35 cmH_2O(100, 101). However, higher opening pressures may be observed especially in patients with higher elastance of the chest wall(101, 102). A case series of patients with early ARDS showed that after RMs with transient airway pressures of 55-60 cmH_2O, less than 5% of the alveolar units remained collapsed(101).

There is marked variability in the response to RMs in patients with ARDS. For example, (103, 104) one study demonstrated that lung recruitment was achieved in all patients on day 1 of ARDS, whereas patients on day 7, who may have developed alveolar fibroproliferation, did not have a significant response(102). Other studies confirmed this observation(84, 101). Indeed, the portion of recruitable lung tissue can vary depending on the cause of ARDS and on the lung morphology(105, 106). ARDS secondary to severe pneumonia and characterized by extensive consolidation may not have a significant response to RMs. Patients with early ARDS and focal distribution of aeration loss had a significant less lung recruitment after a sustained inflation of 40 cmH_2O for 40 seconds than patients with non-focal morphology (48±66 vs. 417±293 mL)(107). Interestingly, a recent study showed that a poor recruitment response to a sustained inflation maneuver in 42 patients with ARDS was independently associated with high lung stress and may predict a greater risk of death(108).

Patients responsive to RMs can have a remarkable increase in oxygenation and compliance(109). In addition, several studies have shown that the duration of these effects is

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maintained only if associated with an increase in PEEP following the RM to avoid collapse(101, 110).

Experimental data show that RMs are associated with a reduced release of pro-inflammatory mediators and markers of lung injury. A physiologic crossover study of 24 patients with early moderate/severe ARDS demonstrated that RMs resulted in a significant reduction of biomarkers of epithelial dysfunction within 1 hour(111). Similarly, in a randomized study on ARDS, patients treated with RMs and PEEP titration had better oxygenation, higher compliance, and significantly lower plasma IL-8 and TNF-alpha, compared to controls(110).

Nonetheless, RMs can also cause several complications(99, 112). Indeed, the delivery of high P_L invariably results in excessive alveolar stress and overdistension of some alveolar units while others are being recruited. The high intrathoracic pressure, although transient, can result in barotrauma and hemodynamic compromise.

Different techniques are used to perform RMs(99, 113), but it is unclear if any one technique is superior to the others. Nonetheless, strategies that use stepwise increases in airway pressure, compared to sustained inflations, seem to be associated with less hemodynamic impairment and better lung recruitment(114).

Despite encouraging experimental evidence, clinical evidence has failed to conclusively demonstrate the efficacy of RMs in improving significant clinical outcomes in patients with ARDS(109). In fact, the systematic review and meta-analysis published in this issue of the journal suggests that LRMs may be associated with reduced mortality, although the confidence in this finding is limited as a result of co-intervention with higher PEEP(115).

Future studies clarifying the interaction between lung volume and VILI will contribute to optimize the clinical application of the open-lung approach in ARDS.

Extracorporeal Lung Support (ECLS)

Venovenous extracorporeal membrane oxygenation (VV-ECMO) can provide adequate oxygenation and carbon dioxide clearance through an artificial lung with minimal or no contribution from the native respiratory system. Patients with severe ARDS requiring VV-ECMO are particularly susceptible to VILI because of the severity of lung injury with extensive alveolar consolidation and very small aerated lung units. In this context, even protective MV settings may induce excessive regional stress and strain. By providing extracorporeal gas exchange, ECLS buys time for the lung to heal from the primary disease process, while minimizing VILI(116). However, there is a paucity of data to support the widespread application of ECLS in patients with ARDS(117, 118).

Very few studies have been performed to identify optimal MV strategies during VV-ECMO. In a French observational study of patients with H1N1-associated ARDS supported with VV-ECMO, a multivariable analysis showed that Pplat during ECMO support was independently associated with ICU mortality(119). These results were confirmed in a recent individual patient data meta-analysis of observational studies on VV-ECMO for refractory hypoxemia, showing that ΔP was the only mechanical ventilation parameter independently associated with in-hospital mortality(120).

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There is a general consensus that during VV-ECMO tidal volumes and alveolar distending pressures should be minimized to mitigate tidal overdistension and cyclic airway opening and closing. However, it is unknown what is the minimal V_T or airway driving pressure required to maximize survival.

Very few data exist regarding the application of PEEP in patients supported with VV-ECMO(116). Higher PEEP during VV-ECMO may prevent worsening lung collapse and atelectasis, which may occur especially when very low tidal volumes are delivered. A multicenter observational study showed that higher PEEP during the first 3 days of VV-ECMO was independently associated with lower mortality(121). Another study in patients supported with VV-ECMO used EIT during a decremental PEEP trial to identify the optimal PEEP, defined as the best compromise between alveolar overdistension and collapse(122). In most of the patients recruited in the study, the optimal PEEP was found to be 15 or 10 cmH_2O, but never zero or 20 cmH_2O.

However, the need to achieve optimal alveolar recruitment with high PEEP is still very controversial(116, 123). During VV-ECMO alveolar recruitment is no longer required to improve oxygenation or to reduce the risk of alveolar overdistension. Nonetheless, it may still improve cardiopulmonary function and facilitate lung healing. However, during VV-ECMO the lung is perfused with oxygenated blood, which reduces the atelectasis-induced local lung tissue hypoxia and the consequent pulmonary vasoconstriction. Moreover, there is experimental evidences showing that atelectatic lung may be less susceptible to inflammation than a partially recruited lung. In an ex-vivo model of MV in rat, lungs at functional residual capacity ventilated

with small tidal volumes had significantly higher concentrations of inflammatory mediators in the bronchoalveolar lavage than atelectatic lungs(124).

There is also uncertainty regarding the risk of allowing spontaneous breathing during VV-ECMO(125). The potential control of the respiratory drive and effort by maintaining normal blood gas tension with the artificial lung may allow a safe switch from controlled to assisted modalities of MV, which may improve diaphragmatic function, hemodynamics and reduce sedation requirements. In this regard, two case series showed that the modulation of carbon dioxide removal by ECMO has a prominent effect on the spontaneous breathing pattern of patients recovering from ARDS, facilitating reduction of the patient inspiratory drive and effort, V_T, and respiratory rate(126, 127). However, blood gases may not be the sole drivers of respiratory drive in patients with ARDS.

Nonetheless, generation of excessive P_L and patient-ventilator asynchrony may worsen during spontaneous breathing especially in patients with very low compliance irrespective of the normal gas exchange. Indeed, in a patient on VV-ECMO recovering from *Pneumocystis jirovecii* infection-induced ARDS, the dynamic lung distending pressure, estimated using esophageal manometry, was extremely high and approximately 38 cmH_2O despite protective MV settings(128).

Low flow extracorporeal carbon dioxide removal (ECCO2R) is another promising extracorporeal modality of respiratory support, whose potential benefit has been suggested by interesting preclinical and some clinical data(129, 130). Overall, although the application of $ECCO_2R$ has been shown to very effective in facilitating the reduction of V_T, its use to prevent VILI and therefore to improve survival requires further investigations.

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Conclusions

A large body of experimental studies has been performed to better understand the pathophysiological effect of MV and inform the design of clinical trials. This remarkable process of translational research has greatly contributed to the improvement in survival of patients with ARDS.

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ANNALSATS Articles in Press. Published on 06-October-2017 as 10.1513/AnnalsATS.201704-345OT

Figure Legend:

Figure 1: MV: mechanical ventilation, V_A: alveolar ventilation, Q: perfusion, VILI: ventilator-induced lung injury, HFOV: high frequency oscillatory ventilation, PEEP: positive end expiratory pressure, LRM: lung recruitment maneuvers, ECLS: extracorporeal life support, LTV: limited tidal volumes and inspiratory pressures

Physiologic mechanisms of VILI

Potential **decreased cardiac output** from:
-decreased pre-load
-increased pulmonary vascular resistance

Decreased compliance

"Baby lung"

High risk of VILI from
excessive trans-pulmonary pressure
with consequent:
-tidal overdistension (volutrauma)
-increased dead space

Lower pleural pressure

Higher V_A/Q

High risk of VILI from:
-**tidal recruitment** (atelectrauma)
-local **stress raisers** resulting in excessive trans-pulmonary pressure

Lower V_A/Q

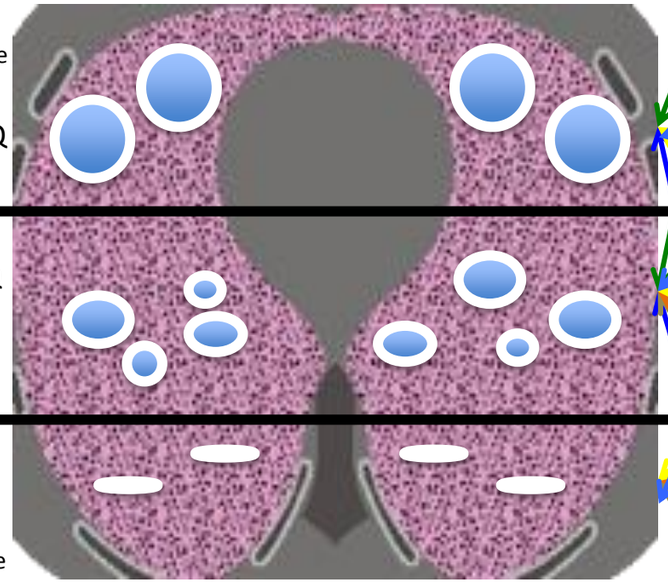
Alveolar inhomogeneity

Lung volume loss
De-recruitment

Low risk of VILI
due to alveolar collapse/consolidation
with no V_A

Shunt

Higher pleural pressure



Potential beneficial mechanisms of each MV intervention

MV with LTV
-Reduction of volutrauma
-Reduction of atelectrauma

Prone position
-Reduction of volutrauma
-More homogeneous distribution of trans-pulmonary pressure
-Improvement of V_A/Q matching
-Reduction of atelectrauma
-Increase of alveolar recruitment

HFOV
-Reduction of volutrauma
-Reduction of atelectrauma
-Increase of alveolar recruitment

Higher PEEP
-Reduction of atelectrauma
-Reduction of alveolar inhomogeneity
-Increase of alveolar recruitment
-Indirect reduction of volutrauma

LRM
-Reduction of atelectrauma
-Reduction of alveolar inhomogeneity
-Increase of alveolar recruitment
-Indirect reduction of volutrauma

ECLS
-Reduction of volutrauma
-Reduction of atelectrauma