

The Role of Rescue Therapies in the Treatment of Severe ARDS

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Summary

ARDS is characterized by a non-cardiogenic pulmonary edema with bilateral chest radiograph opacities and hypoxemia refractory to oxygen therapy. It is a common cause of admission to the ICU due to hypoxemic respiratory failure requiring mechanical ventilation. Corticosteroids are not recommended in ARDS patients. Rescue therapies alleviate hypoxemia in patients unable to maintain reasonable oxygenation: recruitment maneuvers, prone positioning, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation improve oxygenation, but their impact on mortality remains unproven. Restrictive fluid management seems to be a favorable strategy with no significant reduction in 60-d mortality. Future studies are needed to clarify the efficacy of these therapies on outcomes in patients with severe ARDS, and institution of these therapies may be considered on a case-by-case basis. Key words: severe ARDS; refractory hypoxemia; ventilatory setting; rescue therapies; extracorporeal membrane oxygenation; prone position.

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Introduction

ARDS is a life-threatening condition that complicates a variety of critical illnesses, including sepsis, pneumonia, pancreatitis, and trauma.¹ It is characterized by intense lung inflammation, progressive microatelectasis, diffuse alveolar damage, increased pulmonary vascular permeability, increased lung weight, and loss of aerated tissue.² ARDS is clinically associated with severe hypoxemia, pa-

tient-ventilator asynchrony, and high susceptibility to barotrauma and ventilator-induced lung injury (VILI).³

ARDS was first described 50 years ago by Ashbaugh and Petty⁴ in a case series of 12 patients who shared the common features of unusually persistent tachypnea and hypoxemia, opacification on chest radiographs, and poor lung compliance, despite different underlying causes. In 1994, the American and European Consensus Conference

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Table 1. The Berlin Definition of ARDS

Factors	Criteria
Timing	Within 1 week of a known clinical insult or new worsening respiratory symptoms
Chest imaging	Bilateral opacities not fully explained by effusions lobar/lung collapse, or nodules
Origin of edema	Pulmonary edema not fully explained by cardiac failure or fluid overload; objective assessment (eg, echocardiography) is required to exclude hydrostatic edema if no risk factor is present
Oxygenation	Requires CPAP/PEEP > 5 cm H ₂ O
Mild	$P_{aO_2}/F_{IO_2} = 201-300$ mm Hg
Moderate	$P_{aO_2}/F_{IO_2} = 101-200$ mm Hg
Severe	$P_{aO_2}/F_{IO_2} < 100$ mm Hg

proposed a new definition of ARDS that was globally accepted.⁵ In 2012, this definition was revised by an international panel of experts and is now referred to as the Berlin definition of ARDS (Table 1).⁶ A recent large observational study⁷ reported an ARDS prevalence of 10.4% of all ICU admissions and of 23.4% of all subjects receiving mechanical ventilation. ARDS appears to be underrecognized, undertreated, and associated with an especially high mortality rate of 46.1% for patients with severe ARDS.

The primary target for ARDS treatment is to ensure adequate gas exchange while minimizing the risk of VILI. To date, treatment is largely supportive, and mechanical ventilation remains the cornerstone. Some patients are unable to maintain adequate oxygenation despite being supported with conventional mechanical ventilation, and life-threatening refractory hypoxemia may occur. Although a standard definition for refractory hypoxemia is a matter of ongoing debate, in most reports it has been defined as having a $P_{aO_2} < 60$ mm Hg, with an F_{IO_2} of 0.8–1.0 and a PEEP > 10–20 cm H₂O for > 12–24 h. Under these circumstances, physicians may consider a number of supportive therapies, which are a final rescue attempt to prevent severe complications or death from hypoxemia (Fig. 1). Rescue therapies are only temporary methods that can support or replace respiratory function in patients with severe refractory respiratory failure on conventional mechanical ventilator support. Although these strategies improve oxygenation, their impact on mortality remains unproven, and they require a higher cost in terms of increased risk compared with standard care. Institution of these therapies may be considered on an individualized basis, and the choice will often be dictated by local availability and expertise.^{8,9}

Ventilation and PEEP

In a large study conducted by the ARDS Network,¹⁰ mortality was reduced and the number of ventilator-free days was greater in the group treated with lower tidal

volumes (V_T 6 mL/kg of predicted body weight) than in the group treated with traditional V_T . Decreasing plasma interleukin-6 (IL-6) concentrations, suggested that the group treated with lower V_T had less lung inflammation. A reduced systemic inflammatory response to lung injury could contribute to the higher number of days without organ or system failure and the lower mortality in the group treated with lung-protective ventilation.¹⁰ As compared with conventional ventilation, the protective strategy was associated with a higher rate of weaning from mechanical ventilation and a lower rate of barotrauma in patients with ARDS, despite the use of higher PEEP levels and higher mean airway pressures.¹¹ High levels of IL-8, IL-6, TNF- α , IL-1 β in bronchoalveolar lavage of patients with ARDS confirm the relevance of cytokines in the amplification of the inflammatory cascade leading to multi-organ failure and increasing mortality. Ranieri et al¹² compared lung-protective ventilation with conventional ventilator strategy to evaluate the influence of mechanical ventilation on lung and systemic cytokine levels. The concentration of inflammatory mediators was lower 36 h after randomization in the lung-protective ventilation group than in the conventional strategy group. This lung-protective ventilation strategy aims to minimize VILI, which may result from alveolar overdistention or repeated opening and closing of individual lung units.

While in the past the choice of a specific mode of mechanical ventilation (pressure-controlled vs volume-controlled), was considered relevant for patient outcome, 2 recent meta-analyses were not able to show any significant difference in mortality, risk of barotrauma, or other physiologic responses.^{13,14} Despite the use of pressure- and volume-limited ventilatory strategies, lung injury may still persist or progress in some patients, resulting in worsening hypoxemia.¹⁵ Limited aerated lung tissue available to receive tidal ventilation consequently leads to regional hyperinflation and excessive stress; insufficient PEEP leads to excessive shear injury.

Dependent lung regions of patients with ARDS contribute significantly to the development of hypoxemia because of shunts in perfused, nonaerated alveoli. Strategies to open this collapsed lung tissue may improve oxygenation and further reduce mortality. This especially may be an issue in patients receiving low V_T ventilation in which a substantial portion of the lung may remain collapsed due to pressure and volume limitations. Terragni et al¹⁶ obtained pulmonary computed tomography at end-expiration and end-inspiration for 30 subjects treated with lung-protective ventilation. One third of subjects experienced substantial tidal hyperinflation with V_T 6 mL/kg predicted body weight and plateau pressure (P_{plat}) < 30 cm H₂O. In these subjects, the concentration of inflammatory mediators was higher and the number of ventilator-free days was lower than in the two thirds of subjects who experienced

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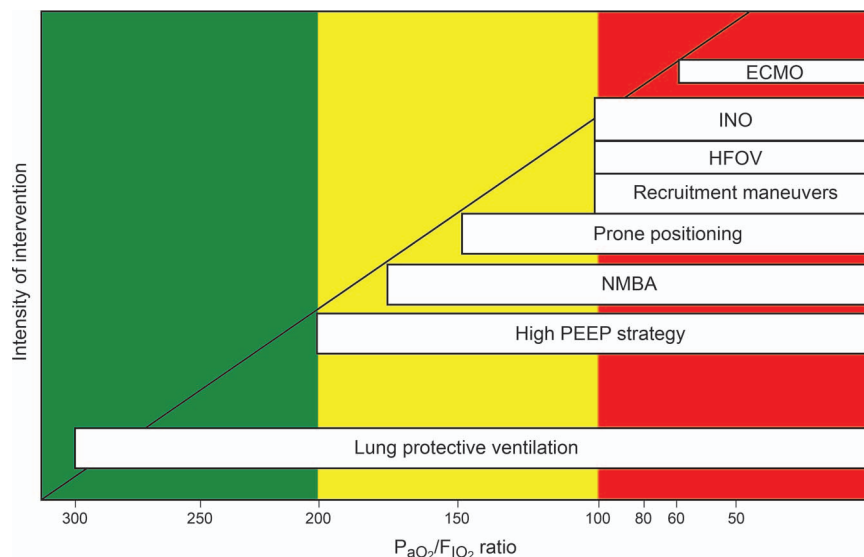


Fig. 1. Rescue therapy in increasing hypoxemia severity. Green indicates mild severity, yellow moderate severity, and red severe. ECMO = extracorporeal membrane oxygenation, HFOV = high-frequency oscillatory ventilation, INO = inhaled nitric oxide, NMBA = neuromuscular blocking agent.

less tidal hyperinflation. $P_{\text{plat}} < 28$ cm H₂O were associated with less tidal hyperinflation than values of P_{plat} of 28–30 cm H₂O. $P_{\text{plat}} < 28$ cm H₂O seems to be associated with the more protective ventilatory settings. The ARDS Network settings may not be sufficient to minimize VILI in patients with ARDS whose disease process is characterized by a distribution of pulmonary lesions with a small, nondependent, normally aerated compartment and a large, dependent, nonaerated compartment. The proportion of nonaerated lung may be recruited by applying higher levels of PEEP than traditionally used (5–12 cm H₂O) in the management of patients with ARDS.^{17,18} Amato et al¹⁹ postulated that cyclic strain predicts lung injury better than V_T . The functional lung size during disease is better quantified by the compliance of the respiratory system than by predicted body weight. Under such conditions, especially when the compliance of the respiratory system varies considerably among patients, cyclic strain, VILI, and survival should all be correlated with driving pressure rather than with V_T .

Although several experimental and observational studies found a beneficial effect for the use of higher PEEP in ARDS, 3 randomized trials, published between 2004 and 2008, did not show any difference in outcome between a low and a high PEEP ventilator strategy.^{20–22} However, when combining these data and considering only the subgroup of the most severe subjects ($P_{\text{aO}_2}/F_{\text{IO}_2} < 200$ mm Hg), the use of higher PEEP levels significantly decreased mortality.²³ This suggests that the greater the severity (and the greater the amount of lung edema), the greater the positive effect of PEEP in reducing VILI. This has also been confirmed in an observational study, in which

higher PEEP levels significantly reduced the opening and closing effects only in subjects with higher recruitability.²⁴ However, the relationship between lung edema and recruitability has been questioned by Cressoni et al,²⁵ who found that the PEEP levels necessary to keep the lung open were independent from total lung recruitability. These results suggest that recruitability depends also on the nature of edema, time of onset, and distribution of the disease within lung parenchyma.

Although several approaches have been proposed to tailor PEEP for the individual patient, the most common is to titrate PEEP according to an oxygenation/saturation target based on a PEEP/ F_{IO_2} table.²¹ In 1975, Suter et al¹⁶ coined the term best PEEP as the point at which the degree of lung recruitment is balanced with the risk of concomitant overdistention. The basis for determining the best PEEP is the quantification of recruitment: to increase PEEP by maintaining a constant V_T , not exceeding a safe limit of P_{plat} 26–28 cm H₂O, or, after a recruitment maneuver, to decrease PEEP until a reduction of compliance appears.²⁷ In a pooled sample of 3,562 subjects with ARDS ventilated with different combinations of V_T and PEEP, the protective effects of higher PEEP were only seen when this was associated with decreased driving pressures, with a cutoff for increased mortality at a driving pressure of 15 cm H₂O.¹⁹ Most important to this discussion was the fact that the relationship between mortality and high P_{plat} was observed only when driving pressure also was above 15 cm H₂O. The airway driving pressure was the factor most associated with the outcome: higher mortality was only found when higher P_{plat} values were observed in subjects with higher driving pressures.

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Many techniques have been proposed to monitor lung recruitment, such as ultrasonography, electric impedance tomography, respiratory mechanics measurements, nitrogen washout techniques, and quantitative computed tomography scan, but none has yet gained general consensus or become routinely used in clinical settings.^{28–32}

Despite the possible uncertainties regarding the end-expiratory absolute esophageal pressure as a reliable estimation of the pleural pressure, better oxygenation and compliance was achieved when PEEP was set according to an end-expiratory transpulmonary pressure of 0–10 cm H₂O.³³ An alternative to using the absolute value of esophageal pressure is to monitor how it changes due to adjustments in PEEP and V_T. This has been used to compute total end-inspiratory transpulmonary pressure, and it is a better marker of lung stress compared with P_{plat} in the presence of alterations in chest wall elastance. Setting high PEEP levels (>15–18 mm Hg) should be accompanied by thorough hemodynamic assessment and might additionally be justified by transpulmonary pressure measurements and assessment of physiological dead space by volumetric capnography.^{34,35}

Recruitment Maneuvers

Recruitment maneuvers are used as a strategy to improve oxygenation and reduce the risk of atelectrauma in patients with ARDS by re-opening and stabilizing collapsed lung regions.¹⁸ Several recruitment maneuvers have been proposed, including sustained inflations with CPAP values of 35–50 cm H₂O for 20–40 s, incremental peak inspiratory pressures, lower V_T (with sighs), intermittent sighs, stepwise increments in PEEP, and slow increases of inspiratory pressure to 40 cm H₂O.³⁶ Recruitment maneuvers attempt to increase the amount of aerated lung tissue to improve gas exchange. However, these may expose regions of healthy lung tissue to increased pressure and the risk of overdistention.

Several studies have shown improved gas exchange with recruitment maneuvers, but this did not translate into improved mortality. Benefits from recruitment maneuvers tend to be short-lived, and the increased airway pressure results in transient adverse events (eg, hypotension, hypoxemia) in a minority of patients. For example, in a recent systematic review, hypotension and decreased saturation occurred in 12% and 8% of subjects, respectively, during or after such maneuvers.^{18,36} However, persistent and severe adverse events related to recruitment maneuvers, such as the development of pneumothorax, remain rare.³⁷ Moreover, studies to date have not elucidated the optimal technique, timing, and frequency of recruitment maneuvers. On the basis of currently available data, although routine recruitment maneuvers are not recommended to treat ARDS, such maneuvers can dramatically

improve oxygenation in certain patients and should be considered as rescue therapy in patients with life-threatening refractory hypoxemia.³⁸

Steroids

Steroids have positive immunomodulatory effects on inflammatory imbalance, reducing edema, hyaline membrane formation, surfactant depletion, and alveolar capillary membrane damage.³⁹ High-dose and short-duration therapy (methylprednisolone 30 mg/kg/d) have demonstrated no improvement in mortality and an increased risk of infection.⁴⁰ A recent meta-analysis investigating lower doses, instituted earlier and for longer duration, appeared to demonstrate improvements in lung function and decreased mortality.⁴¹ However, conclusive evidence about the use of steroids is lacking. Corticosteroids are not recommended as rescue therapy in patients with ARDS, because of improvements have been observed to be delayed and inconsistent.⁴²

Fluid Management

ARDS is a protein-rich inflammatory lung edema into the interstitial space, often associated with a hydrostatic component. The increase in lung weight produces compression atelectasis and impairs lung mechanics and gas exchange. Pulmonary hypertension may be easily associated with increased pulmonary capillary pressure and cardiac failure. While the common mechanisms that cause edema are surgery and pleural effusion, lymphatic flow and capillary reabsorption into the venous side of the pulmonary capillary network are impaired by the positive intrathoracic pressure associated with mechanical ventilation.⁴³ Excessive fluid administration leads to increased extravascular lung water, which is a poor prognostic marker in ARDS. Optimal fluid management provides dry lungs while maintaining organ perfusion.

An ARDS Network trial⁴⁴ was designed to investigate risks and benefits of a fluid management protocol. Subjects with ARDS were randomized to conservative or liberal groups. The conservative group showed improved lung function compared with the liberal group, with fewer days on ventilation and ICU days without increasing non-pulmonary organ failures. There was no significant reduction in 60-d mortality. Over the first 7 d, the liberal group had a fluid balance that increased approximately 1 L/d, whereas those in the conservative group fluid balance remained neutral.

In the subgroup of patients who are hypoproteinemic, there may be a role for accelerated edema clearance when pulmonary capillary permeability and hemodynamic stability is restored, because hypoproteinemic patients may be safely treated with a combination of albumin and fu-

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roseamide. Diuresis, weight loss, and normalization of serum protein concentrations may be achieved, and, over the first 24–48 h of therapy, the P_{aO_2}/F_{IO_2} increased by > 60 mm Hg.⁴⁵ A follow-up study of the same group also reported that P_{aO_2}/F_{IO_2} increased by > 40 mm Hg over 24–72 h compared to a decrease of 13–24 mm Hg in the placebo group.⁴⁶ These represent substantial improvements in oxygenation.

Neuromuscular Blocking Agents

Spontaneous breathing seems to be dangerous in patients with severe ARDS, whereas it appears to be beneficial in patients with mild to moderate ARDS. Neuromuscular blocking agents (NMBAs) should be reserved for the most severe cases to ensure patient–ventilator synchrony and prevent generation of a dangerously high transpulmonary pressure and VILI.⁴⁷

Treatment with a continuous infusion of cisatracurium for 48 h early in the course of severe ARDS reduces 90-d mortality and barotraumas. It also increases the number of ventilator-free days and the number of days outside the ICU. In this context, the risk of ICU-acquired weakness is not increased.⁴⁸ Early use of NMBAs decreases the pro-inflammatory response associated with ARDS and mechanical ventilation. The precise mechanism resulting in improved outcomes is not clear. Better synchrony may lead to more uniform lung recruitment and improved compliance, gas exchange, and systemic oxygenation. With respect to lung inflammation, it is plausible that improved control of inspiratory volumes and pressures reduces volutrauma, while better control of expiratory volumes and pressures reduces atelectrauma; the result is less pulmonary and systemic inflammation.⁴⁹ These potential benefits must be weighed against prevailing concerns about NMBA therapy, including progressive atelectasis due to loss of diaphragmatic tone (with resultant hypoxemia) and, most important, ICU-acquired weakness.⁵⁰

High-Frequency Oscillatory Ventilation

High-frequency oscillatory ventilation (HFOV) is a non-conventional mode that has been proposed to achieve the targets of protective ventilation with very low V_T (equal to or less than the anatomical dead space) at a very high rate (3–6 Hz); sinusoidal flow oscillations are applied around a relatively constant mean airway pressure (\bar{P}_{aw}). This strategy avoids overdistention of alveoli by delivering low V_T (1–3 mL/kg), averting volutrauma, prevents end-expiratory alveolar collapse, and maintains alveolar recruitment by applying a constant \bar{P}_{aw} to facilitate lung recruitment.⁵¹

HFOV theoretically achieves all goals pursued by lung-protective ventilation strategies; however, 2 large randomized clinical trials failed to prove any clinical benefit when

HFOV was applied in adults with moderate to severe ARDS as compared with a strategy with low V_T , high PEEP, and limited P_{plat} . Young et al⁵² did not show any difference in mortality with HFOV compared to conventional mechanical ventilation, whereas Ferguson et al⁵³ reported an increase in mortality with HFOV. High \bar{P}_{aw} suggests that overdistention of some lung regions without increased aeration of collapsed or flooded alveoli occurred, especially among subjects with heterogeneous and nonrecruitable lung. Increased mortality might also be due to the hemodynamic compromise implied by increased requirement of vasopressors and by the right ventricular failure secondary to a considerable increase in afterload. HFOV should not be used routinely in place of conventional lung-protective ventilation, and it should be reserved as a rescue therapy for those patients with refractory hypoxemia and in selected cases of severe ARDS.⁵⁴

The assessment of transpulmonary pressure by measuring esophageal pressure may represent a valid strategy to adopt more physiological \bar{P}_{aw} , reducing the risk of further lung injury and leading to maximal lung recruitment and minimal overdistention.⁵⁵ The EPOCH Study (Clinical Trials.gov NCT02342756) is using this approach to adjust PEEP during conventional mechanical ventilation and \bar{P}_{aw} during HFOV.⁵⁶

Selective Pulmonary Vasodilators

Selective pulmonary vasodilators are commonly utilized for their therapeutic role in improving oxygenation in patients who have developed refractory hypoxemia in ARDS.⁵⁷ These agents localize the drug to lung parenchyma capable of ventilation, improving ventilation-perfusion mismatch. Selective pulmonary vasodilators commonly used include inhaled nitric oxide (INO) and inhaled epoprostenol, a prostacyclin.

INO is a local vasodilator of capillary vessels in well-aerated alveoli, and it improves the ventilation-perfusion match in patients with ARDS and reduces pulmonary vascular resistance, which improves right ventricular output.⁵⁸ The routine use of INO in ARDS is not recommended on the basis of current evidence, but it is frequently used in many institutions. The use of INO in subjects with ARDS showed no significant reduction in mortality.⁵⁹ Use of INO could be considered when patients appear to be at great risk of imminent death from hypoxemia despite all other treatments. INO did not show significant beneficial effects on the duration of mechanical ventilation and stay in the ICU compared to the control group.⁵⁹ Although INO improves oxygenation in the first 24 h by reducing ventilation-perfusion mismatch, over time it will induce vasodilation of poorly ventilated areas, increasing ventilation-perfusion mismatch.⁶⁰

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Improved oxygenation is not associated with increased survival rates because the temporary improvement of oxygenation does not indicate improved lung function, reduction of lung injury, or resolution of the underlying cause of ARDS, including coexisting multi-organ damage.⁶¹ With the use of INO, the difference of pulmonary arterial pressure was initially significant on the first day but no longer present on days 2–4.⁶¹ Nitric oxide is an important regulator of renal vascular tone and a modulator of glomerular function. When INO was first introduced, formation of methaemoglobin, production of reactive nitrogen species, hypotension, and platelet inhibition were the main collateral effects, while nephrotoxicity was not a major concern.^{62,63} Different studies demonstrated that INO increased the risk of renal injury among adult subjects with ARDS and potentially doubled the risk of renal replacement therapy.⁶⁴ Therefore, changes in nitric oxide production could cause acute renal injury by altering the function of mitochondria, various enzymes, and deoxyribonucleic acid. Despite insufficient randomized controlled trials or meta-analyses, the combination therapies with prone positioning or HFOV may help in selected groups of patients or as a salvage therapy because they can enhance the effect of INO better than monotherapy alone.⁶⁵

Inhaled epoprostenol has been suggested as an alternative to INO due to its similar efficacy, lower potential for systemic side effects, ease of administration, and substantially lower cost. Inhaled epoprostenol has been shown to significantly reduce pulmonary artery pressure and increase oxygenation. However, prostacyclin administration is technically challenging given its short half-life and susceptibility to photolysis degradation.⁶⁶ Since it was first publicized for the treatment of ARDS in 1993, efficacy data are lacking.^{57,67} Literature evaluating its use is lacking, and no studies have evaluated mortality as a primary end point. While commonly used as a therapy of final resort, a gap in the literature led to controversy surrounding inhaled epoprostenol with regard to optimal dosing and safety, as well as the target patient population.^{68,69} Iloprost, another selective pulmonary vasodilator traditionally used for treatment of pulmonary hypertension, has theoretical benefits in patients with ARDS, but there is minimal evidence to support its use for this indication.⁷⁰

Prone Position

Prone position was first described 40 years ago as an alternative strategy to improve oxygenation in patients with ARDS.⁷¹ Several mechanisms have been proposed to explain this effect, including a redistribution of lung densities with a recruitment of dorsal regions, an increase in chest-wall elastance, a reduction in alveolar shunt, and a better ventilation/perfusion ratio. A more favorable distribution of stress and strain across a wider and more ho-

mogenous territory (due to chest wall/lung shape matching of ventilation) reduces VILI and reverse right heart failure. As a consequence of lung recruitment, the reversal of hypoxemia and the reduction in driving pressure are the most reasonable explanations for the reduction in pulmonary vascular resistance and right heart dimensions during prone position.⁷² The shift in gravitational forces reduces atelectasis and minimizes compression of lung parenchyma by the heart and mediastinal structures, resulting in improved ventilation–perfusion matching.⁷³

Earlier randomized trials showed inconsistent mortality benefit of prone positioning; however, these studies included all subjects with ARDS (from mild to severe), maintained prone position for 6 h/d, and did not apply protective mechanical ventilation.^{74,75} Despite these limitations, the survival rate increased among subjects with most severe ARDS treated in prone position.⁷⁴ Subsequently, 2 trials, which enrolled more severe hypoxemic subjects with a longer period of prone positioning (20 h/d), did not show any beneficial effects.^{76,77} However, a meta-analysis of previous studies suggested a significant survival benefit for subjects with $P_{aO_2}/F_{IO_2} < 140$ mm Hg at admission.⁷⁸ The PROSEVA trial⁷⁹ was a multi-center randomized controlled trial on early application of prolonged prone position (≥ 16 h/d) in subjects with severe ARDS. In this trial, ARDS severity was defined as $P_{aO_2}/F_{IO_2} \leq 150$ with PEEP ≥ 5 cm H₂O, $F_{IO_2} \geq 0.6$, with an average V_T of 6.1 mL/kg of predicted body weight. The PROSEVA trial showed a major decrease in mortality rate at 28 d and 90 d in subjects treated with prone positioning. Early initiation of prone therapy appears to be an important factor for success. The process of moving a patient to a prone position can be labor-intensive and increases the risk of accidental removal of the endotracheal tube, drains, or catheters, as well as the development of pressure sores.⁷² Although prone positioning presents some technical challenges, when it is performed by a skilled team, the adverse effects are relatively low and they are significantly overcome by the beneficial effects.

Contraindications to prone positioning must be considered, such as increased intracranial pressure or decreased cerebral perfusion, immediate need for a surgical or interventional procedure, recent thoracic surgery, recent facial trauma or surgery, hemodynamic instability, pregnancy or abdominal compartment syndrome, and unstable fractures of the spine, pelvis, or femur.⁸⁰

Extracorporeal Membrane Oxygenation

In severe hypoxemia resistant to conventional treatment, including low-volume, low-pressure ventilation, prone position, INO, and HFOV, extracorporeal membrane oxygenation (ECMO) can be used as a rescue therapy by securing oxygenation as well as carbon dioxide removal

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while the lungs are resting with low ventilator pressure and low oxygen fraction.⁹

ECMO support is commonly performed via veno-venous access in which blood is drained via the superior or inferior vena cava and reinfused in the right atrium. ECMO is indicated when P_{aO_2}/F_{IO_2} is < 80 , when F_{IO_2} is $> 90\%$, and when the lung injury score is 3–4; in this case, the risk of mortality exceeds 80%.⁸¹ In the Berlin definition of ARDS, ECMO is proposed as a rescue therapy for severe hypoxemia when P_{aO_2}/F_{IO_2} is < 50 . ECMO is considered when P_{plat} exceeds 32 cm H₂O, $F_{IO_2} = 100\%$, $S_{pO_2} < 90\%$, or $pH < 7.2$.⁸²

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Indeed, once patients are on ECMO, blood can be well oxygenated with normal P_{aCO_2} and neutral pH; the goal of lung-protective ventilation is achieved and VILI is minimized.⁸³ In patients with particularly severe ARDS who undergo ECMO, V_T is significantly reduced by almost half, which leads to significant reduction in P_{plat} and de-recruitment as PEEP remains stable.⁸⁴ It can take a long time for some patients to re-open their lungs, and there could be a difficult balance between the risk of injury from lung overdistention and the risk of lung under-recruitment.⁸⁴

Over the past few decades, most trials evaluating ECMO demonstrated no benefit because of several factors, including the prolonged interval between ARDS onset and assistance initiation, the poor oxygenation and CO₂ removal capacities of devices used, and the high rate of technical complications such as significant bleeding resulting from intense anticoagulation required to overcome the poor biocompatibility of the circuits.⁸⁵ Recently, however, significant progress has been made in the manufacture of ECMO circuits that are more biocompatible, perform at a higher level, and are more durable.

The United Kingdom-based Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial⁸⁶ and the good outcomes of subjects who received the latest generation of ECMO as rescue therapy during the influenza A (H1N1) influenza pandemic have reignited interest in ECMO for patients with severe ARDS. The CESAR trial in adult subjects with ARDS demonstrated an increase in 6-month survival from 50% to 63% in the ECMO group, but the difference compared to the control group was not significant. When combining the mortality and the 6-month disability end points, the difference became significant in favor of the ECMO group.⁸⁶ However, it is not possible to conclude that ECMO is superior to mechanical ventilation, because all subjects requiring ECMO were allocated only in one skilled center and the control group was not ventilated with a lung-protective strategy.^{87,88}

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Nevertheless, ECMO treatment has a place in clinical practice, as indicated by the Extracorporeal Life Support Organization International Registry Report, in which the number of adult ECMO treatments are expanding.⁸⁹

The currently ongoing ECMO to Rescue Lung Injury in Severe ARDS trial is an international, multi-center, randomized controlled trial comparing conventional mechanical ventilation with prone positioning to ECMO in subjects with very severe ARDS (ie, $P_{aO_2}/F_{IO_2} < 80$ mm Hg).⁹⁰ Early initiation of an ECMO strategy might decrease mortality from 45–50% to $< 20\%$, with potentially less cognitive and psychiatric impairment and improved health-related quality of life in long-term survivors.⁹¹ The possible benefits of extracorporeal support have to be balanced against dangerous complications such as bleeding, thrombosis, infection, and distal limb ischemia.⁸³ There is no absolute contraindication for ECMO; all cases have to be discussed, and indications and limits will likely change as future studies are performed.

Summary

ARDS is a syndrome caused by different diseases and leads to life-threatening refractory hypoxemia. A continuous escalation of therapies may be considered on an individualized basis. Despite several decades of investigation into potential treatment strategies, use of lung-protective ventilation with V_T of 6 mL/kg predicted body weight and $P_{plat} < 30$ cm H₂O remains the only proven therapy to decrease mortality in ARDS. An oxygenation/saturation target based on a PEEP/ F_{IO_2} table is a common approach to set PEEP, but a relationship between mortality and high P_{plat} was observed only when driving pressure also was above 15 cm H₂O. In patients with ARDS, recruitment maneuvers improve oxygenation, but this is a temporary approach that doesn't improve mortality. Evidence supporting steroid use is lacking, and a conservative fluid balance is not superior to a liberal one. NMBAs ensure uniform lung recruitment, prevent generation of dangerous high transpulmonary pressure, and decrease the pro-inflammatory response associated with ARDS, but this approach must be provided within the first 48 h to prevent diaphragm atrophy and ICU-acquired weakness. HFOV theoretically achieves all of the goals of lung-protective ventilation strategies, however, randomized clinical trials failed to prove any clinical benefit. INO temporarily improves oxygenation, but it is not associated with an increased survival rate and hasn't shown any benefit to lung function. Prone positioning in patients with severe ARDS promotes a shift in gravitational forces, minimizes compression of lung parenchyma by the heart and mediastinal structures, and improves ventilation–perfusion matching. ECMO is being increasingly used to support critically ill adults who have failed conventional management, and it may be an effective salvage treatment for patients with ARDS presenting with rapid refractory respiratory failure; however, controlled trials are needed to better define indications and best practices for this therapy.

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AUTHOR QUERIES

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A—Au: Please confirm/correct the accuracy of all authors' names, academic degrees, and affiliations. Please provide middle initials, if any, for all authors.

B—Au: Please check that values cited in text match those provided in the tables and figures.

C—Au: Please confirm that "surgery" is an acceptable edit to replace "operating."

D—Au: This statement appears to call for a reference. Please provide a reference if needed, maintaining numerical order for all references.

E—Au: Journal style for airway pressure is P_{aw} ; the "m" was removed from the original acronym in the HFOV section. If "mean airway pressure" was intended, please add "mean" to the term and indicate that the acronym should be \bar{P}_{aw} .

F—Au: In the EPOCH study name, please spell out mP_{aw} and CMV.

G—Au: Please confirm this sentence as edited to avoid use of "proning."

H—Please confirm the addition of the equals sign in " $F_{IO_2} = 100\%$."

I—Au: Please clarify the "difference" here: is it the difference between the ECMO group and a control group? Another trial group?

J—Au: The original reference 81 was a duplicate of reference 9. Ref. 81 has been deleted and subsequent references were renumbered.
