

# Rescue strategies for refractory hypoxemia: a critical appraisal

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## Abstract

Mechanical ventilation is the most important aspect of supportive care of patients with severe acute respiratory failure. Most research directed to improving the prognosis of these patients has focused on improving support of the injured lung. In this report, current knowledge on innovative ways to manage refractory hypoxemia and ventilation without further damaging the injured lung is briefly discussed.

## Introduction and context

Acute respiratory failure due to severe acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) is one of the most challenging problems of patients in intensive care units (ICUs). For years, mechanical ventilation (MV), using conventional mechanical ventilators, was the only supportive form of therapy providing adequate oxygenation and carbon dioxide elimination. MV provides time for disease-specific therapy to reverse the cause of failure and for recovery of respiratory function. The adverse effects of conventional MV are the direct consequence of pulmonary pressure or volume changes induced by cyclic mechanical insufflations of diseased lungs or both. Specifically, high-peak alveolar pressures, cyclic opening and closing of unstable lung units, and high concentrations of oxygen can cause lung injury during MV.

The aim of this short review is to summarize the current literature on a number of alternative techniques (currently in use worldwide or under evaluation) to improve oxygenation and ventilation in ALI/ARDS patients with refractory hypoxemia. Today, refractory hypoxemia is rare and is an infrequent cause of death (<10% of ARDS deaths). There is no standard definition for refractory hypoxemia in terms of a predetermined arterial partial

pressure of oxygen (PaO<sub>2</sub>) value under a specific oxygen concentration (fraction of inspired oxygen, or FiO<sub>2</sub>) and applied positive end-expiratory pressure (PEEP) level during a certain period of time. In most reports, it has been defined as having a PaO<sub>2</sub> of less than 60 mm Hg, an FiO<sub>2</sub> of 0.8-1.0, and a PEEP of greater than 10-20 cm H<sub>2</sub>O for more than 12-24 hours. For the purpose of this article, we did not review current techniques that improve oxygenation by minimizing oxygen consumption, such as muscle paralysis [1], or that are designed to open collapsed alveoli early in the course of persistent ARDS, such as the use of recruitment maneuvers followed by a decremental PEEP trial [2,3]. A recruitment maneuver is defined as applying a pressure higher than that applied during a normal breath either intermittently (for 2-3 minutes) or sustained for a short period of time (up to about 40 seconds). In a recent meta-analysis [4] of seven clinical trials involving 1170 patients with ALI/ARDS, there was no significant difference in survival between groups receiving an 'open-lung' ventilatory strategy that included recruitment maneuvers and groups given standard ventilatory care. However, the main limitation of that systematic review was the design of trials that either did not isolate recruitment maneuvers from other variables or assessed only short-term outcomes, and few of these trials determined the patient-specific

PEEP level (by decremental trial) following the recruitment maneuvers, a key to the successful use of recruitment maneuvers.

## Recent advances

### **Extracorporeal membrane oxygenation**

This technique was originally applied in patients with acute respiratory failure of such severity that it was impossible to provide adequate oxygenation by conventional MV [5]. To supplement gas exchange, a portion of the cardiac output must go through the extracorporeal membrane oxygenation (ECMO) circuit. During ECMO, carbon dioxide is removed by the extracorporeal circuit, but this technique is usually supplemented with conventional MV at low ventilatory rates and high PEEP levels and with tidal volumes to maintain a plateau pressure of below 28 cm H<sub>2</sub>O. Most long-term adult ECMO [6] is performed using the venovenous approach. Access for both blood removal and return is via the femoral, saphenous, or jugular veins. Despite the excitement generated by earlier reports of success, the results of ECMO trials led to a loss of enthusiasm for its use in acute respiratory failure. However, some investigators believe that there exists a role for ECMO in young adult patients with single organ system failure who are deemed to have potentially reversible pulmonary dysfunction when all other conventional modalities have failed [7].

Recently, a large multicenter adult ECMO trial was completed. Referred to as the CESAR trial (Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure) [8], this randomized controlled trial (RCT) assessed the effectiveness of extracorporeal lung assist in 180 patients with severe ARDS. The results of this study [9] represent the first positive RCT on adult ECMO application in severe respiratory failure. Survival at 6 months or absence of severe disability was achieved in 63% of the ECMO patients compared with 47% of the control group ( $P = 0.03$ ). However, there are a number of major concerns and limitations with this study. First, patients allocated to conventional management (control group) were treated with conventional MV or with high-frequency ventilation. Second, patients in the control group were ventilated with a nonstandardized protocol; to ensure the collaboration of participating centers, physicians were allowed to choose any ventilatory strategy. Third, 30% of patients in the control group were not ventilated with a lung-protective strategy. Fourth, no data regarding ventilatory parameters at study entry and during the MV period are presented. Fifth, all ECMO patients were treated in the same center. Sixth, the ECMO center did not treat patients randomly

assigned to the conventional management group. Seventh, many patients randomly assigned to ECMO did not receive ECMO. In fact, 103 patients who were screened for eligibility were excluded because a bed was unavailable for ECMO and 22 patients (25%) assigned to be transferred to the ECMO center never received ECMO (16 improved with conventional management). Finally, a more critical analysis of outcome data when comparing overall patients who actually received ECMO (68 out of 90) with those who were treated with MV and had information about mortality (87 plus 22) showed that the mortality rates were similar in the two groups (48.5% for ECMO versus 43.1% for MV) ( $P = 0.64$ , calculated by JV and RMK). In addition, the ICU and hospital lengths of stay were more than double in the ECMO group.

### **High-frequency oscillatory ventilation**

Our understanding of the mechanisms and importance of ventilator-induced lung injury has advanced over the last three decades. High-frequency oscillatory ventilation (HFOV) should theoretically be an ideal mode to ventilate patients with severe lung damage [10]. It achieves gas exchange by delivering very small tidal volumes (often less than the anatomic dead space) at frequencies ranging from 3 to 15 Hz around a relatively constant mean airway pressure. HFOV is not a difficult technique. In fact, it is easier than conventional MV: it incorporates fewer and simpler controls and they are not interrelated as they are in conventional mechanical ventilators. Recent prospective observational studies have reported that HFOV is a feasible and efficient method of ventilation that results in rapid and sustained improvement in oxygenation in patients with severe ARDS [11-14]. However, a critical examination of RCTs comparing HFOV with conventional ventilation demonstrates that there is equivalence between conventional ventilation and HFOV [15,16]. Specifically, there is no evidence that conventional MV with low tidal volumes, high PEEP, and limited plateau pressures is more harmful than HFOV. All of the RCTs to date have compared HFOV with a less-than-optimal approach to conventional ventilation [15]. However, there are at least two trials that are just beginning that promise to compare HFOV with more appropriately applied conventional ventilation.

### **Prone positioning**

Changes in posture can have profound effects on the pulmonary function of patients with severe respiratory failure. Most changes in pulmonary physiology with posture occur due to the influence of gravity and chest wall shape on the mechanical properties of the lung. By tradition, patients with respiratory failure are cared for in a supine position. In critically ill patients, the supine

posture is associated with a decrease in functional residual capacity (FRC) below the closing capacity, resulting in ventilation-perfusion mismatching and a drop in PaO<sub>2</sub>. During acute respiratory failure, a reduction of FRC results in supine hypoxemia regardless of age. The proposed mechanisms by which prone positioning improves oxygenation include an increase in FRC, a change in regional diaphragm motion, redistribution of perfusion to better ventilated lung units, redistribution of ventilation to better perfused lung units, and improved secretion clearance [17].

The act of turning is labor-intensive; at least three experienced staff members are required in order to avoid losing vascular accesses or the airway. Meticulous care must be used in positioning the patient. Placing a neck roll or a pillow under the patient's shoulders and turning the head to one side is the recommended way to support the patient when prone. In addition, prone positioning may require an increased need for sedation. Although complications such as skin injury, facial edema, catheter removal or compression, hypotension, arrhythmias, and extubation may occur, prone positioning in general can be performed safely if staff are appropriately trained.

Although there are sufficient data to conclude that oxygenation frequently improves when patients with ARDS are turned prone (in about 70% of patients), prone positioning is still not widely implemented. Three recent systematic reviews and a meta-analysis [18-20] in patients with ALI/ARDS have shown that prone positioning does not reduce mortality or duration of MV despite improved oxygenation and a decreased risk of pneumonia.

#### **Inhaled vasodilators**

Anti-inflammatory agents and vasodilators have been tried experimentally in animals and humans as prophylaxis or treatment of ARDS. Prostaglandins, ibuprofen, pentoxifylline, inhaled nitric oxide (iNO), inhaled prostacyclin, almitrine, and corticosteroids have all been tried. None of them has shown any major benefit on outcome in large randomized human trials, even though significant improvements in oxygenation have been observed with some of these agents [21].

NO is important for the regulation of pulmonary vascular smooth muscle. NO appears to be pivotal in acute and chronic hypoxic pulmonary vasoconstriction. Pulmonary hypertension is a typical feature of ARDS and is a bad prognostic factor in respiratory failure. iNO selectively dilates pulmonary vasculature without systemic effects [22]. Over the last 15 years, an increasing

number of clinical studies assessing different aspects of iNO in ARDS patients and addressing the ability of NO to attenuate ALI have been published. In spite of the fact that many clinicians consider iNO a useful rescue treatment for ARDS patients, no RCT has demonstrated an outcome benefit. A recent systematic review and meta-analysis of 12 RCTs including a total of 1237 patients with severe ALI/ARDS found that, as a whole, NO is associated with limited improvement in oxygenation at 24 hours of therapy, has no effect on duration of ventilation, does not confer mortality benefits, and may cause harm [23].

#### **Implications for clinical practice**

As a result of this brief review of recent advances for the treatment of severe acute hypoxemic respiratory failure, our interpretation is that (a) there is not enough evidence to date from well-performed RCTs to routinely recommend the use of ECMO as rescue therapy in adults with severe ARDS, (b) there is no ventilatory mode (including HFOV) that has been proven to be superior to limiting end-inspiratory plateau pressures and tidal volumes and appropriately setting PEEP, (c) altering body position is part of the routine clinical care in most patients with respiratory failure but there is no evidence to support the routine use of prone positioning, and (d) none of the pharmacologic therapies evaluated in ALI/ARDS, including inhaled vasodilators, has been shown to reduce morbidity or mortality when compared with placebo or conventional treatment. The good news is that none of these therapies that improve oxygenation significantly increases morbidity or mortality. As a result, when conventional therapy fails, all can be considered. However, remember that the only thing they may accomplish is increasing costs!

#### **Abbreviations**

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FiO<sub>2</sub>, fraction of inspired oxygen; FRC, functional residual capacity; HFOV, high-frequency oscillatory ventilation; ICU, intensive care unit; iNO, inhaled nitric oxide; MV, mechanical ventilation; NO, nitric oxide; PaO<sub>2</sub>, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial.

#### **Competing interests**

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