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WHAT'S NEW IN INTENSIVE CARE

Adjunct and rescue therapies for refractory hypoxemia: prone position, inhaled nitric oxide, high frequency oscillation, extra corporeal life support

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The mortality of severe acute respiratory distress syndrome (ARDS), defined with a PaO_2/FiO_2 ratio of 100 mmHg or less with at least 5 cm H_2O of PEEP, still exceeds 40% [1]. Furthermore, although it is true that more ARDS patients die from multi-organ failure than hypoxemia per se, an important subgroup of severe ARDS do die from refractory hypoxemia often defined as a $PaO_2 < 60$ mmHg despite FiO_2 1.0 [2]. Therefore, rescue treatments aiming at preventing hazardous hypoxemia are crucial. In this paper, we will cover prone position, inhaled nitric oxide (iNO), high-frequency oscillation (HFO) and extracorporeal life support (ECLS) as interventions to treat refractory hypoxemia. For each of them, we will discuss mechanism of action to improve hypoxemia (Fig. 1), potential benefits and risks, and make a personal recommendation about use. Before moving towards these measures, clinicians should ensure the basics are attended to—intravascular volume optimized, cardiac output sufficient [3], and patient sedated and paralyzed. We assume that lung protective mechanical ventilation is ongoing including lower tidal volumes and sufficient PEEP, the latter of which should usually involve at least a trial of higher PEEP (15–20 cm H_2O) [4]. When patients remain severely hypoxemic despite these measures, rescue therapy for refractory hypoxemia must be considered (Fig. 1).

Prone position consists of delivering mechanical ventilation with the chest facing down. The principal benefit of prone positioning is ventilator-induced lung injury prevention, due to homogenization of the distribution of lung stress along the vertical gradient. In addition, oxygenation typically improves, due to increasing ventilation and aeration in vertebral lung regions that continue to receive most pulmonary blood flow. Side effects include risk of airway-related complications, like endotracheal tube obstruction or displacement, vascular lines kinking/withdrawal and pressure sores [5]. These complications can be minimized by implementing protocols and increasing experience. In practice, prone position can be performed using standard ICU beds for long sessions and should be started early after recognition of severe ARDS. Prone position use is supported by positive results from an individual patient-data meta-analysis and a subsequent trial in selected patients. A strong recommendation was recently made to use prone position in sessions lasting at least 12 h in severe ARDS patients [6]. Clinicians seem reluctant to largely adopt this intervention, which was used in only 10–15% of severe ARDS and about 25% of patients with refractory hypoxemia [2]. A more recent survey found that 32.9% of patients with severe ARDS were in a prone position [7]. In the ICU in Lyon, we use prone positioning as performed in the Proseva trial, which showed a benefit on selected ARDS patients ($PaO_2/FiO_2 < 150$ mmHg with PEEP ≥ 5 cmH_2O) [8].

The iNO is a selective pulmonary vasodilator administered as a gas at a recommended starting dose of 5–10 ppm through the tracheal route. Its benefit relates to oxygenation improvement resulting from diverting pulmonary blood flow towards well-ventilated lung areas.

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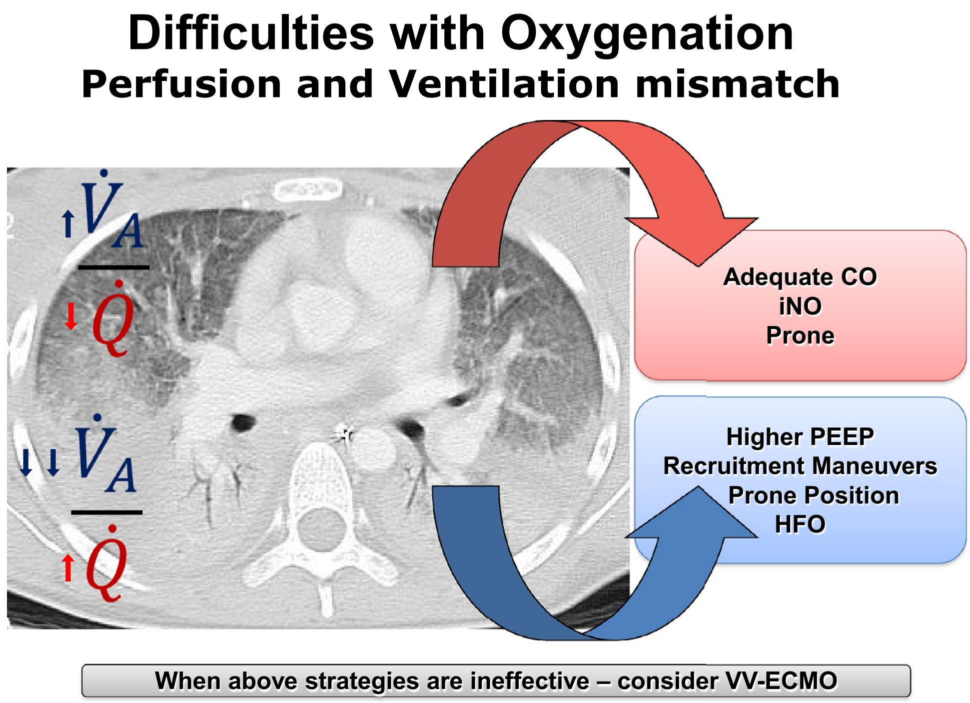

Fig. 1 Mechanisms of action of adjunct therapies during severe ARDS on ventilation/perfusion $\left(\frac{\dot{V}_A}{\dot{Q}}\right)$ distribution. Due to massive loss of aeration and increase in lung tissue as shown on the lung CT slice, hypoxemia results from large amounts of shunt and $\frac{\dot{V}_A}{\dot{Q}}$ mismatch, which may be due to low alveolar ventilation $(\dot{V}_A)$ as compared to lung perfusion $(\dot{Q})$ or to more lung perfusion relative to $\dot{V}_A$. This latter occurs when hypoxic pulmonary vasoconstriction is impaired making the lung perfusion predominant in non-aerated lung regions. To improve $\frac{\dot{V}_A}{\dot{Q}}$ matching and hence oxygenation, interventions may act on both sides of the equation. By increasing perfusion in well ventilated regions, inhaled nitric oxide (iNO) and intravenous fluid challenges redistribute lung perfusion and cardiac output (CO) to well-aerated areas and better match $\frac{\dot{V}_A}{\dot{Q}}$. PEEP can increase aeration in non- or poorly ventilated areas thereby improving $\frac{\dot{V}_A}{\dot{Q}}$. CO may decrease with PEEP, which also contributes to $\frac{\dot{V}_A}{\dot{Q}}$ improvement. High frequency oscillation and recruitment maneuvers improve $\frac{\dot{V}_A}{\dot{Q}}$ by increasing $\dot{V}_A$. Prone position increases $\dot{V}_A$ in the vertebral lung regions where $\dot{Q}$ remains prevalent and, furthermore, makes the distribution of $\frac{\dot{V}_A}{\dot{Q}}$ homogeneous across the lung

Oxygenation improvement with iNO is enhanced when hypoxic pulmonary vasoconstriction is preserved. Furthermore, iNO reduces elevated pulmonary artery pressure and right ventricle afterload, and reduces the risk of acute cor pulmonale, an independent factor of mortality [9]. Prone position and iNO have an additive effect on oxygenation. The potential harmful effects of iNO include platelet aggregation inhibition, elevation of pulmonary artery occlusion pressure, and risk of acute kidney injury. Randomized trials showed improvement in oxygenation but failed to demonstrate improvement in patient mortality [10]. Therefore, systematic use of iNO is not recommended in ARDS. Of note, lung protective ventilation was not used in these trials. It is unknown if their results would have been different if lower tidal volumes had been used. Inhaled NO can be used in refractory hypoxemia on a case-by-case basis. Reassessment of the response should be done after 1–2 days to allow for dose reduction,with the dose being tapered over a few hours to minimize the risk of rebound hypoxemia and increased pulmonary artery pressures. During iNO exposure vasoconstrictive molecules like endothelins are increasingly produced to balance the vasodilator effect of iNO, and, after the sudden iNO interruption, they become predominant potentially leading to a deleterious rebound effect.

High-frequency oscillation (HFO) is a non-conventional ventilatory support where rapid and small cyclical swings in pressure are around a relatively constant mean airway pressure. The potential benefits stem from the delivery of very small tidal volumes at higher mean airway pressures—functionally equivalent to PEEP—while still avoiding cyclic alveolar overdistention. The side effects include the need of a specific device, the uncertainty about the real applied intrathoracic pressure due to the resistive pressure drop, and the risk of hemodynamic compromise. Initial clinical trials in ARDS were promising. Enthusiasm for adult HFO has, however, waned significantly since the publication of two large trials in a broader population of moderate-severe ARDS patients, which showed no effect on mortality, and even increased mortality in HFO patients [11]. These trials drove a recent strong recommendation to not use HFO routinely in moderate-to-severe ARDS patients [6]. A practice audit conducted 2 years after these studies were published showed that even among OSCILLATE study centres, HFO was now used in only 12% of patients with refractory hypoxemia [2]. More recent secondary analyses suggest however, that HFO may have a role as rescue therapy. An individual patient-data meta-analysis of four HFO trials showed that baseline hypoxemia was an important effect modifier with HFO being associated with harm among patients with a PaO_2/FiO_2 above 100, whereas it appeared to have a significantly protective effect with lower mortality among refractory hypoxemia patients treated with HFO [12]. In the ICU at Toronto General we use HFO for severe ARDS patients who have persistent severe hypoxemia after becoming prone and who are not candidates for extracorporeal supports.

Extra-corporeal life support (ECLS) typically takes the form of veno-venous extra-corporeal membrane oxygenation (vvECMO) [13] for patients with refractory hypoxemia. Blood is pulled from the right side of the heart by a centripetal pump and pushed through a membrane oxygenator, returning fully oxygenated back to the right side of the heart. Arterial oxygenation on vvECMO is dependent on the relative amount of ECMO circuit blood flow to the patient's cardiac output. In patients with refractory hypoxemia and minimal contribution to oxygenation from the lungs, high flow rates in the range of 4–6 L/min are required, necessitating the use of large cannula up to 27–31 French [14]. The benefits are the improvement in oxygenation and resting the lung. The side effects are due to the potential of life-theatening mechanical, hemorrhagic and infectious complications related to the use of large canulae and anticoagulation. A RCT showed that referral and transfer to an ECMO center improved 6-month survival without disability. Many clinicians would agree that there are certain patients who benefit from vvECMO—the debate is about the selection of *which* patients [6, 15]. In the recently completed EOLIA trial, patients were included with (1) $PaO_2/FiO_2 < 50$ mmHg with $FiO_2 \geq 80\%$ for more than 3 h; or (2) $PaO_2/FiO_2 < 80$ mmHg with $FiO_2 \geq 80\%$ for more than 6 h; or (3) pH ≤ 7.20 with $PaCO_2 \geq 60$ mmHg for more than 6 h. While we await the results of this trial, in experienced high-volume centers, VV ECMO seems a reasonable option after having at least considered prone positioning.

In summary, a prone position should probably be used much earlier than at the stage of refractory hypoxemia. In case of refractory hypoxemia, a prone position should be used immediately in association with neuromuscular blockade and the addition of iNO, if available. HFO and vvECMO are exceptional techniques limited to specialized centers; however we believe that severe ARDS patients are best cared for in regional centres of expertise where such techniques are likely to be available.

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Compliance with ethical standards

Conflicts of interest

The authors declare no conflict of interest.

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