

# Management Options for Refractory ARDS

## A Concise Clinical Review

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### Abstract

Some patients with severe acute respiratory distress syndrome (ARDS) experience hypoxemia during lung-protective ventilation, refractory to a fraction of inspired oxygen of 1.0 and high levels of positive end-expiratory pressure. Management options for refractory ARDS are discussed, including neuromuscular blocking agents (NMBA), prone positioning, inhaled pulmonary vasodilators, high-frequency oscillatory ventilation (HFOV), and extracorporeal membrane oxygenation (ECMO).

### Case Presentation

A previously healthy 45 year-old man presents to the hospital with 3 days of progressive dyspnea and fever. He is diagnosed with community-acquired pneumonia and started on appropriate antibiotics. Nonetheless, he develops hypoxemic respiratory failure requiring endotracheal intubation. Chest radiograph demonstrates diffuse bilateral infiltrates. He receives deep sedation and is placed on an assist control, volume-cycle mode of mechanical ventilation with a tidal volume of 6 mL per kg predicted body weight, a fraction of inspired oxygen (FIO<sub>2</sub>) of 1.0, and a positive end-expiratory pressure (PEEP) of 20 cm H<sub>2</sub>O. An arterial blood gas demonstrates a partial pressure of oxygen in arterial blood (PaO<sub>2</sub>) of 45 mmHg.

*What strategies should be considered to further manage this patient's ARDS?*

### Principles of management of severe ARDS

This patient meets criteria for a diagnosis of the acute respiratory distress syndrome (ARDS), defined as the acute onset of hypoxemia in the setting of bilateral pulmonary infiltrates consistent with pulmonary edema that is not fully explained by cardiac failure.<sup>1</sup> Based on the ratio of PaO<sub>2</sub> to FIO<sub>2</sub> of less than 100, his ARDS would be classified as severe, which has an associated mortality as high as 52% in some cohorts.<sup>1</sup> The mortality associated with a PaO<sub>2</sub> to FIO<sub>2</sub> significantly below 100, as in the case above, is likely higher, although this uncommon subset of very severe ARDS has not been well characterized.

The primary focus of the management of ARDS is treatment of the underlying disease which is driving the syndrome as well as minimization of ventilator-associated lung injury (VALI), believed to contribute significantly to the morbidity and mortality associated with ARDS.<sup>2,3,4</sup> A lung-protective ventilation strategy, which emphasizes low tidal volumes and airway pressures, has been accepted as the standard of care mechanical ventilatory approach for patients with ARDS.<sup>3,5</sup> The ARMA trial, a multicenter, randomized controlled trial conducted by the Acute Respiratory Distress Syndrome Network (ARDSNet), demonstrated a significant reduction in mortality (31% vs 39.8%,  $p = 0.007$ ) with tidal volumes of 6 mL per kg and plateau airway pressures of less than 30 cm H<sub>2</sub>O compared to more traditional volumes and pressures (12 mL per kg and less than 50 cm H<sub>2</sub>O).<sup>5</sup>

In addition to a low-volume, low-pressure ventilation strategy, a fluid-restrictive approach has generally been accepted as a way of mitigating the extent of respiratory failure in the setting of increased capillary permeability and excess alveolar edema. In the Fluid and Catheter Treatment Trial (FACTT),<sup>6</sup> patients with ARDS who were randomized to a conservative (as compared to liberal) fluid strategy had more ventilator-free days (14.6 vs. 12.1,  $p < 0.001$ ) and ICU-free days (13.4 vs. 11.2,  $p < 0.001$ ) without increasing the rate of non-pulmonary organ failure, although there was no difference in 60-day mortality (25.5% vs 28.4%,  $p = 0.30$ ).

Lung-protective ventilation and conservative fluid management may be applied to all patients with ARDS. Additionally, high PEEP strategies, with or without recruitment maneuvers, have been investigated, without any significant difference in overall mortality in large randomized controlled trials, although meta-analyses suggest that the subset of patients with more severe ARDS may derive a benefit from a high PEEP strategy.<sup>7,8,9,10,11,12</sup> In the setting of ARDS that is persistently severe despite the implementation of these strategies, several other approaches have been investigated, including the use of neuromuscular blocking agents (NMBAs), prone positioning, inhaled pulmonary vasodilators, high-frequency oscillatory ventilation (HFOV), and extracorporeal membrane oxygenation (ECMO).

## Neuromuscular blocking agents

Neuromuscular blocking agents (NMBAs) have been proposed as a means of improving patient-ventilator synchrony in an effort to optimize oxygenation and further minimize lung injury. Their use in moderate to severe forms of ARDS was evaluated in the ACURASYS trial, a randomized trial of 340 patients with ARDS for less than 48 hours with a PaO<sub>2</sub> to FIO<sub>2</sub> ratio less than 150 mmHg.<sup>13</sup> After being deeply sedated, subjects received fixed-dose cisatracurium or placebo for 48 hours. Adjusting for the degree of hypoxemia, severity of illness, and plateau airway pressure, the intervention arm had a significant reduction in 90-day mortality (hazard ratio 0.68, 95% CI, 0.48 to 0.98, p=0.04), an effect that was isolated by subgroup analysis to those with PaO<sub>2</sub> to FIO<sub>2</sub> ratios less than 120 mmHg. The cisatracurium group also had more ventilator-free and ICU-free days, without any significant difference in ICU-acquired paresis. It should be noted that the protocol did not include an objective assessment of the degree of neuromuscular blockade achieved (i.e., no train-of-four monitoring). In addition, these results should only be applied specifically to cisatracurium, with steroidal neuromuscular blocking agents (i.e. vecuronium, rocuronium, pancuronium) potentially having a different effect.

Based on the existing data, the use of NMBAs, particularly cisatracurium, is recommended in early ARDS for those with sufficiently severe gas exchange abnormalities despite deep sedation.

## Prone positioning

ARDS typically results in consolidation and atelectasis preferentially affecting the more dependent portions of the lung, resulting in shunt physiology in these areas. Ventilation, in contrast, preferentially distributes to the non-dependent areas, putting those alveoli at risk for overdistention and VALI. Prone positioning may reduce ventilation-perfusion mismatch and minimize VALI through recruitment of atelectatic lung, more homogenous distribution of ventilation, and alterations in chest wall compliance.<sup>14</sup> There had previously been a suggestion of a mortality benefit from prone positioning in severe forms of ARDS in post-hoc analyses of several randomized studies.<sup>16</sup><sup>17</sup> These findings prompted a randomized controlled trial of prone versus supine positioning, the PROSEVA trial, focusing on those with moderate to severe ARDS (PaO<sub>2</sub> to FIO<sub>2</sub> ratio less than 150 mmHg).<sup>18</sup> The prone group had a significantly lower mortality at 28 days (16.0% vs. 32.8%, HR 0.42, p < 0.001) and 90 days (23.6% vs 41.0%, HR 0.48, p < 0.001). Cardiac arrest was more common in the supine group,<sup>18</sup> whereas pressure ulcers (predominantly anterior) were more common in the prone group.<sup>19</sup>

It is important to note that all centers enrolling in the study had at least five years experience in performing prone positioning for patients with ARDS. The favorable impact of prone positioning on survival was further corroborated by a recent meta-analysis, which found that prone positioning improved survival over supine positioning in patients with ARDS who were managed with lung-protective ventilation, lending further strength to the argument that the benefit of prone positioning seen in the PROSEVA trial is consistent with past evidence, at least in the setting of modern standard-of-care ventilation strategies.<sup>20</sup>

In light of these results, prone positioning is becoming standard management for patients with more severe forms of ARDS at centers experienced in its use.

## Inhaled pulmonary vasodilators

Inhaled pulmonary vasodilators, of which epoprostenol and nitric oxide are most commonly used, are ideally delivered to alveoli in order to promote vasodilation of the adjacent pulmonary vascular beds, thereby improving blood flow and gas exchange in well-ventilated areas of lung and diverting blood flow away from poorly-ventilated areas. Despite its ability to improve oxygenation, there is no proven survival benefit from inhaled vasodilator therapy.<sup>21</sup><sup>22</sup><sup>23</sup> Likewise, the use of pulmonary vasodilators may be associated with adverse effects from systemic absorption, including worsening of hypoxemia if pulmonary vasodilation occurs in areas that are poorly ventilated. Drug-specific side effects may include cyanide toxicity, methemoglobinemia, and renal insufficiency with nitric oxide, and flushing and hypotension with epoprostenol.<sup>21</sup><sup>22</sup><sup>23</sup><sup>24</sup>

There is insufficient data to recommend inhaled pulmonary vasodilators for routine use in ARDS. However, they may have a temporizing role in the setting of severe, refractory hypoxemia.

## High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV), which delivers very low tidal volumes by oscillating around a fixed mean airway pressure, has been used as a means of maintaining alveolar patency and moderate amounts of PEEP while avoiding excessively high airway pressures. Early randomized data suggested a survival benefit in severe ARDS,<sup>25</sup><sup>26</sup> however two large randomized controlled trials failed to show a benefit from HFOV,<sup>27</sup><sup>28</sup> with one of the trials terminated early due to increased mortality in the intervention arm.<sup>27</sup>

As a result of these studies, HFOV is not currently recommended for routine use in patients with ARDS.

## Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) consists of an extracorporeal circuit that directly removes carbon dioxide and delivers oxygen to the blood. In venovenous ECMO, which is the form of ECMO most commonly used in ARDS, blood is drained from the venous system via an external pump, passed through a semipermeable membrane that allows for gas exchange, and returned to the venous system.<sup>29</sup> ECMO may be considered in cases of refractory ARDS when invasive mechanical ventilation is unable to provide adequate oxygenation or ventilation, when acceptable levels of gas exchange are achieved only at the expense of excessively high airway pressures, or when adherence to a lung protective ventilation strategy results in intolerable levels of hypercapnia and acidemia. With the ability to manage gas exchange by way of an extracorporeal circuit, there may be an opportunity to reduce tidal volumes and airway pressures below the current standard of care, with the potential to reduce VALI beyond what was achieved in ARMA.<sup>30-31-32</sup>

ECMO technology has evolved significantly over the last several decades, with an increasing body of evidence suggesting improved survival over conventional management in cases of severe, refractory ARDS, along with an improving risk profile<sup>33-34</sup>. The most recent randomized controlled trial, Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR), demonstrated improved survival without disability at six months when patients were referred to a specialized center for consideration of ECMO compared to those that were managed conventionally (37% vs. 53%, relative risk 0.69, 95% CI, 0.05-0.97; p=0.03). A lack of standardization in the control arm and the fact that several patients referred for ECMO were successfully managed without ECMO limit the conclusions that can be drawn from this study.

A large multicenter randomized controlled trial is currently underway to further elucidate the role of ECMO versus standard of care conventional management, including prone positioning and NMBAs, in severe, refractory ARDS<sup>35</sup>

## Recommendations for management of refractory ARDS

The patient in the vignette has refractory hypoxemia despite standard of care mechanical ventilation and deep sedation. Reasonable next steps in this patient's management would include the addition of a NMBA and prone positioning, along with volume removal as tolerated. Inhaled pulmonary vasodilators may be initiated to provide some improvement in oxygenation, with close monitoring for adverse effects, including worsening hypoxemia. If his hypoxemia remains refractory despite these interventions, it would be reasonable to consider referral for venovenous ECMO at a center experienced in its use.

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