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Expert Review

Management Strategies for Severe and Refractory Acute Respiratory Distress Syndrome: Where Do We Stand in 2018?

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ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) is an acute and diffuse inflammation of the lung causing severe respiratory failure and has been characterized as a devastating illness since its discovery in the 1970s. The mainstay of management has been supportive care with mechanical ventilation and treatment of inciting causes. The conceptual approach to the treatment of ARDS has been evolving over the last few decades and now is centered on maintaining oxygenation and adequate organ support, mitigating ventilation-induced lung injury, treating the underlying causes and coexisting illnesses, and preventing and addressing complications of prolonged intensive care. The present review describes the evidence and rationale behind major concepts of ARDS treatment with a focus on recently published trials on the open lung approach with recruitment maneuvers and the use of extracorporeal life support in severe ARDS. Key established treatments such as low tidal volume ventilation, positive end-expiratory pressure, neuromuscular blockers, and prone position ventilation also are discussed. The use of corticosteroids; inhaled vasodilators; conservative fluid strategy; and novel modes of ventilation, such as high frequency oscillation and airway pressure release ventilation, are other important aspects but are beyond the scope of this review.

ACUTE RESPIRATORY distress syndrome (ARDS) is an acute and diffuse inflammation of the lung occurring in the context of a known clinical insult, leading to severe respiratory failure. It is a devastating critical illness that frequently is lethal, and many survivors experience a variety of long-lasting physical disabilities, such as contractures, muscle weakness, and neurologic and psychiatric problems, such as cognitive decline, depression, and posttraumatic stress disorder.[1] Supportive care with mechanical ventilation is the mainstay of ARDS management, along with treatment of the underlying causes. However, mechanical ventilation itself may lead to progression of lung injury and contribute to organ failure and mortality.[2] The optimal strategy for mechanical ventilation; the use of positive end-expiratory pressure (PEEP), recruitment maneuvers (RMs), prone position ventilation, and neuromuscular paralysis; and the role of extracorporeal membrane oxygenation (ECMO) in ARDS have been studied extensively and debated for the last 2 decades.

ARDS has been defined as a type of acute, diffuse inflammatory lung injury occurring within 1 week of a known clinical insult, with chest imaging showing evidence of bilateral opacities (not fully explained by effusions, lobar/lung collapse, or nodules) and with respiratory failure not fully explained by cardiac failure or fluid overload.[3] According to the Berlin consensus definition, ARDS is classified as mild, moderate, or severe

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based on the ratio of partial pressure of arterial oxygen and fraction of inspired oxygen (PaO_2/F_iO_2), with PaO_2/F_iO_2 <300 and PEEP ≥5 cmH_2O being mild, PaO_2/F_iO_2 <200 and PEEP ≥5 cmH_2O being moderate, and PaO_2/F_iO_2 <100 and PEEP ≥5 cmH_2O being severe.[4] Pneumonia from aspiration of gastric contents and sepsis account for more than 85% of cases of ARDS. Some other associated clinical insults are inhalational injury, near drowning, nonthoracic trauma or hemorrhagic shock, pancreatitis, major burns, and drug overdose.[3]

Principles of Ventilator Support: Initial Ventilator Settings

Using the ARDS Network protocol, the predicted body weight should be calculated using the patient's height. The initial tidal volume should be set at 8 mL/kg and then be decreased in 1 mL/kg equivalents ≤2 hours apart until a goal of 6 mL/kg is reached. This may be decreased to 4 mL/kg to achieve a plateau pressure of <30 cmH_2O or may be increased to 8 mL/kg in cases of ventilator dyssynchrony if the plateau pressure goal is not exceeded. The respiratory rate should approximate baseline ventilation (but not exceed 35/min).

Evidence and Rationale

The use of a ventilatory strategy with low tidal volumes (4-8 mL/kg) normalized to predicted body weight and lung size and lower inspiratory pressures (plateau pressures <30 cmH_2O) is perhaps the most well-studied and validated critical care intervention in recent times. The first major randomized control trial on lung protective ventilation, by Amato et al.[5] in 1998, demonstrated that a lung protective strategy of low tidal volumes (6 mL/kg of predicted body weight), higher PEEP, and permissive hypercapnia resulted in lower mortality, lower incidence of ventilator-induced barotrauma, and earlier weaning compared with conventional ventilation. Subsequently, the larger ARDS Network Trial[6] randomly assigned 861 patients to tidal volumes of 6 mL/kg of body weight and plateau pressure of ≤30 cmH_2O versus tidal volumes of 12 mL/kg of body weight and a plateau pressure of ≤50 cmH_2O. That trial showed that the low tidal volume group demonstrated a significant mortality benefit. Criticisms of the Amato et al. and ARDS Network trials have focused on the very high airway pressures in the conventional ventilation arms, leading to the suggestion that the benefit of low tidal volumes may be a function of plateau pressures.[7] A meta-analysis performed on this topic by the American Thoracic Society in its official clinical practice guideline for mechanical ventilation in ARDS[2] showed that trials with larger tidal volume gradients between studied and control groups have a lower mortality risk for low tidal volumes. In addition, trials that protocolized low tidal volume with high PEEP cointervention demonstrated significantly reduced mortality. In summary, although the beneficial effect of low tidal volumes may be affected by airway pressures and PEEP cointerventions, the official 2017 American Thoracic Society clinical practice guideline for mechanical ventilation of adults with ARDS strongly recommends the use of low tidal volumes (4-8 mL/kg) and airway pressures (plateau pressure <30 cmH_2O) with a moderate confidence in effect estimates.[2]

PEEP: Evidence and Rationale

Based on the Berlin consensus definition, the initial PEEP should be set using the ARDS Network protocol high PEEP/F_iO_2 table.[6] Historically, PEEP has been used in acute respiratory failure mainly to improve oxygenation; however, after the discovery of atelectrauma and ventilator-induced lung injury (VILI), the aim of the PEEP setting shifted from oxygenation to lung protection.[8] PEEP recruits and stabilizes collapsed airways and small alveoli, improves the compliance of the respiratory system, and reduces intrapulmonary shunting.[9-12] However, excess PEEP may propagate VILI by stressing the pulmonary fibrous skeleton[13] and overdistending healthy alveolar units. It also may compress the pulmonary microvasculature and result in increased vascular resistance and dead-space ventilation, which may reduce cardiac output and systemic oxygen delivery.[12] There are multiple approaches to setting PEEP for a patient with ARDS. The ARDS Network protocol PEEP/F_iO_2 tables assign a PEEP value to every F_iO_2 value, with a low PEEP and high PEEP table.[6] These tables are based on how PEEP and F_iO_2 were adjusted by expert physicians in the 1990s in clinical practice at hospitals participating in the study.[14] They were not derived from robust trial data, nor were they individualized to a patient's respiratory mechanics or clinical context. Some investigators have proposed setting individualized best or optimal PEEP, derived from plotting a pressure-volume curve for each patient by stepwise changes in applied airway pressure (with or without RMs) and setting the PEEP slightly above the lower inflection point of this curve.[15] The aim of this conceptual approach was to recruit as much collapsed lung as possible to improve oxygenation and mitigate VILI by avoiding repetitive opening and closing of alveolar units and overdistention of healthy alveoli. This elusive individualized best PEEP, or optimal PEEP, has been titrated based on static or dynamic respiratory system compliance,[12,15,16] with or without RMs using the open lung approach,[17] using the concept of lower driving pressure,[18] using computed tomography imaging to assess lung aeration,[19] or using esophageal probes to estimate transpulmonary pressures.[20] The results of the large Alveolar Recruitment for Acute Respiratory Distress Syndrome trial (ART)[17] have tempered the enthusiasm for the open lung approach using aggressive lung recruitment followed by decremental PEEP titration.[21] After decades of research, none of the physiologically elegant approaches to setting PEEP have been shown to be superior to, or improve, clinical outcomes over the ARDS Network PEEP/F_iO_2 tables[22,23] designed in the 1990s. Gattinoni et al. suggested that the best way to determine optimal or ideal PEEP has not been found perhaps because an optimal, or ideal, PEEP value does not exist[8] or does not matter as much as some believe it should. The 2017 ATS guidelines

recommend the use of high PEEP over low PEEP for adults experiencing moderate to severe ARDS,[2] based on a meta-analysis of individual patient data from 3 large randomized controlled trials that showed that use of higher PEEP is associated with a statistically significant reduction in mortality.[24] In summary, a reasonable approach would be to set PEEP on the basis of the PEEP/F_iO_2 tables, using the higher PEEP table for severe ARDS, which could be individualized by experienced clinicians to the clinical context and respiratory mechanics during the course of illness.

The Role of Prone Position Ventilation: Evidence and Rationale

After a 12- to 24-hour stabilization period with a low tidal volume and high PEEP strategy, the ARDS patient should be placed in a completely prone position for 12 to 16 consecutive hours per day. Prone position ventilation may improve oxygenation and decrease VILI by improving ventilation–perfusion matching and by altering chest wall mechanics.[25] Prior randomized controlled trials performed on prone ventilation showed improved mortality only in subgroups with severe ARDS, those on longer duration of prone position (>12 h/d), and those with concomitant low tidal volume ventilation.[2] The strongest evidence of better clinical outcomes comes from the large PROSEVA study,[26] which randomly assigned 466 patients with severe ARDS (mean PaO_2/F_iO_2 100 ± 30 mmHg) to 16 hours per day of prone-position ventilation compared with supine ventilation. All patients received low tidal volume ventilation, and the majority also received neuromuscular blockade. There was a significant mortality benefit in the prone group, although the rate of endotracheal tube obstruction and pressure sores was higher. Furthermore, the mean PEEP levels in that trial were only around 10 cmH_2O, and thus it remains to be seen whether the benefits of prone ventilation persist with a higher PEEP cointervention and outweigh the risks outside of expert centers that have considerable experience and training in the management of prone patients. The ATS 2017 guidelines strongly recommend prone position ventilation for severe ARDS (moderate-to-high confidence in effect estimates).[2]

Evidence and Rationale for Neuromuscular Blocker Agents in ARDS

ARDS patients should receive neuromuscular blocker agents (NMBAs) for 48 hours by continuous infusion early during their illnesses, with careful monitoring of the depth of blockade along with adequate sedation and analgesia.

Low tidal volume ventilation in critically ill patients may lead to severe patient ventilator asynchronies in up to 26% of patients.[27] Breath stacking and patient–ventilator asynchrony may result in ineffective gas exchange and lead to unintended high tidal volume exposure, which could propagate VILI.[28] The use of NMBAs may ameliorate asynchrony and improve gas exchange; however, some adverse effects include complications of increased sedation requirements and development of prolonged neuromuscular weakness. Randomized controlled trials have shown an improved PaO_2/F_iO_2 ratio[29] and reduced levels of proinflammatory cytokines[30] in patients with severe ARDS treated early with 48 hours of cis-atracurium infusion. In the ARDS et Curarisation Systematique (ACURASYS) trial,[31] which enrolled 340 patients with severe ARDS (PaO_2/F_iO_2 <150), those treated with a high fixed dose of cis-atracurium had an increased 90-day survival, more ventilator-free days, and decreased barotrauma compared with the placebo-treated patients. No difference was detected between groups in the development of intensive care unit–acquired weakness.[31] The overwhelming majority of patients with moderate to severe ARDS in recent large randomized controlled trials received neuromuscular blockers as a cointervention. Use of neuromuscular blockers for early and severe ARDS (PaO_2/F_iO_2 <150) for a period of 48 hours is endorsed by the Society of Critical Care Medicine.[32,33]

Evidence and Rationale for RMs in ARDS

RMs should not be performed routinely in ARDS. There are significant risks of performing an RM in these patients because of their hemodynamic status, and their efficacy is controversial at best.

RMs are transient elevations in applied airway pressure intended to reopen collapsed and airless alveolar units, leading to increased end-expiratory lung volume for improved gas exchange, uniform distribution of tidal volume, and reduction in VILI by avoiding repetitive opening and closing of unstable alveolar units. Conversely, RMs also could overdistend already aerated lung units and cause lung injury and barotrauma. RMs commonly cause transient hypotension or oxygen desaturation, but life-threatening complications such as pneumothorax, arrhythmias, and cardiovascular collapse may occur.[34] Whether RMs are safe and effective currently is controversial because clinical studies have yielded conflicting results, perhaps because the overall clinical outcome is dependent on multiple factors, which vary widely among trials.[35] Some of these factors include the magnitude and duration of the applied airway pressure; the method of application (such as a sustained inflation or incremental PEEP); whether the RM is performed early or late in the course of illness; frequency of the RM (twice daily, daily, alternative days); and cointerventions used (neuromuscular blockade, PEEP, and fluid balance strategy). The ATS 2017 guidelines[2] suggest that RMs should be performed (conditional recommendation, with low to moderate confidence in effect estimates); however, this guideline did not incorporate the results of the recently published ART trial,[17] a prospective randomized controlled trial that enrolled 1,013 patients to compare lung recruitment and a titrated PEEP strategy ("open lung strategy") with the ARDS Network low PEEP strategy.[17]

The open lung strategy included an initial RM followed by setting an optimal PEEP level that was determined by static respiratory compliance during a decremental PEEP trial, followed by a second RM. The open lung strategy resulted in higher 28-day mortality (55%) compared with the ARDS Network low PEEP

strategy (49%) after adjustment of relevant covariates, with a significant increase in the incidence of pneumothorax requiring drainage, other barotrauma, and the need for vasopressors in the intervention group. During the entire course of the trial, RMs had to be interrupted in 16% of patients, mostly owing to hemodynamic instability or oxygen desaturation, and halfway through the trial, the RM was changed to lower the targeted plateau pressure from 60 to 50 cmH_2O because of 3 cardiac arrests associated with the procedure. A recent systematic review of 7 randomized controlled trials with 2,480 patients that incorporated the ART trial concluded that lung RMs did not improve mortality, ventilator-free days, or intensive care unit length of stay.[36] A reasonable and cautious conclusion is that RMs are best avoided routinely and should be considered only on a case-to-case basis as a salvage therapy for early severe ARDS with consideration for chest wall mechanics and underlying pre-existing lung disease and with careful attention to the respiratory and hemodynamic status during the maneuver.

The Role of ECMO in ARDS

ECMO should be considered for severe ARDS with refractory severe hypoxemia or evolving cardiovascular failure despite low tidal volume ventilation with permissive hypercapnia, optimal PEEP, fluid restrictive strategy, neuromuscular blockade, and prone positioning for >2 h/day. However, whether heroic measures such as ECMO ultimately improve meaningful survival over conventional ARDS treatment and justify the risks and costs still is controversial. The decision to initiate ECMO for severe ARDS should be based on the resources and expertise available and be individualized to the patient's clinical circumstances, comorbidities, estimated prognosis, and overall quality-of-life concerns.

Evidence and Rationale

ECMO is an extracorporeal life support technique using cardiopulmonary bypass technology to support gas exchange independent of mechanical ventilation.[37] This permits the use of lower tidal volumes and airway pressures in severe acute respiratory failure and decreases the overall mechanical power applied to the lungs, potentially minimizing injurious aspects of mechanical ventilation, which may perpetuate lung injury.[38] ECMO also can remove carbon dioxide and provide cardiovascular support to the failing right ventricle, which is a common complication of ARDS.[39]

ECMO, like all invasive techniques, has associated risks and complications. According to the extracorporeal life support registry report from January 2017, the average run time for venovenous ECMO for adult respiratory failure is 279 hours, with common complications being culture-proven infections (17%), renal injury (16%), and cannulation and surgical site bleeding (10%-12%). Intracranial hemorrhage remains one of the most devastating complications of ECMO, occurring in 3% to 4% of patients.

ECMO has been used extensively for decades in patients with ARDS, particularly those with potentially reversible acute respiratory failure, such as severe influenza infection.[40] However, despite the growing use of venovenous ECMO in patients with ARDS,[41] the supporting evidence remains controversial.

Since 1979, 4 randomized controlled trials[42-45] have examined extracorporeal life support for acute respiratory failure in adults, but both knowledge of ARDS and technology for extracorporeal life support have advanced drastically since the early negative trials by Zapol et al. in 1979[42] and Morris et al. in 1994.[43] The Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial by Peek et al. in 2009[44] was a large, multicenter, randomized control trial that assigned 180 patients with ARDS to conventional ventilation or referral to a specialized center for ECMO treatment. Sixty-three percent (57/90) of patients allocated to consideration for treatment with ECMO survived to 6 months without disability compared with 47% (41/87) of those allocated to conventional management (relative risk 0.69, 95% confidence interval 0.05-0.97; $p = 0.03$), which translates to an absolute risk reduction of 16% and a number-needed-to-treat of 6.2. The results of the CESAR trial make a compelling case for referral to a specialized ECMO center (1 life could be saved for every 6 referrals) but not necessarily for ECMO itself because only 76% of patients randomly assigned to the intervention group received ECMO (24% were treated with conventional strategies). Also, the heterogenous ventilation strategies (including larger than recommended tidal volumes) and the lack of strict management protocols in the control arm perhaps led to a bias in favor of the intervention. To overcome limitations of prior trials, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial[45] enrolled 240 patients with established diagnosis of severe ARDS if they had undergone endotracheal intubation and had been receiving ventilation for fewer than 7 days and if they met disease-severity criteria as follows: PaO_2/F_iO_2 <50 mmHg >3 hours; PaO_2/F_iO_2 <80 mmHg for >6 hours; or an arterial blood pH of less than 7.25 with a partial pressure of arterial carbon dioxide of at least 60 mmHg, >6 hours with respiratory-system compliance <0 mL/cmH_2O, driving pressure >16 cmH_2O, and Sequential Organ Failure Assessment score >10. Patients were enrolled within 7 days of diagnosis. One hundred twenty-one of 124 patients enrolled in the EOLIA trial who were randomly assigned to the intervention arm of ECMO received it, and the ECMO approach was highly standardized. It was encouraged that all patients receive NMBAs and prone positioning before randomization. Also, the protocol for the control group for ventilator management was according to current recommendations and included low tidal volume ventilation, RMs with PEEP, prone positioning (used in 90% of the patients in the control group), and neuromuscular blockade (used in 100%). Crossover from the control arm was allowed for prolonged of arterial oxygen desaturation <80%. The trial was stopped after 67 months owing to futility on the basis of prespecified criteria, and although there was an 11% reduction in 60-day mortality in the ECMO group, this failed to reach statistical significance. The trial investigators concluded that ECMO did not change the 60-day mortality for severe ARDS. Criticisms of the trial focused on the decision of the data safety monitoring board, which stopped the trial early based on its statistical prediction of an eventual negative outcome. This was done for patient safety but ultimately precluded the clinical certainty that was so desperately sought for the use of ECMO in severe

ARDS.[46] Although there was no statistically significant difference in 60-day mortality, 35 (28%) patients in the control group crossed over to the intervention group for rescue ECMO owing to severe hypoxemia and hemodynamic compromise (9 for cardiac arrests), 15 of whom survived. It is unlikely that those 15 patients would have survived without rescue ECMO, and for them, the statistical conclusions of this trial probably are meaningless. In conclusion, it appears that the debate regarding ECMO for severe ARDS will continue.[46] The believers may make positive conclusions from a negative trial with good reason, and the sceptics may justifiably remain unmoved.

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