Optimal Strategies for Severe Acute Respiratory Distress Syndrome

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KEYWORDS

• Acute respiratory distress syndrome • Lung protective ventilation
• High-frequency oscillatory ventilation • Neuromuscular blockade • Prone positioning
• Pulmonary vasodilators • Extracorporeal membrane oxygenation
• Physical conditioning

KEY POINTS

- Acute respiratory distress syndrome (ARDS) occurs in more than 10% of intensive care unit admissions and nearly 25% of ventilated patients.
- Low-volume, low-pressure lung protective ventilation remains the mainstay of ARDS management.
- In severe ARDS, early use of neuromuscular blockade and prone positioning improve survival.
- High-frequency oscillatory ventilation has no clear mortality benefit and may harm some patients.
- Extracorporeal membrane oxygenation consultation should be obtained early to permit initiation in appropriate patients before multisystem organ failure and severe musculoskeletal deconditioning occur.

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INTRODUCTION

Much has transpired in the 5 years since a volume of this publication was dedicated to acute respiratory failure.[1] The most significant developments include:

- A new definition of acute respiratory distress syndrome (ARDS), termed the Berlin definition
- Numerous landmark clinical trials in ventilator and nonventilator management strategies for ARDS
- The reincarnation of the ARDS Network (ARDSNet) research network as the PETAL (Prevention and Early Treatment of Acute Lung Injury) Network
- A commitment by the European Society of Intensive Care Medicine to study ARDS globally

The consensus-based Berlin definition of ARDS (**Box 1**) has allowed investigators and clinicians to more readily identify patients with ARDS in order to optimize management and design impactful clinical trials.[2] This definition has been quickly and comprehensively applied across numerous intensive care unit (ICU) populations to further the understanding of this challenging clinical syndrome. It also provides a framework for matching treatment strategies to severity of ARDS (**Fig. 1**).

Concurrent with the development and dissemination of this new definition, several important clinical trials (**Table 1**) and systematic reviews on various aspects of ARDS management have been or will soon be published. The results of these trials and their practical application are discussed at length in this article.

In addition, the future of ARDS research in both the United States and abroad has been well funded, in keeping with the burdens of both morbidity and mortality that result from ARDS. The ARDSNet research network has transformed to include many of the original centers along with several new centers, and these have established a reputation for providing new insights into the diagnosis and management of ARDS. Funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH), this new consortium has been termed the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network.[3,4] Similarly, the European Society of Intensive Care Medicine (ESICM) has shown a commitment to supporting ARDS research, as manifested by the recently published LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure)

Box 1
Berlin definition of acute respiratory distress syndrome

Respiratory failure within 1 week of a known clinical insult or new/worsening respiratory symptoms

Bilateral opacities on CXR or chest CT not fully explained by effusions, lobar/lung collapse, or nodules

Respiratory failure not fully explained by cardiac failure or fluid overload (need objective assessment [eg, echocardiography] to exclude hydrostatic edema if no risk factor present)

Mild	PFR 201–300 mm Hg with PEEP or CPAP $\geq$5 cm H_2O
Moderate	PFR 101–200 mm Hg with PEEP $\geq$5 cm H_2O
Severe	PFR $\leq$100 mm Hg with PEEP $\geq$5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; CT, computed tomography; CXR, chest radiograph; PEEP, positive end-expiratory pressure; PFR, Pao_2/fraction of inspired oxygen ratio.

From Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307(23):2526–33.

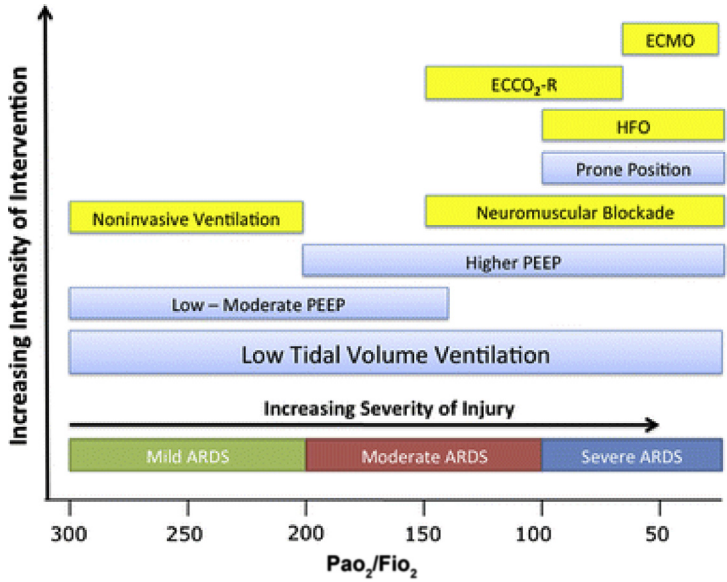

Fig. 1. Therapies for treatment of ARDS matched to severity of ARDS. ECCO2-R, extracorporeal CO2 removal; ECMO, extracorporeal membrane oxygenation; Fio_2, fraction of inspired oxygen, HFO, high-frequency oscillation; PEEP, positive end-expiratory pressure. (*From* Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38(10):1573–82; with permission of Springer.)

observational study results.[5] This and future planned studies by this group will doubtless shape the understanding and management of ARDS for years to come.

A useful framework for conceptualizing ARDS management aligns interventions with the severity of illness. Diaz and colleagues[6] provided practical guidance using such an approach in 2010. A similar framework has now been published by the creators of the Berlin definition.[7] Most patients with mild ARDS and many with moderate ARDS can be safely managed with well-established ventilator-based strategies. However, as the hypoxemia and resulting tissue hypoxia worsen, advanced maneuvers may be required.[8] This article focuses specifically on the safe application of these advanced ventilator and adjunctive management approaches typically reserved for patients with severe ARDS.

EPIDEMIOLOGY OF SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME

The review of acute lung injury (ALI) and ARDS epidemiology by Blank and Napolitano[9] summarized the most current trends in respiratory survival development and outcomes in modern ICU care. These investigators made the following observations:

- This is a heterogeneous condition that occurs in heterogeneous ICU populations
- The incidence of ALI/ARDS is declining because of a decrease in hospital-acquired respiratory failure
- The mortality associated with ARDS remains high at 20% to 25% in randomized controlled trials and 40% outside of clinical trials

The newly established Berlin definition of ARDS (see **Box 1**) is now widely accepted for diagnosing ARDS and for prognostication.[2] Most significantly, this definition

Table 1
Landmark trials and publications in severe acute respiratory distress syndrome management 2012 to 2016

Authors	Study Name/Subject	Population (n)	Main Findings
Bellani et al,[5] 2016	LUNG SAFE/ARDS incidence and outcomes	All patients admitted to an ICU over a 4-wk period (29,144) including 3022 with ARDS	ARDS occurs in 10.4% of ICU admissions and in 23.4% of ventilated patients. ARDS is underdiagnosed and lung protective ventilator settings are underused. Hospital mortality is 40%
Young et al,[30] 2013	OSCAR/HFOV	Patients with a PFR $\leq$200 mm Hg: HFOV (398) vs usual ventilation support (397)	30-d mortality no different between the HFOV vs usual ventilation support groups (41.7% vs 41.1%)
Ferguson et al,[31] 2013	OSCILLATE/HFOV	Patients with a PFR $\leq$200 mm Hg and an Fio_2 $\geq$0.5: HFOV (275) vs pressure control ventilation (273)	Study stopped early because of worse in-hospital mortality in HFOV vs pressure control ventilation (47% vs 35%)
Papazian et al,[41] 2010	ACURASYS Study/NMB	Patients with a PFR <150 mm Hg, PEEP $\geq$5 cm H_2O and V_T 6–8 mL/kg PBW: NMB (178) vs placebo (162)	After a preplanned adjustment for baseline PFR, P_{PLAT}, and APACHE II to ensure matched patient groups, 90-d mortality was improved with NMB (OR, 0.68; 95% CI, 0.48–0.98). 28-d unadjusted mortality was 23.7% with NMB vs 33.3% with placebo (P = .05)
Guerin et al,[43] 2013	PROSEVA/proning	Patients with a PFR <150 mm Hg: prone (237) vs supine (229)	28-d and 90-d mortality were decreased in the prone vs supine groups (28-d 16.0% vs 32.8% and 90-d 23.6% vs 41.0%)
Schmidt et al,[58] 2014	RESP score/ECMO prognosis	Adult patients with severe ARDS on ECMO in the ELSO registry (2355) externally validated on 140 patients	The RESP score can accurately predict ECMO survival (c = 0.74), which was externally validated with excellent discrimination (c = 0.92)
Combes et al,[60] 2014	ECMO Net/consensus statement	Patients with severe ARDS on VV ECMO	ECMO should be conducted in high-volume regional centers that support the community with an ECMO transport program
International ECMO Network[71]	EOLIA/early VV ECMO	Patients with PFR <80 mm Hg	Trial ongoing

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ELSO, extracorporeal life support organization; Fio_2, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; ICU, intensive care unit; LUNG SAFE, Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure; NMB, neuromuscular blockade; OR, odds ratio; OSCAR, oscillation in ARDS; OSCILLATE, oscillation for acute respiratory distress syndrome treated early; PBW, predicted body weight; PFR, Pao_2/Fio_2 ratio; P_{PLAT}, plateau pressure; PROSEVA, proning severe ARDS patients; RESP, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction; V_T, tidal volume; VV, venovenous.

incorporates ventilator settings as an important determinant of ARDS severity classification. Some clinicians argue that classification of ARDS should be made with the ventilator adjusted to a positive end-expiratory pressure (PEEP) of exactly 5 cm H_2O rather than at higher levels of PEEP to avoid underestimating the patient's severity of respiratory failure.[10] This approach is not always safe or practical, especially in patients with tenuous oxygenation on high levels of PEEP.

A recently completed international observational study (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure [LUNG SAFE]) of nearly 30,000 ICU admissions used automated metrics to identify patients who met ARDS criteria.[5] By the Berlin definition of ARDS, 10.4% of patients admitted to ICUs and 23.4% on mechanical ventilation develop ARDS at some point during their stay. Patients with ARDS required a median of 8 days of ventilator support and remained in the ICU for a median of 10 days. The incidence of ARDS varied by geographic region, with the highest rates in Oceana (0.57 cases per bed every 4 weeks), Europe (0.48 cases per bed every 4 weeks), and North America (0.46 cases per bed every 4 weeks). The distribution of ARDS severity included 30% mild, 46.6% moderate, and 23.4% severe. Of the patients with mild ARDS, 4.5% progressed to severe ARDS, whereas 12.7% of those with moderate ARDS progressed to severe ARDS. Hospital mortality increased significantly with ARDS severity: mild ARDS, 34.9% mortality; moderate ARDS, 40.3%; and severe ARDS, 46.1%.

In addition to these demographics, this study revealed that ARDS is frequently underdiagnosed and that potentially beneficial, well-established therapies are thus not applied even when indicated. At the time ARDS criteria were first met, only 34% of cases were clinician recognized, and only 60.2% were clinician recognized at some point during the patient's ICU course. The rate of recognition increased in mechanically ventilated patients and with increasing ARDS severity but still was only recognized 78.5% of the time in severe ARDS. Similarly, therapies with potential benefit, such as neuromuscular blockade, prone positioning, and extracorporeal membrane oxygenation (ECMO), were infrequently used (**Table 2**). Tidal volume did not change with clinical recognition of ARDS, whereas PEEP and the use of neuromuscular blockade and prone position all increased with ARDS recognition.

Table 2
Clinician recognition and application of adjunctive therapies in patients with acute respiratory distress syndrome

	Total MV + ARDS (n = 2377)	Severe ARDS (n = 729)
Clinician Recognition	1525 (64.2%)	437 (78.5%)
Recruitment Maneuver	496 (20.9%)	238 (32.7%)
HFOV	28 (1.2%)	11 (1.5%)
Neuromuscular Blockade	516 (21.7%)	274 (37.8%)
Prone Positioning	187 (7.9%)	119 (16.3%)
Inhaled Vasodilators	182 (7.7%)	95 (13.0%)
ECMO	76 (3.2%)	48 (6.6%)
Any of the Above	946 (39.8%)	445 (61.0%)

Abbreviation: MV, mechanical ventilation.

Adapted from Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315(8):788.

The mechanisms whereby ARDS causes death are myriad, but, in patients with severe ARDS, hypoxemia resulting in an accumulating oxygen debt[11,12] as well as cytokine release from lung injury (both iatrogenic and disease related) are all likely contributing factors.[13–15] Although conventional wisdom holds that most patients with ARDS die with ARDS rather than from ARDS, this likely does not hold true in those with severe ARDS. Thus, clinicians should identify patients with severe and rapidly progressive respiratory failure early and ensure that supportive measures and interventions with a demonstrated benefit are safely applied. A range of therapies that should be considered in patients with severe ARDS are reviewed later.

VENTILATOR MANAGEMENT

Standard Ventilator Management

The goal of the management of severe ARDS is to safely support gas exchange without further injuring the patient's lungs.[16] The optimal initial approach seems to be a low-volume, low-pressure ventilation strategy with volume control ventilation, which showed a survival benefit in the ARDSNet ARMA (Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome) trial.[17] This lung protective strategy limits the patient's tidal volume (V_T) to 4 to 8 mL/kg predicted body weight (PBW) combined with some level of PEEP, which keeps the plateau pressure (P_{PLAT}) less than or equal to 30 cm H_2O.[17,18] During the initial management, a V_T of 8 mL/kg may be used, but this should be decreased to 6 mL/kg within 2 to 4 hours. If the P_{PLAT} remains greater than 30 cm H_2O, the tidal volume can be further reduced to 4 mL/kg while concomitantly increasing the respiratory rate to afford adequate ventilation.[6,17] Gas exchange goals should include oxygen saturation greater than or equal to 88% to 95% and pH greater than or equal to 7.3 with a normal lactate level and base excess showing adequate end-organ oxygen delivery.

PEEP can be adjusted by one of the ARDSNet PEEP/fraction of inspired oxygen (Fio_2) tables,[19] by titrating based on measured transpulmonary pressures,[20] or by using a pressure-volume curve.[21] The ARDSNet tables include one with lower PEEP/higher Fio_2 and another with higher PEEP/lower Fio_2.[19] The risks of using this protocolized approach to PEEP adjustment include excessive PEEP resulting in both inadequate venous return leading to hypoperfusion and barotrauma in those patients with poorly recruitable lungs.[22] Furthermore, there does not seem to be a clear benefit of one table rather than the other,[19] although there is a trend toward improved mortality using the high-PEEP table in patients with moderate to severe ARDS.[23] A clinical trial that examined a so-called open-lung approach by adding recruitment maneuvers and higher PEEP levels to a low-tidal-volume strategy did not show an improved all-cause mortality (36.4% open lung vs 40.4% control; $P = .19$).[24] However, there were lower incidences of refractory hypoxemia and death with refractory hypoxemia with the open-lung strategy. Another trial that adjusted PEEP to target a P_{PLAT} of 28 to 30 cm H_2O similarly showed no significant mortality benefit.[25] However, this approach did result in more ventilator-free days and less multiorgan failure. Looking at this another way, minimizing the driving pressure (P_{PLAT} – PEEP) may optimize the patient's chances of survival.[26]

Deviating from this approach risks further lung injury through what is likely the combined mechanisms of barotrauma (P_{PLAT} >30 cm H_2O or peak inspiratory pressure >35 cm H_2O), volutrauma (V_T >6–8 mL/kg PBW), atelectrauma (low or no PEEP resulting in repeated opening and closing of alveolar units in the setting of injured lungs), and inflammatory biotrauma from various injury mechanisms.[16] Notwithstanding, adherence to these ventilator parameters in modern ICUs by

clinicians familiar with ARDS and its poor outcomes remains surprisingly low, as described earlier.[5] In particular, with regard to ventilator management, recognition of ARDS did not result in significant changes in ventilator management. In this study, 35% of patients with severe ARDS were managed with a V_T of greater than 8 mL/kg PBW, whereas the median PEEP in this group was 10 cm H_2O, and only 40% of patients with ARDS had a measured P_{PLAT} during the course of their ICU stay. The mainstay of hypoxemia management seemed to be increased Fio_2. More than a decade and a half following publication of the ARDSNet ARMA trial, there remains significant room for improvement in applying these fundamental ventilator management principles to patients with ARDS.

Alternative Ventilator Strategies

The standard approach to lung protective ventilation established by the ARDSNet ARMA trial is volume-controlled ventilation. Alternative ventilator strategies include pressure-controlled ventilation, pressure-regulated volume-cycled ventilation, inverse ratio ventilation, high-frequency ventilation, airway pressure release ventilation (APRV), and neurally adjusted ventilator assist. All of these modes can be adjusted to minimize iatrogenic ventilator-associated lung injury; however, most have not been thoroughly evaluated in patients with ARDS to fully elucidate their role in managing these patients. A detailed review of all of these modes of ventilation is beyond the scope of this article but significant developments in several of these modes are highlighted.

In patients with severe ARDS doing poorly on volume-controlled ventilation, lung protective ventilation can be achieved using other modes of ventilation.[27] Triggers that may lead clinicians to consider another ventilator approach include patient dyssynchrony refractory to deep sedation, air trapping and auto-PEEP from a high respiratory rate, or patient discomfort. In patients with refractory hypoxemia, before changing ventilator modes, the authors advocate for PEEP optimization as discussed earlier, consideration of neuromuscular blockade, and prone positioning (discussed later). A so-called low-level recruitment maneuver can also be considered. This maneuver is performed by holding a pressure of 40 cm H_2O for 40 seconds.[8] Before this maneuver, the physician must prepare to manage unstable hemodynamics from decreased venous return. After this maneuver, the patient's oxygenation status can be reevaluated. If the oxygenation improves, this suggests that the patient still has recruitable lung and may benefit from a higher PEEP level.[28] If none of these maneuvers improve the patient's oxygenation, alternative ventilator modes or ECMO should be pursued (**Fig. 2**).

High-frequency ventilation

High-frequency ventilation can be provided in several different forms. The most common types in an ICU setting are either high-frequency oscillatory ventilation (HFOV) or high-frequency percussive ventilation (HFPV). Some enthusiasm for HFOV in the adult critical care specialties began when Derdak and colleagues[29] published a multicenter randomized controlled trial in patients with moderate to severe ARDS comparing conventional ventilation (CV) (V_T 6–10 mL/kg) with HFOV. Oxygenation improved within 24 hours in the HFOV group, and there was a trend toward improved 30-day (63% HFOV vs 48% CV) and 90-day (53% vs 41%) survival, although neither reached statistical significance.

However, 2 recent clinical trials, Oscillation in ARDS (OSCAR)[30] and Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE),[31] failed to show any mortality benefit for HFOV compared with conventional ventilation with either usual ventilator management modeled after ARDSNet ARMA (OSCAR) or a pressure-controlled lung protective strategy (OSCILLATE) in moderate to severe

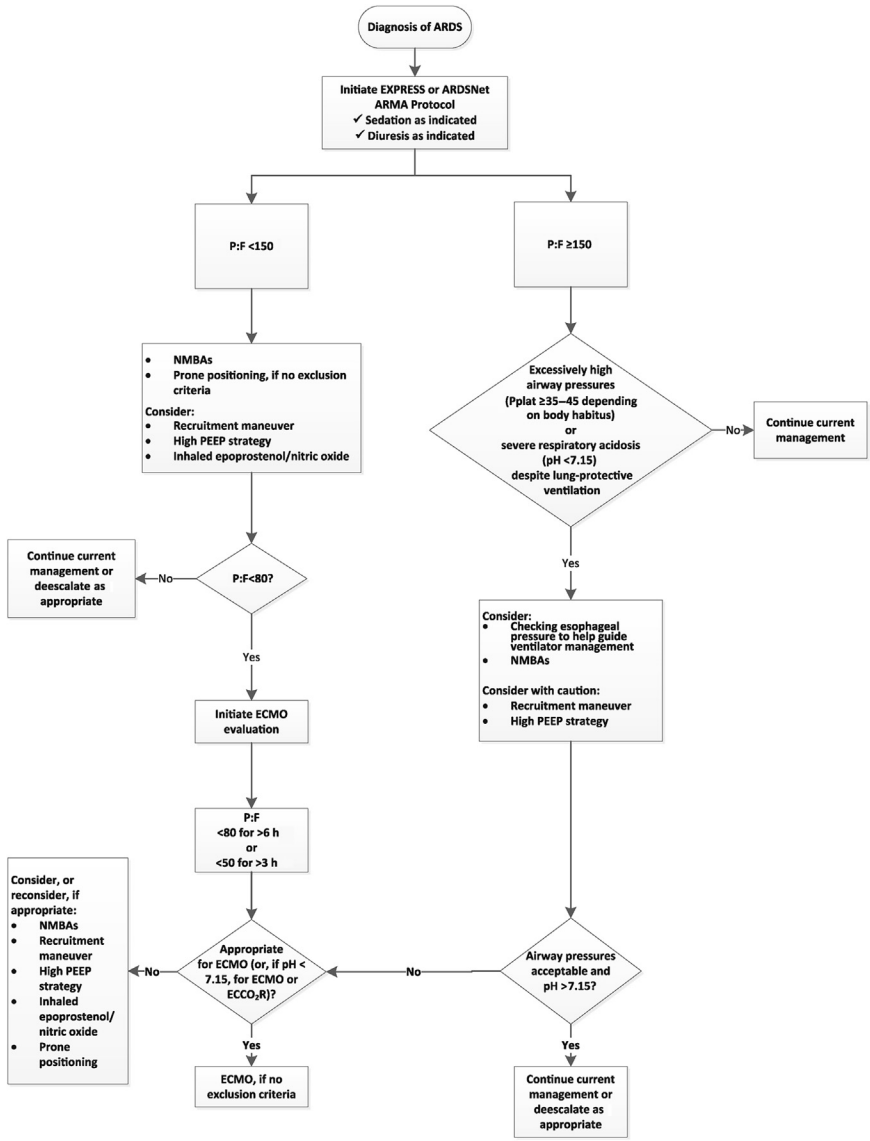

Fig. 2. Stepwise management of patients with moderate to severe ARDS, showing the sequential application of therapies up to and including venovenous ECMO. NMBA, neuromuscular blocking agents. EXPRESS, expiratory pressure study group; P:F, Pao2/fraction of inspired oxygen ratio. (*Adapted from* Brodie D, Guérin C. Rescue therapy for refractory ARDS should be offered early: no. Intensive Care Med 2015;41(5):926–9.)

ARDS. OSCILLATE was terminated early because of increased mortality in the HFOV arm. Thus, the role for HFOV in managing severe ARDS remains unclear. In our practice, the ready availability of ECMO in circumstances in which traditional management is failing largely removes the need for HFOV.

HFPV is a pressure-regulated ventilatory mode that provides oscillatory ventilation around 2 different set pressures. This mode of ventilation effectively mobilizes

secretions, thus it is widely used in patients with inhalation injury and those with tenacious, purulent secretions.[32,33] Its role in patients with ARDS outside these specific populations remains ill defined,[34] although HFPV was shown to improve oxygenation at lower peak and mean airway pressures in 1 small study of patients with ARDS.[35]

Airway pressure release ventilation

APRV is a form of inverse ratio pressure-controlled ventilation applied with a special release valve that allows patients to exhale at any time during the respiratory cycle.[36] Thus, this mode of ventilation allows patients to autoregulate their degree of stretch, thereby theoretically limiting the possibility of overdistending normal portions of the diseased lung while optimally recruiting other areas. APRV has been advocated by clinicians who believe that low-volume volume-controlled ventilation underemphasizes lung recruitment and leads to continued ventilation-perfusion mismatching as a result, whereas APRV is thought to reduce so-called alveolar microstrain or dynamic alveolar heterogeneity.[37,38]

Clinical studies of APRV have yet to fully delineate its role in the management of ARDS. One small randomized controlled trial in patients with trauma in which a small minority had moderate to severe ARDS showed no significant differences in outcomes between APRV and low-tidal-volume ventilation.[39] A more recent retrospective study suggests that early application of APRV may reduce the progression to ARDS in high-risk patients with trauma compared with conventional ventilation.[40] In our practice, ideal patients for APRV include those who are stable enough to not require deep sedation and neuromuscular blockade but who have evidence of recruitable lung on chest radiograph in the setting of moderate to severe ARDS. Theoretically, on APRV, sedation can be lightened and the patient may be able to participate in physical therapy activities while still receiving the benefit of lung recruitment. Furthermore, ventilator support can easily be weaned on APRV by slowly decreasing the inspiratory pressure and lengthening the time at this pressure until the patient is on straight continuous positive airway pressure.

ADVANCES IN NONVENTILATOR MANAGEMENT

Nonventilatory adjunctive therapies also play an important role in the management of patients with moderate to severe ARDS. In recent years, important studies have shown a potential survival benefit with the use of these therapies, whereas others have not been proved beneficial or have even been found to be associated with harm. The roles of neuromuscular blockade, prone positioning, and inhaled pulmonary vasodilators in patients with severe ARDS are discussed later in this article.

Neuromuscular Blockade

Neuromuscular blockade has been associated with ICU-acquired weakness. However, in patients with severe forms of ARDS or rapidly worsening ARDS, a short course (48 hours) of neuromuscular blockade may facilitate the application of lung protective ventilator settings while eliminating such problems as ventilator dyssynchrony. One randomized controlled clinical trial of early neuromuscular blockade (within 48 hours of ARDS diagnosis) showed no crude mortality benefit in patients with moderate to severe ARDS (Pao_2/Fio_2 ratio [PFR] <150 mm Hg), but, after making prespecified adjustments for differences in severity of illness, plateau pressure, and PFR, a benefit was shown. A mortality benefit was also identified in a prespecified subgroup with worse hypoxemia (PFR <120 mm Hg).[41] Cisatracurium (Nimbex) was used in this study and does not require dose adjustment in renal or hepatic insufficiency[42]; thus we preferentially use this agent in patients with ARDS. The PETAL Network is currently

conducting the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) trial (https://clinicaltrials.gov/ct2/show/NCT02509078) to reexamine the efficacy of this strategy.

Prone Positioning

If the patient's disease is primarily in the lower lobes (based on chest radiograph or computed tomography findings), a trial of prone positioning for 2 to 6 hours should be performed and the patient's clinical response assessed. This repositioning improves lower lobe aeration, thereby optimizing ventilation-perfusion matching, among other potential benefits (**Fig. 3**). The PROSEVA (Proning Severe ARDS Patients) trial enrolled patients with moderate to severe ARDS (PFR <150 mm Hg) and showed a mortality benefit to prone positioning protocolized to a minimum of 16 h/d.[43] Other investigators have shown that this technique can be performed in and may have benefits for a range of ICU patients, including patients with burns[44] and even patients receiving ECMO.[45]

This approach is best implemented in the setting of specific training for clinicians performing the prone positioning.[45] This should include education on the indications and contraindications, training on the proper technique for prone positioning (see online video Prone Positioning of Patients with the Acute Respiratory Distress Syndrome, available at http://www.nejm.org/doi/full/10.1056/NEJMoa1214103#t=article), an overview of routine nursing care of prone patients, and a review of emergency procedures (ie, response to patients who develop unstable cardiac rhythms).

Pulmonary Vasodilators

Inhaled pulmonary vasodilators, including inhaled nitric oxide (iNO) and inhaled prostacyclins, afford the theoretic benefit of optimizing ventilation-perfusion matching by specifically dilating pulmonary vascular beds within aerated lung regions.[46] These therapies typically improve oxygenation in patients with severe ARDS.[47,48] However, showing further outcomes benefits to these therapies has proved elusive. iNO has recently been associated with increased acute kidney injury presumably caused by systemic effects on renal perfusion.[47] Initiation of these agents can be used to trigger an evaluation for ECMO because they can potentially signify patients with refractory hypoxemia more reliably than ventilator settings and PFR. In our practice, these agents are used for short-term rescue in patients with rapidly progressive hypoxemic respiratory failure until more labor-intensive therapies, such as prone positioning or ECMO, can be instituted.

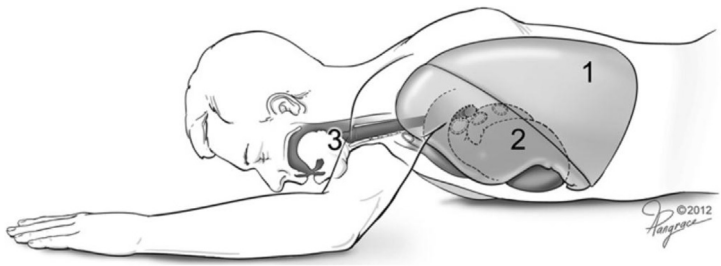

Fig. 3. The benefits of prone positioning for patients with severe ARDS. Benefits include (*1*) improved ventilation to the lower lobes, which reduces ventilation-perfusion mismatch; (*2*) reduced compression of the lower lungs by the heart; and (*3*) postural drainage of secretions. (*From* James MM, Beilman GJ. Mechanical ventilation. Surg Clin North Am 2012;92(6):1463–74. *Courtesy of* Joseph A. Pangrace, DO, MPH, Minneapolis, MN.)

EXTRACORPOREAL MEMBRANE OXYGENATION

Venovenous ECMO (VV ECMO) has assumed an important role in the management of patients with severe ARDS (**Fig. 4**). In the past decade, the number of adults with severe ARDS managed with ECMO and the number of self-identifying adult ECMO centers has increased greatly.[49,50] The landmark Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial and the influenza A (H1N1) pandemic served to raise awareness of the technologic advances in this field and of the excellent outcomes that could potentially be achieved with good patient selection and careful management.[51,52] Since that time, several small studies and 1 large clinical trial (ECMO to Rescue Lung Injury in Severe ARDS [EOLIA], ClinicalTrials.gov identifier NCT01470703) have been conducted to further elucidate the role of ECMO in managing patients with severe ARDS. The most significant insights gained in this field since 2009 are summarized later. For further detailed reading, several excellent reviews[53–55] and a monograph on ECMO[56] are available.

Patient Selection

Making the decision to proceed with ECMO requires a careful assessment of the risks and benefits associated with this support modality in each center or region. General guidance has been published[57] and remains useful for establishing local practices. However, these guidelines do not account for the heterogeneity of severe ARDS by cause and pattern of illness, the trajectory of individual patients, or the experience and qualifications of the ECMO team, and are not evidence based. In the landmark CESAR trial, which compared referral of patients with severe ARDS to a regional ECMO center in the UK versus usual care in conventional management centers, patients randomized to be considered for ECMO had a mean PFR of 76 mm Hg, PEEP of 14 cm H_2O, pH of 7.1, and an ALI score of 3.5 out of 4. Note that very few received a trial of high-frequency ventilation (7%), prone positioning (4%), or iNO (10%).[51] In our practice, we undertake a brief trial of the ventilator-based and non–ventilator-based therapies described earlier in patients with severe ARDS. If the patient's oxygenation status and hemodynamics stabilize with these maneuvers,

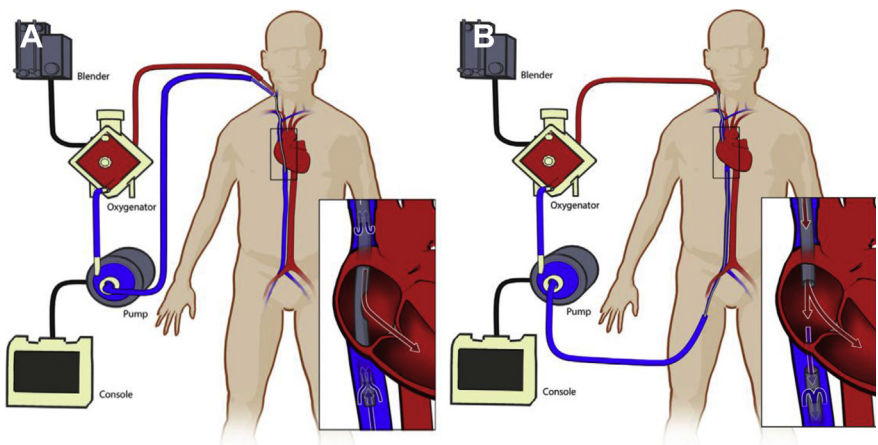

Fig. 4. VV ECMO cannulation options. (*A*) Double-lumen venous cannula (27–31 Fr) for single-site VV ECMO support. (*B*) Two single-lumen cannulas used for femoral venous drainage and internal jugular blood return. (*Reprinted from* https://collectedmed.com/.)

they are continued. However, if the patient remains unstable in any respect or shows progressive hypoxia despite optimal application of these measures, we initiate VV ECMO (see Fig. 2).

The only absolute contraindication to ECMO for severe ARDS is a preexisting condition incompatible with patient recovery. Relative contraindications that may warrant consideration include advanced physiologic age, poor preexisting functional status, and high mechanical ventilation settings for more than 7 days. The recently developed Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score can be used to determine a patient's projected survival on ECMO, although it does not provide a comparison with survival without ECMO.[58] This score ranges from −22 (poor prognosis) to +15 (good prognosis), with a score of 0 representing a predicted survival of approximately 50%. It accounts for patient features, the cause of respiratory failure, and the particulars of pre-ECMO care. An online calculator is available for quick reference (http://www.respscore.com/). Because this tool provides no estimate of the patient's outcome without ECMO,[59] careful judgment and a thoughtful discussion with the patient's family or representative are required any time ECMO is undertaken.

Regionalization and Transport

ECMO should be performed by physicians and teams experienced in the many nuances of long-term extracorporeal care. If ECMO is initiated urgently in a low-volume center, measures should be taken to transfer the patient to a high-volume regional center. These principles were affirmed in a recent consensus statement by global ECMO leaders.[60] In summary, ECMO for adult respiratory failure should be performed by centers that maintain a minimum case volume of 20 patients per year with at least 12 patients managed on ECMO for respiratory failure. In general, a population base of 2 million to 3 million patients is required for 1 ECMO center. Subsequent analysis of the Extracorporeal Life Support Organization (ELSO) registry showed improved outcomes in adult centers with more than 30 annual ECMO cases (of all types) compared with those with fewer than 6.[61]

Regional ECMO transport teams can help ensure that patients with severe ARDS do not become marooned in centers that are unable to provide ECMO support.[60,62,63] In addition, ECMO centers should register with ELSO and submit registry data to help optimize patient selection and outcomes. The authors also believe that regional centers should seek designation as ELSO centers of excellence, which requires a rigorous review of site-specific policies, practices, and outcomes, similar to trauma center verification by the American College of Surgeons.

Ventilator Management During Extracorporeal Membrane Oxygenation

ECMO does not intrinsically provide any therapy to patients with severe ARDS. Instead, it permits safe gas exchange while allowing the reduction of ventilator settings to less injurious levels and potentially permitting the elimination of rescue therapies, such as neuromuscular blockade and deep sedation, that may contribute to the poor long-term functional outcomes experienced by patients with severe ARDS.[64,65] However, to date, the optimal approach to ventilator management in patients with ARDS receiving ECMO has not been determined. A recent study has shown that survival is independently associated with higher levels of PEEP during the first 3 days of ECMO support.[66] This finding might be balanced by rapidly decreasing the driving pressure, thereby restoring a safe level of open-lung ventilator support, which does not rely on the lungs for gas exchange. Other unproven measures that may hasten lung recovery during ECMO include frequent bronchoscopy, early tracheotomy, and

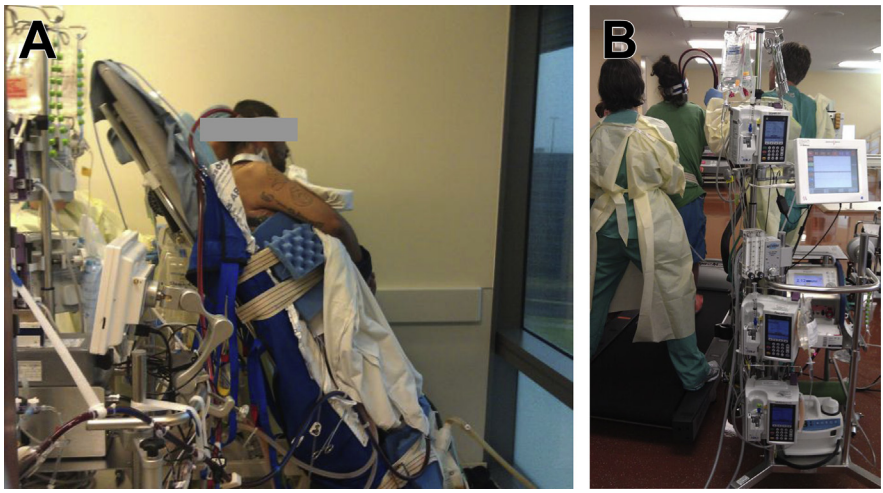

Fig. 5. Physical conditioning in patients on ECMO. This conditioning may include a tilt table in patients with continued lower extremity weakness (*A*) or even walking on a treadmill before lung transplant (*B*).

aggressive elimination of extravascular lung water with diuresis (combined with albumin if the patient is malnourished) or renal replacement therapy with hemofiltration.

Physical Conditioning

The major long-term morbidity of severe ARDS is neurologic and/or musculoskeletal disability related to prolonged inactivity.[64,65] Consequently, the authors advocate a daily awakening trial[67] once the patient has been stabilized on ECMO as well as an aggressive program of early mobilization (**Fig. 5**). These reconditioning programs involve multidisciplinary support and consist of a staged approach beginning with passive range of motion (performed multiple times daily by providers, nurses, therapists, coworkers, and family) and then progressing to sitting up at the side of the bed, moving from bed to chair, and ambulating with assistance.[68,69] Some limited data suggest that such aggressive physical therapy measures can safely be applied in ECMO patients.[70]

SUMMARY

Several insights into the clinical entity of ARDS have been gleaned over the past several years even as the care of these patients has continued to advance in many ways. Nonetheless, much work is still required to promote early diagnosis of ARDS and the application of evidence-based ventilator management principles in these patients. High-frequency ventilation has not shown a clear benefit in patients with severe ARDS, but other modes of ventilator support, such as APRV, may have a continued role in select patients. Nonventilator adjuncts, such as neuromuscular blockade and prone positioning, should be applied early in patients with severe forms of ARDS even as ECMO is being considered. ECMO should ideally be performed in high-volume centers, which should support the surrounding region with a transport program. During ECMO support, safer ventilator settings can be restored and physical reconditioning can be initiated to improve functional survival in these critically ill

patients. Results of the EOLIA trial, which should be published soon, may further illuminate the role of ECMO in the management of patients with severe ARDS.

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