CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will assimilate the findings of important studies in acute respiratory distress syndrome

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# Acute respiratory distress syndrome: Implications of recent studies

## ABSTRACT

Acute respiratory distress syndrome (ARDS) remains challenging to diagnose and manage. This article reviews the new definition of ARDS and the key findings of landmark studies over the last 5 years of prone-position ventilation, high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), and neuromuscular blockade in patients with ARDS.

## KEY POINTS

The new definition of ARDS categorizes it as mild, moderate, or severe on the basis of oxygenation, specifically, the $Pao_2/Fio_2$ ratio.

Neuromuscular blockade and prone positioning, used early in moderate or severe cases of ARDS, have shown some promise in trials, but questions remain about their application in critically ill patients.

Based on two large trials, HFOV is no longer recommended as a primary therapy for ARDS, but it may still be considered as a rescue therapy in patients with refractory hypoxemia.

In light of observational studies and randomized trials, ECMO should be considered an option in cases of refractory hypoxemia.

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Continued progress in understanding the pathophysiology of acute respiratory distress syndrome (ARDS) is translating into changes in the way we diagnose and manage it. Over the past 20 years, low tidal volume,[1] positive end-expiratory pressure (PEEP),[2] and fluid restriction[3] have become the standard of care. A multidisciplinary approach, including targeted use of sedatives, early mobilization, and protocols for weaning from the ventilator, has also brought about substantial changes in ARDS management and its outcomes.[4–6]

In this article, we review the most relevant articles about ARDS in the last 5 years. We include the new definition of ARDS and studies of ventilatory and nonventilatory therapies that have implications in managing patients with ARDS.

## A STANDARDIZED APPROACH

ARDS is characterized by damage to the alveolar architecture, severe hypoxemia, and bilateral parenchymal opacities.

The working definition of ARDS developed in 1994 by the American-European Consensus Conference (AECC) was the basis for enrollment in most of the landmark trials and observational studies over the past 20 years.[7,8] However, it was limited in its reliability and validity.

### An updated definition

In 2011, the ARDS Definition Task Force, using a novel consensus process, updated the ARDS definition,[9] focusing on its feasibility, reliability, and validity in predicting response to therapies and outcomes in ARDS. This new "Berlin" definition is not substantially different from the old, but defines the criteria more specifically:

## Studies discussed in this article

**ACURASYS**—*ARDS et Curarisation Systématique*[37]

**CESAR**—Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure[28]

**OSCAR**—Oscillation in ARDS[21]

**OSCILLATE**—Oscillation for Acute Respiratory Distress Syndrome Treated Early[23]

**PROSEVA**—Proning Severe ARDS Patients[15]

## Abbreviations used in this article

**AECC**—American-European Consensus Conference[7,8]

**ARDS**—acute respiratory distress syndrome

**CPAP**—continuous positive airway pressure

**ECMO**—extracorporeal membrane oxygenation

**HFOV**—high-frequency oscillatory ventilation

**$Pao_2/Fio_2$ ratio**—The partial pressure of arterial oxygen divided by the percentage of inspired oxygen

**PEEP**—positive end-expiratory pressure

**The Berlin definition needs to be validated in clinical practice**

- Bilateral opacities, unexplained by nodules, atelectasis, or effusion, on chest radiography or computed tomography
- New or worsening respiratory symptoms, or a clinical insult associated with ARDS within 7 days of diagnosis
- Objective assessment of cardiac function (eg, with echocardiography) to exclude cardiogenic pulmonary edema
- Hypoxemia, with a partial pressure of arterial oxygen divided by the percentage of inspired oxygen ($Pao_2/Fio_2$ ratio) of 300 mm Hg or less despite noninvasive or invasive mechanical ventilation with PEEP or continuous positive airway pressure (CPAP) of at least 5 cm $H_2O$.

In addition, the new definition classifies the severity of disease on the basis of the degree of hypoxemia, ie, the $Pao_2/Fio_2$ ratio:

- Mild: $Pao_2/Fio_2$ ratio > 200 and ≤ 300 mm Hg
- Moderate: $Pao_2/Fio_2$ ratio > 100 and ≤ 200 mm Hg
- Severe: $Pao_2/Fio_2$ ratio ≤ 100 mm Hg.

The term "acute lung injury" has been eliminated, as has the previous criterion of a pulmonary artery wedge pressure of 18 mm Hg or less.

The panel also evaluated four ancillary variables for predicting outcomes in severe ARDS:

- Compliance of the respiratory system less than or equal to 40 mL/cm $H_2O$
- Radiographic severity (involvement of three or four quadrants on chest radiography)
- PEEP of 10 cm $H_2O$ or greater
- Corrected expired volume 10 L/min or greater.

The task force evaluated the reliability and validity of this definition in a meta-analysis of 4,400 patients previously enrolled in randomized controlled trials or observational studies.

**Findings.** The Berlin definition predicted the risk of death better than the AECC definition. The mortality rate increased with the severity of ARDS, from 27% with mild disease to 32% with moderate disease to 45% with severe disease. The four ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition.

Thille et al[10] retrospectively reviewed autopsy findings from 712 patients and found that the new definition identified a homogeneous group who had severe ARDS.[10]

**Conclusions.** The new definition may overcome some of the limitations of the old one, but it needs to be validated in clinical practice, especially its ability to predict death.

## VENTILATORY SUPPORT

Prompt recognition, lung-protective ventilation, and a conservative fluid strategy remain the cornerstones of ARDS management. However, other strategies are being tested.

### Prone-position ventilation in severe ARDS: The right therapy in a specific population

Prone-position ventilation was first described almost 30 years ago, but it has been used inconsistently in clinical practice.

Physiologic and observational studies indicated that prone positioning might improve survival in patients with ARDS, but several randomized trials failed to demonstrate any positive effect on outcomes.[11,12] Some trials also reported a higher rate of complications with this intervention.[13] However, meta-anal-

yses suggested that prone-position ventilation might have a beneficial effect in patients with severe ARDS (defined as a $Pao_2/Fio_2$ ratio ≤ 100 mm Hg).[14]

In view of these findings, investigators conducted a trial of prone-position ventilation exclusively in patients with severe ARDS.

### The PROSEVA study

The Proning Severe ARDS Patients (PROSEVA) study was a randomized controlled trial designed to determine whether prone-position ventilation, applied early, would improve outcomes in patients with severe ARDS.[15]

In PROSEVA, 466 patients with severe ARDS (defined as a $Pao_2/Fio_2$ ratio < 150 mm Hg, $Fio_2$ ≥ 60%, and PEEP ≥ 5 cm $H_2O$) underwent either at least 16 hours of prone positioning or were left in the supine position after 12 to 24 hours of initial conventional mechanical ventilation. The patients were recruited from centers in France and Spain where prone-position ventilation had been used in daily practice for more than 5 years.

The primary outcome studied was the rate of death at 28 days. The secondary end points were the death rate at day 90, rates of successful extubation, the length of stay in the intensive care unit, and complications.

**Findings.** At study entry, the patients in the supine group were sicker, more of them required a vasopressor, and fewer of them were receiving neuromuscular blocking agents than those in the prone group. These baseline differences may have influenced the outcomes; the unadjusted 28-day mortality rate was 16.0% in the prone group compared with 32.8% in the supine group ($P < .001$). However, the hazard ratio for death with prone positioning was 0.39 (95% confidence interval [CI] 0.25–0.63) even after adjusting for severity and the use of vasopressors and neuromuscular blocking agents. Prone-position ventilation was not associated with a higher incidence of complications, and the rate of successful extubation was higher.

**Conclusions.** In patients with severe ARDS, early use of prolonged prone positioning significantly decreased the 28-day and 90-day mortality rates. This trial has made prone positioning one of the strategies in managing patients with early severe ARDS. To minimize complications such as pressure ulcers and line or tube dislodgement, personnel caring for these patients must follow a protocol and undergo specific training.

These results were corroborated by a meta-analysis by Beitler et al[16] that found a significant decrease in mortality rate with prone-position ventilation even in older studies when lung-protective ventilation strategies were separated from high-tidal-volume ventilation.

### High-frequency oscillatory ventilation: No benefit in two trials

Observational data and experimental studies suggested that high-frequency oscillatory ventilation (HFOV) is superior to conventional mechanical ventilation in ARDS patients.[17,18] However, outdated and cumbersome equipment, lack of protocols, and a lack of high-quality evidence led to limited and inconsistent use of HFOV, mainly as a rescue therapy in ARDS.[19]

Over the last few years, HFOV has been gaining acceptance, especially earlier in the course of ARDS.[20] After preliminary clinical trials reported promising results, two trials conducted in Canada and the United Kingdom compared HFOV vs conventional mechanical ventilation in patients with ARDS.

**The death rate with prone positioning was less than half that with supine positioning**

### The OSCAR study

The Oscillation in ARDS (OSCAR) study[21] was a "pragmatic" trial[22] (ie, it had minimal exclusion criteria) of the safety and effectiveness of HFOV as a primary ventilatory strategy for ARDS. It included 795 patients randomized to receive conventional ventilation (n = 397) or HFOV (n = 398). Research centers followed detailed algorithms for HFOV management and adopted their usual practice for conventional ventilation. Medical care was given according to the clinician's judgment.

The primary outcome studied was survival at 30 days. The secondary outcomes were all-cause mortality in the intensive care unit and the hospital, duration of mechanical ventilation, and use of antimicrobial, sedative, vasoactive, and neuromuscular-blocking drugs.

**Findings.** The patient baseline characteristics were similar in both groups.

There was no significant difference in intensive care unit mortality rates, hospital

mortality rates, or mortality rates at 30 days (41.7% in the HFOV group vs 41.1% in the conventional ventilation group; $P = .85$, 95% CI 6.1–7.5) even after adjustments for center or severity of illness.

The duration of mechanical ventilation was similar in both groups (14.9 ± 13.3 days in the HFOV group vs 14.1 ± 13.4 days in the conventional ventilation group, $P = .41$). However, sedatives and neuromuscular-blocking drugs were used more often and longer in the HFOV group than in the conventional ventilation group. There was no difference in the use of vasoactive or antimicrobial medications.

**Conclusions.** This multicenter randomized control trial did not demonstrate any benefit from using HFOV for routine management of ARDS. Its pragmatic design made it less likely to reach a firm conclusion,[22] but it at least made a case against routinely using HFOV in patients with ARDS.

### The OSCILLATE study

The Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) study[23] assessed the safety and efficacy of HFOV as a treatment for early-onset moderate-to-severe ARDS.

**Two trials have quelled enthusiasm for routine HFOV**

The inclusion criteria were similar to those in the OSCAR trial except that pulmonary symptoms had to be present less than 2 weeks and ARDS assessment was done under standard ventilator settings. As this was an efficacy trial, it had more exclusion criteria than the OSCAR trial. A total of 548 patients were randomized to receive conventional ventilation (n = 273) or HFOV (n = 275). The baseline characteristics were similar between groups.

Conventional ventilation was given according to a protocol used in an earlier trial[2] and included recruitment maneuvers. HFOV was given in centers that had experience in this treatment, and there were protocols for ventilation management, hemodynamic optimization, and weaning. All other care was left to the clinician's choice.

The primary outcome studied was in-hospital mortality. The investigators also evaluated whether there were interactions between the treatment and baseline severity of lung injury and center experience with HFOV.

**Findings.** The trial was stopped after an interim analysis found that HFOV might be harmful, although the statistical threshold for stopping was not reached. The in-hospital mortality rate was 47% in the HFOV group and 35% in the control group (relative risk of death with HFOV 1.33, 95% CI 1.09–1.64, $P = .005$). HFOV was worse than conventional ventilation regardless of the severity of disease or center experience. The HFOV group had higher mean airway pressures but similar $F_{IO_2}$ compared with the conventional ventilation group.

The HFOV group received significantly more vasopressors, sedatives, and neuromuscular blockers. This group's fluid balance was higher as well, but not significantly so. Refractory hypoxemia (defined as $P_{AO_2} < 60$ mm Hg for 1 hour with an $F_{IO_2}$ of 1.0 and neuromuscular blockade) was more frequent in the conventional ventilation group, but the number of deaths in the subgroup with refractory hypoxemia was similar with either treatment.

**Conclusions.** This multicenter randomized controlled trial demonstrated that HFOV was harmful when used routinely to manage ARDS. The trial's protocol was based on the results of a pilot study carried out by the same investigators, which provided the best evidence available regarding the safety of HFOV at that time.

The results of the OSCAR and OSCILLATE trials have quelled enthusiasm for early, routine use of HFOV in ARDS. Although there are concerns that the protocol (ie, the way HFOV was implemented) rather than HFOV itself may have led to worse outcomes, there is no signal to support its routine use. We need further studies to define if it remains a viable rescue therapy.

### Extracorporeal membrane oxygenation: Is it a viable option in severe ARDS?

Extracorporeal membrane oxygenation (ECMO) uses cardiopulmonary bypass technology to provide gas exchange. In patients with severe hypoxemia, ECMO can ensure adequate oxygenation and ventilation while ensuring the optimization of lung-protective ventilation. But ECMO was never as successful in adults with ARDS as it was in children and neonates.[24]

The first two trials of ECMO in ARDS[24,25] reported equal or worse survival rates compared with conventional ventilation, and the overall mortality rate in these studies was staggeringly high. However, these studies were carried out before the era of lung-protective ventilation and at a time when ECMO technology was relatively primitive.

With new technology such as venovenous circuits and smaller cannulas, ECMO has gained more acceptance. It was used in patients with severe or refractory hypoxemia associated with ARDS during the H1N1 pandemic.[26,27]

### The CESAR trial

The Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial[28] assessed the safety, clinical efficacy, and cost-effectiveness of ECMO in managing severe ARDS. It compared best standard practice vs a protocol that included ECMO. The trial was conducted from 2001 to 2006.

Patients with severe ARDS, as defined by a Murray score[29] greater than 3 or uncompensated hypercapnea, were prospectively randomized and recruited from an ECMO center and 148 tertiary intensive care units and referral hospitals in England. This was a pragmatic trial, with minimal exclusion criteria (essentially, mechanical ventilation with high pressures and high $F_{IO_2}$ for more than 7 days, intracranial bleeding, or contraindication to heparinization).

A total of 180 patients were randomized in a one-to-one ratio to receive ECMO or conventional management. The ventilator management in the conventional treatment group was not done according to a protocol but in general was low-volume and low-pressure. All patients randomized to ECMO were transferred to the ECMO center and treated according to a standardized ventilation protocol. After 12 hours, if predefined goals were not reached, venovenous ECMO was started. Patients assigned to conventional management could not cross over to ECMO.

The primary outcomes were death or severe disability at 6 months after randomization, and cost-effectiveness. The secondary outcomes were hospital resource use (eg, rescue techniques, length of stay, duration of ECMO) and health status after 6 months.

**Findings.** The groups were similar at baseline. Sixty-eight (75%) of the 90 patients randomized to receive ECMO actually received it. Of the 22 patients who did not receive ECMO, 16 (18% of the 90) improved on conventional therapy, 5 (6%) died during or before transfer, and 1 could not receive heparin.

Two patients had severe complications in the ECMO group: one had an arterial puncture, and one had an oxygen delivery failure during transport. In each case, these events contributed to the death of the patient.

More patients in the ECMO group received lung-protective ventilation, 84 (93%) vs 63 (70%).

The primary outcome, ie, death or severe disability at 6 months, occurred in 33 (37%) of the 90 patients in the ECMO group and in 46 (53%) of the patients in the conventional management group (relative risk 0.69, 95% CI 0.05–0.97, $P = .03$). More patients in the ECMO group survived, but the difference was not statistically significant (relative risk of death 0.73, 95% CI 0.52–1.03, $P = .07$). The most common cause of death in the ECMO group was multiorgan failure (42%), whereas in the conventional management group, the most common cause of death was respiratory failure (60%).

Length of stay in the hospital and in the critical care unit and health care costs were double for patients in the ECMO group. There was no difference in quality-of-life markers at 6 months in the survivors.

**Conclusions.** This pragmatic trial demonstrated that a protocol that includes ECMO could improve survival rates in ARDS.

Of note, the ECMO group got care in regional centers that used protocols. Therefore, in interpreting the results of this trial, we have to consider that being in a center with protocol-specified care for ARDS could drive some of the difference in mortality rates.

Regardless, this trial demonstrated that ECMO is feasible and led to better outcomes than expected. The findings were encouraging, and spurred the use of ECMO in severe ARDS during the 2009 H1N1 pandemic. Two propensity-matched studies and a number of case series reported a survival benefit associ-

**The success of ECMO has opened new possibilities in the management of ARDS**

ated with the use of ECMO in patients with severe ARDS.[27,30]

A recent meta-analysis also reported that ECMO might lower the mortality rate in ARDS; however, the patients in the H1N1 pandemic were younger and usually had isolated respiratory failure.[31]

The success of ECMO has opened new possibilities in the management of ARDS. As the technology improves and our experience increases, ECMO will likely gain more acceptance as a treatment for severe ARDS.

### Airway pressure release ventilation

The use of airway pressure release ventilation and other ventilator modalities in ARDS is not supported by current evidence, though results of clinical trials may influence our practice in the future.

## PHARMACOTHERAPY IN ARDS

The pathogenesis of ARDS includes damage to the alveolar-capillary membrane, with leakage of protein-rich edema fluid into alveoli. This damage is propagated by a complex inflammatory response including but not limited to neutrophil activation, free-radical formation, dysregulation of the coagulation system, and extensive release of inflammatory mediators.[32,33] As a consequence, there are multiple potential targets for pharmacologic therapy in ARDS.

**Effective drug therapy for ARDS remains extremely limited**

A variety of drugs, including corticosteroids, anti-inflammatory agents, immune-modulating agents, pulmonary vasodilators, antioxidants, and surfactants, have been studied in patients with ARDS.[34] But effective pharmacotherapy for ARDS remains extremely limited.

### Neuromuscular blockade in early severe ARDS

Mechanical ventilation can result in injurious stretching of the lung parenchyma, either from alveolar overdistention (volutrauma) or from continual recruitment and derecruitment of unstable lung units during the ventilator cycle (atelectrauma).[35] Ventilator-induced lung injury can be exacerbated by asynchronous breathing.

In theory, neuromuscular blockers could minimize patient-ventilator asynchrony and provide much better control of tidal volume and pressure in patients with ARDS. This may result in less volutrauma and atelectrauma associated with asynchronous breathing. Data also suggest that cisatracurium (Nimbex), a neuromuscular blocking agent, may have a direct effect on the amount of inflammation in lungs with ARDS.[36]

### The ACURASYS study

The *ARDS et Curarisation Systématique* (ACURASYS) study[37] was a randomized trial in 340 patients undergoing mechanical ventilation for severe ARDS to evaluate the impact of neuromuscular blockade within the first 48 hours in this population.

The primary outcome was the mortality rate before hospital discharge or within 90 days of study entry. Secondary outcomes included the 28-day mortality rate, the rate of intensive care unit-acquired paresis, and the number of ventilator-free days. To be included, patients had to have been mechanically ventilated for less than 48 hours and to meet the AECC criteria for severe ARDS, with a $Pao_2/Fio_2$ ratio less than 150 mm Hg.

The intervention group received a continuous infusion of cisatracurium for 48 hours, while the control patients received placebo. Muscle strength was evaluated by clinical scoring of strength in different muscle groups.

**Findings.** The study groups were similar at baseline.

The crude 90-day mortality rate was lower in the cisatracurium group (31.6% vs 40.7%, $P = .08$). Regression analysis showed an improved 90-day survival rate with the use of this neuromuscular blocker after adjustment for severity of illness and the severity of ARDS (based on degree of hypoxemia and plateau pressures) (hazard ratio for death at 90 days 0.68; 95% CI 0.48–0.98; $P = .04$). The rate of paresis acquired in the intensive care unit did not differ significantly between the two groups.

**Conclusion.** In patients with severe ARDS, giving a neuromuscular blocking agent early improved the survival rate and increased the time off the ventilator without increasing muscle weakness.

These data are in line with similar findings from two other studies published by the same group.[38,39] A meta-analysis of 432 pa-

tients showed that the use of neuromuscular blockade in early severe ARDS is associated with a statistically significant effect on early mortality (relative risk 0.66, 95% CI 0.50–0.87).[40] The pooled analysis of these trials did not show any statistically significant critical-illness polyneuropathy.

These results need to be interpreted carefully, as we have inadequate data to see if they generalize to different intensive care units, and the evaluation and categorization of critical-illness polyneuropathy remains to be defined.

Cisatracurium is a promising treatment for moderate to severe ARDS and merits investigation in a large confirmatory randomized controlled trial.

## Other pharmacologic agents

A number of other drugs have been studied in ARDS patients, including both inhaled and intravenous beta agonists,[41,42] statins,[43] and nutritional supplements.[44] But as with other drugs previously studied in ARDS such as corticosteroids, *N*-acetylcysteine, and surfactant,[34] these agents showed no effect on outcomes. In fact, a recent trial of intravenous salbutamol in ARDS patients was stopped after an interim analysis because of a higher incidence of arrhythmias and lactic acidosis with this agent.[42]

These findings reaffirm that pharmacologic therapy needs to be carefully considered, and potential harms associated with these therapies need to be addressed before they are introduced in the care of critically ill patients.

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