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To ventilate, oscillate, or cannulate?☆

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Abstract Ventilatory management of acute respiratory distress syndrome has evolved significantly in the last few decades. The aims have shifted from optimal gas transfer without concern for iatrogenic risks to adequate gas transfer while minimizing lung injury. This change in focus, along with improved ventilator and multiorgan system management, has resulted in a significant improvement in patient outcomes. Despite this, a number of patients develop hypoxemic respiratory failure refractory to lung-protective ventilation (LPV). The intensivist then faces the dilemma of either persisting with LPV using adjuncts (neuromuscular blocking agents, prone positioning, recruitment maneuvers, inhaled nitric oxide, inhaled prostacyclin, steroids, and surfactant) or making a transition to rescue therapies such as high-frequency oscillatory ventilation (HFOV) and/or extracorporeal membrane oxygenation (ECMO) when both these modalities are at their disposal. The lack of quality evidence and potential harm reported in recent studies question the use of HFOV as a routine rescue option. Based on current literature, the role for venovenous (VV) ECMO is probably sequential as a salvage therapy to ensure ultraprotective ventilation in selected young patients with potentially reversible respiratory failure who fail LPV despite neuromuscular paralysis and prone ventilation. Given the risk profile and the economic impact, future research should identify the patients who benefit most from VV ECMO. These choices may be further influenced by the emerging novel extracorporeal carbon dioxide removal devices that can compliment LPV. Given the heterogeneity of acute respiratory distress syndrome, each of these modalities may play a role in an individual patient. Future studies comparing LPV, HFOV, and VV ECMO should not only focus on defining the patients who benefit most from each of these therapies but also consider long-term functional outcomes.

Abbreviations: ARDS, acute respiratory distress syndrome; CV, conventional ventilation; HFOV, high-frequency oscillatory ventilation; ECLS, extracorporeal life support; VILI, ventilator-induced lung injury; EIT, electric impedance tomography; RM, recruitment maneuver; NO, nitric oxide.

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1. Introduction

Acute respiratory distress syndrome (ARDS) has been traditionally defined as acute severe hypoxemia (Pa_{O_2}/F_{IO_2} “”<200 mm Hg) in the presence of bilateral pulmonary infiltrates on chest radiography that are not primarily caused by elevated left atrial pressures [1]. The most recent revised definition incorporates positive end-expiratory pressure (PEEP), making it more robust [2]. Despite the advances in intensive care management, the ARDS mortality remains high, ranging between 34% and 58% [3-5]. Acute respiratory distress syndrome can be a manifestation of direct lung injury from an infection or aspiration, or indirect injury resulting from an extrapulmonary process [6]. Regardless of the insult, the end result is often a diffuse alveolar damage with the disruption of alveolar capillary integrity resulting in pulmonary edema [7]. The alveolar injury results in the release of proinflammatory cytokines such as tumour necrosis factor, interleukin (IL)-1, IL-6, and IL-8 [8,9]. These cytokines recruit neutrophils to the lungs that mediate further damage to the capillary endothelium and alveolar epithelium [10]. Despite decades of laboratory, animal, and clinical research, our understanding of ARDS is still incomplete.

Mechanical ventilation with low tidal volumes (VTs) and high PEEP often referred to as *lung-protective ventilation* (LPV) is an integral part of ARDS management along with other supportive care [11]. Lung-protective ventilation involves the provision of mechanical ventilation with a plateau pressure of less than 30 cm of water and VTs normalized to predicted body weight [12] to minimize alveolar distension and barotrauma and the addition of PEEP to minimize repeated opening/closure of alveolar units and prevent atelectrauma [13] and biotrauma [14]. There are occasions when LPV fails to provide satisfactory gas exchange while maintaining lung protection. Rescue strategies for severe hypoxemia have been an area of interest and research over the last 2 decades [15]. More recently, oxygenation targets in ARDS themselves are under scrutiny [16], and the optimal targets are yet to be defined. An ideal rescue therapy should improve gas exchange while limiting further ventilator-induced lung injury (VILI), whether it is complementary or not to LPV.

One of the major advances in ARDS management has been the realization that mechanical ventilation induces a number of sequelae, initiated in the lung, which are termed *VILI* [17], but which can become systemic. The development of LPV strategies has led to the subsequent improvement in outcomes [18-22]. The pathogenesis of VILI is complex and represents the shear stress and strain on the pulmonary parenchyma and interstitial and vascular elements. It occurs as a result of cyclical collapse of the unstable alveoli at end-expiration, resulting in shear stress, excessive VTs, excessive distending pressures, and propagation of systemic inflammation with associated other-organ failures [18,19]. Despite LPV having been shown to improve mortality in ARDS [21], it is likely that VILI still occurs through a number of mechanisms. Although there are no objective markers to determine the threshold at which VILI occurs and to quantify it clinically, it may be important to consider long-term functional outcomes in addition to mortality effects when choosing one rescue therapy over another.

The heterogeneous nature of the lung injury may mean that the different modalities of LPV, high-frequency oscillatory ventilation (HFOV), and extracorporeal membrane oxygenation (ECMO) have different effects in individual patients. Conceptually, HFOV delivers very small VTs while maintaining alveolar recruitment and appears to be lung protective. Alternatively, venovenous (VV) ECMO may further minimize VILI by causing little cyclic alveolar closure during tidal breaths, which is often referred to as *lung rest*. More studies are required to guide clinicians about which patient subgroups will benefit and when these therapies should be initiated. This review aims to discuss the available evidence so as to guide physicians to decide the most appropriate rescue therapy strategy in patients with severe hypoxemia refractory to LPV.

2. Lung-protective ventilation—is it adequate?

Mechanical ventilators have now become an indispensable device in the intensive care unit (ICU). These have evolved from being volume and pressure generators to devices that use sophisticated rapid response flow sensors and triggering mechanisms to improve patient comfort and ventilator synchrony [23]. However, their rapid advancement has been based more on engineering developments than clinical results. It should be emphasized that owing to a lack of viable alternate options, mechanical ventilation itself has not been rigorously tested in clinical trials. Similarly, the data on safety, efficacy, and outcomes of various modes of ventilation are limited. There has been significant improvement in survival in the past 2 decades as a result of refinements in ventilator techniques, complimented by improved overall ICU care including restrictive fluid management, early treatment of sepsis, and better source control practices [24].

2.1. Low-tidal-volume ventilation

A low-VT ($\leq$ 6 mL/kg of predicted body weight) and low-pressure (inspiratory plateau pressure $<$30 cm H_2O) strategy is now the standard of care. The ARDS Network study demonstrated an absolute risk reduction in mortality of 9% with this approach [21]. Data from animal studies suggest that VILI can occur even at lower plateau pressures [25], and patients with ARDS may benefit from further reductions in VTs if practically feasible. It is still unclear if this benefit can be extended to patients without ARDS who receive conventional ventilation (CV). There are data suggesting