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Review article

Salvage therapies for refractory hypoxemia in ARDS

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is a condition of varied etiology characterized by the acute onset (within 1 week of the inciting event) of hypoxemia, reduced lung compliance, diffuse lung inflammation and bilateral opacities on chest imaging attributable to noncardiogenic (increased permeability) pulmonary edema. Although multi-organ failure is the most common cause of death in ARDS, an estimated 10–15% of the deaths in ARDS are caused due to refractory hypoxemia, i.e. hypoxemia despite lung protective conventional ventilator modes. In these cases, clinicians may resort to other measures with less robust evidence –referred to as “salvage therapies”. These include proning, 48 h of paralysis early in the course of ARDS, various recruitment maneuvers, unconventional ventilator modes, inhaled pulmonary vasodilators, and Extracorporeal membrane oxygenation (ECMO). All the salvage therapies described have been associated with improved oxygenation, but with the exception of proning and 48 h of paralysis early in the course of ARDS, none of them have a proven mortality benefit. Based on the current evidence, no salvage therapy has been shown to be superior to the others and each of them is associated with its own risks and benefits. Hence, the order of application of these therapies varies in different institutions and should be applied following a risk-benefit analysis specific to the patient and local experience. This review explores the rationale, evidence, advantages and risks behind each of these strategies.

1. Introduction

The Berlin definition categorizes severe ARDS based on the degree of hypoxemia, as a PaO₂/FiO₂ ratio less than 100, with a mortality rate of 45% [1]. According to the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory failure (LUNGSAFE study), the estimated incidence of ARDS is around 34 cases per 100,000 patients per year in the United States [2,3]. 23.4% of the patients in this group had severe ARDS defined based on the Berlin criteria [2]. The in hospital mortality reported for severe ARDS was 46.1% with a median duration of mechanical ventilation among survivors of 11 days and median ICU length of stay of 14 days [2].

Supportive treatment with mechanical ventilation along with conservative fluid management strategies forms the cornerstone of management of ARDS [4,5]. The “lung protective ventilation” (LPV) with recommended parameters of tidal volume of 4–8 ml/kg ideal body

weight (IBW) with a modest positive end expiratory pressure (PEEP), while maintaining a plateau pressure (P_{plat}) of < 30 cm H₂O [6] has become the paradigm for mechanical ventilation in ARDS. The goal of this approach is to minimize ventilator induced lung injury (VILI) (Table 1) [7]- a collective term used to describe the different mechanisms of lung injury caused secondary to mechanical ventilation. VILI develops as a result of four different mechanisms; a) Volutrauma-lung injury caused by alveolar overdistension secondary to increased transpulmonary pressure (alveolar pressure – pleural pressure), b) barotrauma-lung injury secondary to increased transpulmonary pressure causing alveolar rupture and air leaks, resulting in pulmonary interstitial emphysema, pneumothorax and pneumo-mediastinum, c) atelectrauma-shearing lung injury caused by repetitive opening and closing of alveoli and d) biotrauma-activation and release of pro-inflammatory cytokines which further promotes pulmonary and extrapulmonary injury, predisposing to multi-organ failure [7–9].

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Table 1
Key concepts/terms in VILI [8,43].

Term	Definition
Atelectrauma	Lung injury caused by shear forces from cyclic opening and collapse of atelectatic but recruitable lungs.
Barotrauma	Lung injury caused by high transpulmonary pressure
Volutrauma	Lung injury caused by alveolar overdistension
Biotrauma	Additional lung and extrapulmonary organ injury caused by proinjurious inflammatory response to mechanical lung injury.
Stress	Force applied to an area; in lung- represented by transpulmonary pressures.
Strain	Physical deformation or change in shape of an alveolus, caused by stress.

Most of the mortality in ARDS is due to multi-organ failure, but an estimated 10–15% of patients die of refractory hypoxemia [4], which may be defined as persistent or worsening hypoxemia unresponsive to LPV. Although no standard definition exists for refractory hypoxemia; for the purpose of this review we define refractory hypoxemia as PaO₂/Fio₂ less than 150 while on PEEP of 5 cm H₂O or greater on LPV settings, as most rescue interventions in ARDS patients have focused on this subset of patients [10]. In this group, most of which have severe ARDS, the clinicians may need to use additional and/or alternative “salvage” therapies to mitigate life-threatening hypoxemia [4] while the lung injury resolves. Salvage therapies by definition includes therapies that are given when conventional therapies fail, which in this case-refers to failure to alleviate hypoxemia by conventional modes of mechanical ventilation, while on lung protective ventilator settings.

These salvage therapies will be the focus of this review, where we will discuss the evidence, benefits, risks and disadvantages of each of the commonly used salvage therapies. Most of the studies evaluating salvage therapies have employed them within 36–48 h, a time at which potential for alveolar recruitment is highest [11]. However we suggest that these strategies may be employed as early as after 6 h, if maximal ventilator support with LPV cannot correct hypoxemia. Indeed, in the LUNG SAFE study, one or more salvage therapies was used in 61% of patients [2] After discussing the various rescue strategies (Table 2) in more detail, we outline our algorithm for considering them in the conclusion.

2. Prone positioning

The physiological benefits of prone positioning are believed to primarily involve improvement of ventilation-perfusion (V/Q) by reducing ventral-dorsal transpulmonary pressure difference. This effect results in more homogeneous lung inflation and reduced VILI compared to the supine posture [12,13]. Moreover, the now open dorsal lung regions remain well perfused despite their non-dependent orientation, which minimizes shunt. The other added speculated benefits include better drainage assisted by gravity yielding decreased infection rates [12–17].

More than 30 years ago, observational studies reported that prone positioning improved oxygenation in many patients with acute respiratory failure [18,19]. However, several trials performed with prone positioning in patients with ARDS [20–23] showed mixed results with consistent improvement in oxygenation, but no major impact on mortality. A meta-analysis of studies prior to 2013 suggested a survival benefit of patients with PaO₂/Fio₂ less than 140 mm Hg at admission [24]. Based on this background, Guerin et al. conducted a multicenter study, termed the PROSEVA study (Prone positioning in Severe ARDS patients), which was designed with longer proning sessions (> 16 h/day), applied only in severe and early ARDS, used protocols of lung protective ventilation and neuromuscular blockade and was conducted by staff experienced in the techniques of prone positioning and ARDS management [14].

This trial compared prone positioning of patients with severe ARDS

within 36 h of onset with standard care in the supine position only. Enrolled patients had a PaO₂/Fio₂ ratio less than 150 mm Hg with a Fio₂ of 0.6 and PEEP of at least 5 mm Hg. All were managed with low tidal volume ventilation. Patients randomized to the intervention group spent at least 16 consecutive hours in the prone position daily until pre-specified oxygenation improvements were achieved or safety issues arose. Patients in the prone group underwent an average of 4.4 sessions. 28-day mortality in the prone positioning group was 16% versus 32.8 in the supine group [16]. Of note, a recent meta-analysis suggested prone positioning works best in the context of open lung protective ventilation whereas studies which have evaluated prone positioning without concomitant use of lung protective ventilation have not shown important benefits [25].

Complications that have been described with proning include development of pressure ulcers [26] airway obstruction, vomiting, increased abdominal pressure with resultant hepatic and renal dysfunction, loss of venous access and dislodgement of endotracheal tubes [23]. However, many of these complications develop during the initial turning of the patient, and can be prevented by using a careful and regimented prone positioning protocol followed by an experienced team [27]. Contraindications to prone positioning include severe facial, neck trauma, elevated intracranial pressure, pelvic/spinal instability, hemoptysis or a high probability of patient requiring cardiopulmonary resuscitation [14].

With these caveats in mind, prone positioning should be considered for any patient with moderate-severe ARDS and refractory hypoxemia [27], applied for extended periods of time, early in the course of the disease and executed by well-trained personnel to minimize complications. The authors of recently published evidence-based guidelines recommend that patients with severe ARDS receive prone positioning for more than 12 h per day (strong recommendation, moderate to high confidence in effect estimates) [28].

3. Neuromuscular blocking agents

Neuromuscular blocking agents (NMBA) are frequently used to abolish the inspiratory and expiratory efforts of patients, in order to improve patient-ventilator synchrony and to minimize the muscle oxygen consumption. In addition, paralytics can reduce the stress/strain generated in the lung by attenuating the negative pleural pressure during spontaneous efforts [29], thus avoiding the generation of harmful increases in regional trans-pulmonary pressures [30]. Hence, they modify thoraco-pulmonary mechanics and the V/Q ratio, with associated increase in functional residual capacity and decrease in intra-pulmonary shunt. The positive effects of NMBA could also be related to a decrease in VILI [31].

Three randomized trials evaluating the use of NMBA in ARDS have been performed. The first trial by Gannier et al., in 2004, randomized 56 patients with severe ARDS, defined as PAO₂/Fio₂ less than 150 while on PEEP of 5 cm H₂O or greater to two groups with one group receiving NMBA while both groups remained on conventional ventilation with low tidal volumes. They observed consistently better oxygenation and a decrease in PEEP levels at 48, 96 and 120 h in the NMBA group [32]. The same group performed another randomized control trial involving 36 patients with ARDS within 48 h of onset, with PaO₂/Fio₂ less than 200 and PEEP of 5 cm H₂O and greater with NMBA infusion compared to placebo while on conventional lung protective ventilation and confirmed the same findings: the NMBA group again had better oxygenation and also had significantly lower pulmonary and systemic inflammatory response as measured by decreased IL-6 and IL-8 compared to the non NMBA group [33]. The third and the largest trial—the ARDS et curarisation systematique (ACURASYS) randomized 340 patients with severe ARDS (defined as PaO₂/Fio₂ less than 150 while on PEEP of 5 cm H₂O and higher) to receive a 48-h continuous infusion of NMBAs or placebo while on conventional low tidal volume ventilation. Compared to placebo, the NMBA group had lower mortality (31%

Table 2
Table showing different salvage therapies for ARDS.

Salvage therapies	Physiology/mechanism	Pros	Cons	Proposed benefits	Adverse effects
Proning [12–14]	<ul style="list-style-type: none"> - Improvement of V/Q, - Facilitates more homogeneous aeration of lung - Decreases VILI - Improves mobilization of secretions 	<ul style="list-style-type: none"> - No equipment requirement - Low cost and widely available 	<ul style="list-style-type: none"> - Risk of local complications (pressure sores, facial edema) - Need for training personnel and specialized equipment such as proning bed or special foams - Unfamiliarity - Difficulty with regular nursing care - Need for increased sedation and paralytics - Risk of delirium due to concomitant sedation - Prolonged weakness 	<ul style="list-style-type: none"> - Mortality benefit - Possible decrease in infection risks 	<ul style="list-style-type: none"> - Risk of arrhythmias, - Accidental dislodgement of ET tube, invasive lines - Increased abdominal pressure with hepatic/renal dysfunction
NIMBA [31,34,35]	<ul style="list-style-type: none"> - Improvement of patient ventilator asynchrony. - Improvement of V/Q - Decreases VILI 	<ul style="list-style-type: none"> - Low cost, widely available 	<ul style="list-style-type: none"> - Risk of delirium due to concomitant sedation - Prolonged weakness 	<ul style="list-style-type: none"> - Mortality benefit - Increases ventilator free days. - Decreases risk of barotrauma and pneumothorax. 	<ul style="list-style-type: none"> - Possible increased risk of neuromyopathy, weakness
Recruitment maneuvers [39,40,50,51]	<ul style="list-style-type: none"> - Recruitment of alveoli by elevated transpulmonary pressure, followed by high PEEP keeps alveoli open at end-expiration, minimizing atelectrauma. 	<ul style="list-style-type: none"> - Easily applied through any standard mechanical ventilator by ancillary staff 	<ul style="list-style-type: none"> - Difficult to determine “optimal” PEEP - Unlikely that “one size fits all” - Need for increased sedation and paralytics 	<ul style="list-style-type: none"> - Decreases need for other salvage therapies, especially in patients with recruitable lungs. 	<ul style="list-style-type: none"> - Risk of overdistension, volutrauma and barotrauma - Risk of hemodynamic compromise - May worsen mortality
APRV [53,56]	<ul style="list-style-type: none"> - Improvement in shunt, dead space, V/Q - Spontaneous ventilation can improve cardiac output 	<ul style="list-style-type: none"> - Available on most ventilators 	<ul style="list-style-type: none"> - Unfamiliarity - Lack of RCT - No mortality benefit 	<ul style="list-style-type: none"> - Improvement in patient ventilator synchrony, - Decreased need for sedation and paralysis - Helps mobilization of secretions. 	<ul style="list-style-type: none"> - Risk of barotrauma - AutoPEEP in obstructive lung diseases - Risk of hemodynamic instability due to high mean airway pressures - Increased mortality.
HFOV [53,66,69,71,73]	<ul style="list-style-type: none"> - Decreases atelectrauma - Smaller tidal volumes at high frequencies and high mean airway pressure maintains lung recruitment. 	<ul style="list-style-type: none"> - Possible mortality benefit with very low PaO₂/PiO₂ ratio of < 60 	<ul style="list-style-type: none"> - Need for increased sedation and/or NMBAs. - Barrier to transportation. 	<ul style="list-style-type: none"> - Helps mobilization of secretions. 	<ul style="list-style-type: none"> - Higher risk of hemodynamic instability due to high mean airway pressures. - Risk of worsening RV afterload - NO may cause methemoglobinemia and/or renal failure
Inhaled pulmonary vasodilators [76,77,80]	<ul style="list-style-type: none"> - Local delivery allows selective vasodilation of ventilated lung units, thus increasing V/Q matching 	<ul style="list-style-type: none"> - Ease of delivery (except for NO) and no systemic effects 	<ul style="list-style-type: none"> - Lack of data that supports its use - NO requires special equipment for delivery 	<ul style="list-style-type: none"> - Reduction in pulmonary vascular pressures and hence RV afterload. 	<ul style="list-style-type: none"> - Risk of local complications with cannulation (vascular injury), thrombus formation in circuit. - Risk of hemorrhage, intracerebral bleeds
ECMO [85–87]	<ul style="list-style-type: none"> - Ensures adequate tissue oxygenation while maintaining LPV settings. - Negates risk of VILI 	<ul style="list-style-type: none"> - Allows for protective lung settings. - “Buys time” for lungs to heal 	<ul style="list-style-type: none"> - No mortality benefit - Requires additional equipment and personnel - Cannot be used when there is a major contraindication to systemic anticoagulation - Not widely available. Often requires referral to specialized centers 	<ul style="list-style-type: none"> - Survival benefit reported in young patients with severe ARDS in the setting of influenza in the range of 63–77%. - Early institution in severe ARDS within 7 days may result in mortality benefits and decreased incidence of renal failure. 	

vs. 40%) at 90 days, increased number of ventilator free days (53% vs. 44%) and lower incidence of pneumothorax (4% vs. 11%) with no increase in myopathy [34]. A meta-analysis considering all the above-mentioned three randomized controlled trials showed that use of NMBA in the early phase of ARDS improves outcomes with a trend towards lower mortality, more ventilator-free days at day 28, higher PaO₂/FiO₂ ratios and less barotrauma [35]. A much larger randomized multicenter trial- Reevaluation of Systemic Early Neuromuscular blockade (ROSE) (NCT 02509078) is currently underway to assess the mortality benefit of NMBA in moderate to severe ARDS.

Thus, NMBAs should be considered in patients with moderate-severe ARDS within the first 48 h, particularly in the subset of patients with PaO₂/FiO₂ less than 150. However, risks of ICU-acquired weakness should be considered especially patients with hyperglycemia, patients receiving steroids and care should be taken to minimize use of NMBA beyond 48 h due to increased risk of weakness [31].

4. Recruitment maneuvers and high PEEP

A recruitment maneuver (RM) is a transient sustained increase in transpulmonary pressure in an attempt to open previously collapsed alveoli and thus increase lung compliance and improve gas exchange [36]. ARDS is associated with dependent atelectasis, which is compounded by increased lung weight from interstitial and alveolar edema as well as low tidal volume ventilation [4,37]. Atelectasis exacerbates lung injury by reducing the size of the lung available for mechanical ventilation as well as increasing stress at the interface between atelectatic and aerated lungs and worsening atelectrauma [28,38]. RMs applied to reverse atelectasis followed by high PEEP to keep the recruited alveoli open forms the basis of the “open lung approach” which aims to improve gas exchange and minimize VILI by reducing stress and atelectrauma [39].

Several methods for performing recruitment maneuvers have been studied. The most common one used is sustained inflation with continuous positive airway pressure (CPAP) mode with applied pressure of 30–40 cmH₂O applied for 30–40 s period [40]. Still other methods use ‘sighs’ [41,42] stepwise recruitment maneuvers with incremental PEEP with constant driving pressure (eg- 15 cm H₂O) or fixed tidal volumes (4–8 ml/kg IBW) [10,43]. Stepwise recruitment maneuvers have been suggested as more effective approaches with less risk of hemodynamic compromise [43]. Once the lungs are recruited, they must be kept open by maintaining extrinsic PEEP at a pressure above the point of derecruitment, as determined at the bedside by changes in compliance and/or oxygen desaturation [43]. Sedation along with paralytics is commonly used, which maximize the effectiveness of recruitment.

Most of the meta-analyses on RMs in patients with moderate to severe ARDS have been confounded by the co-intervention with higher PEEP, poor sample size in trials and a high risk of bias [28,43,44]. A single multicenter randomized controlled trial which did not involve the co-intervention of PEEP in patients with moderate or severe ARDS compared recruitment maneuvers along with conventional ventilation to conventional ventilation alone and reported mortality benefit (32.7% vs 52.7% in ICU and 41.8 vs 56.4% in hospital) with the use of RMs, however this trial had methodological limitations due to limited sample size, imprecision and risk of bias [44,45].

Three large randomized controlled trials of higher PEEP with or without RMs in patients with ARDS and a PaO₂/FiO₂ of 300 or less did not demonstrate any significant mortality benefit compared to lower PEEP settings; with all groups maintained on low tidal volume ventilation [46–48]. An individual patient data meta-analysis of these three trials suggested that higher PEEP reduced mortality in patients with more severe hypoxemia, i.e PaO₂/FiO₂ of 200 or less [49]. However, a recent well conducted multicenter trial (Alveolar Recruitment for ARDS trial- or ART) randomized 1010 patients with moderate to severe ARDS to receive lung recruitment maneuvers and high PEEP titrated to respiratory system compliance against conventional low PEEP settings,

and showed increased 28-day (55.3% vs. 49.3%) and 6-month mortality in the group receiving recruitment maneuvers and high PEEP (65.3 vs. 59.9%) with increased incidence of barotrauma (5.6% vs. 1.2%) and pneumothorax requiring drainage (3.2 vs. 1.2%) [50]. Both groups were maintained on low tidal volume ventilation. Thus, high PEEP may not be “patient-protective” in spite of the physiological benefits [51]. Other potential risks of PEEP include increase in right atrial pressure affecting venous return and consequently cardiac output as well as increase in pulmonary vascular resistance leading to cor pulmonale [28,51].

The open lung approach has consistently shown to improve oxygenation in moderate-severe ARDS [51]. RMs along with high PEEP may still therefore have a role in selected patients with refractory hypoxemia, particularly following an episode of extensive alveolar derecruitment, such as endotracheal suctioning, disconnection from the ventilator or bronchoscopy and in patients with a substantial amount of recruitable nonaerated lung tissue [40,52], which can be ascertained based on the response to RMs with improvement in oxygenation and lung compliance (usually better seen in early ARDS between 4 and 5 days of onset and ARDS secondary to non pulmonary causes) [43,44]. Caution must be exercised in the application of RMs however in hypovolemia or in shock [28]. The authors of recently published evidence-based clinical practice guidelines suggest that patients with ARDS receive recruitment maneuvers (conditional recommendation, low to moderate confidence in the effect estimates) [28]. However, these guidelines were published prior to the ART trial and future guidelines may change based on the findings of this study.

5. Unconventional ventilator modes

5.1. Airway Pressure Release Ventilation

Airway Pressure Release Ventilation (APRV) is a time cycled, pressure targeted mode of ventilation which consists of continuous positive airway pressure (CPAP) that is intermittently released to allow a brief expiratory interval. APRV provides increased airway pressure as a potential recruitment mechanism [53].

Benefits of APRV are unproven and speculated to be linked to spontaneous breathing and include: 1. Better patient-ventilator synchrony 2. Improvement in ventilation/perfusion matching by promoting a more physiological gas distribution to non-dependent lung regions. 3. Decreased need for sedation and paralysis 4. Improvement in cardiac performance due to reduced sedation and decreased intrathoracic and right atrial pressures [53] 5. Decrease in VILI associated with cyclic recruitment and atelectrauma [54,55]. However, the mode does not have a mechanism for limiting tidal volume, and patients can potentially receive very large transpulmonary pressures, which increase the risk of overdistension. Given that most of the benefits of APRV are related to spontaneous breathing, this method is not usually applied for patients who require deep sedation and neuromuscular blockade [53]. Also, given the very low time allotted for the expiratory phase, it is relatively contraindicated in patients with obstructive lung diseases due to potential of developing auto-PEEP [56].

The few published randomized controlled trials (RCTs) evaluating APRV have had small sample sizes and did not compare APRV with best practices in conventional mechanical ventilation for ARDS. Moreover, they used surrogate endpoints such as sedation levels and yielded conflicting results [53,57–59]. The only RCT that compared APRV with the conventional low tidal volume ventilation was in a series of adult trauma patients in acute respiratory failure, which did not show any mortality benefit-rather a trend towards increased duration of mechanical ventilation and ICU days was noted in the APRV group [60]. While some studies show improvement in oxygenation [61], improvement in respiratory mechanics [61,62] others have shown increases in ventilator days [63] or no difference in clinically significant outcomes [64]. In short, most studies show physiological benefits and

improvement in some short-term clinical outcomes such as oxygenation and respiratory mechanics, but no mortality benefit [53].

In the absence of mortality benefit and lack of universality from the available evidence so far, a definite recommendation for the use of APRV cannot be made and controversy regarding its use will continue to exist until a well-designed multi-center RCT assessing patient related outcomes is completed [10]. However, it continues to be used in several centers and may be considered in refractory hypoxemia, especially in patients with recruitable lung in ARDS.

5.2. High frequency oscillatory ventilation

High frequency oscillatory ventilation (HFOV), delivers a small tidal volume (1–4 ml/kg) at a frequency range of 3–15 Hz while maintaining a high mean airway pressure [65]. In HFOV, the lungs are held inflated with high pressures to maintain oxygenation while carbon dioxide is cleared by small volumes of gas moved in and out of the respiratory system at high frequencies, which aim to facilitate alveolar recruitment and minimize atelectrauma [66]. Observational Studies and trials [67,68] showed improvement in oxygenation in patients with ARDS with HFOV but were limited by the use of outdated conventional ventilator strategies and small sample sizes.

Two large randomized controlled trials of HFOV in ARDS published in 2013 showed no mortality benefit in ARDS compared to lung protective ventilation strategy in conventional ventilation modes, and one of the two trials showed harm [66,69]. The High-frequency oscillation in early acute respiratory distress syndrome (OSCILLATE) trial [69] randomized 548 patients with early moderate to severe ARDS, with PaO₂/FiO₂ less than 200 in a 1:1 ratio to either HFOV or conventional low volume ventilation and high PEEP and showed an absolute increase in hospital mortality (47% in HFOV vs. 35% in conventional lung protective ventilation modes). The mechanism of poor outcomes with HFOV was unclear but may relate to hemodynamic influences of high airway pressure, worsening right ventricular failure secondary to increased afterload and/or substantial sedation requirements of this approach [70] [71]. A Cochrane review of 10 randomized controlled trials showed no mortality benefit in the 1779 patients with moderate or severe ARDS on HFOV, despite improved oxygenation in 18–26% [72]. A recent patient level meta-analysis confirmed increased mortality with HFOV in mild-moderate ARDS, but suggested a survival benefit in very severe ARDS with PaO₂/FiO₂ less than 60 [73].

The authors of recently published evidence-based clinical practice guidelines recommend that HFOV not be used routinely in patients with moderate or severe ARDS (strong recommendation, moderate to high confidence in effect estimates) [28]. However it continues to be used in many centers in the setting of severe refractory ARDS, perhaps because HFOV is less well studied in the rescue setting.

6. Pulmonary vasodilator therapy

Inhaled pulmonary vasodilators will theoretically dilate the blood vessels preferentially in the well-ventilated lung units. Redirection of blood flow from the poorly ventilated lung zones will thus improve the V/Q mismatch [74]. They may also reduce hypoxia mediated vasoconstriction and pulmonary hypertension [75]. The localized delivery and short half-life of these medications substantially reduces their systemic effects. However, despite the physiological benefits of inhaled vasodilators, studies performed in ARDS patients have not established any mortality benefit [76,77]. Of note, clinical trials in some cases were designed to reduce PEEP by protocol in the context of iNO induced oxygenation improvement; arguably, this strategy may have offset any potential benefits of iNO if the PEEP were indeed lung protective.

Nitric oxide: Inhaled nitric oxide (iNO) when delivered at concentrations of 5–80 ppm, can diffuse across alveolar walls and dilate the capillaries in those lung units that are well-ventilated. Once initiated, parameters of improvement usually monitored are PaO₂ and

pulmonary vascular pressures. Use of iNO is considered when the patient is not responding to conventional management and requires high FiO₂ and PEEP. Inhaled NO is also not routine therapy for adults with ARDS, since studies have not proven a mortality benefit [76,78,79]. Additionally, iNO is associated with more complications, particularly methemoglobinemia and increased renal impairment [80]. Methemoglobin levels should be checked before and monitored during therapy. iNO also requires a specialized delivery system, resulting in iNO being largely replaced by inhaled prostacyclins.

Prostacyclins: Inhaled prostacyclins (PGI₂ or epoprostenol) may be especially useful for patients with refractory hypoxemia accompanied by pulmonary hypertension and right ventricular dysfunction [77]. It is usually initiated at doses of 50 ng/kg/min followed by monitoring of PaO₂ and pulmonary artery pressures (if available), and titrated down based on improvement of these parameters.

The major advantage of inhaled prostacyclin compared to inhaled NO is its ease of delivery. Aerosolized prostacyclin can be delivered via nebulizer connected to the mechanical ventilation circuit. Additionally, inhaled epoprostenol is considerably less expensive than inhaled NO [81]. Adverse events with the use of prostacyclin are infrequent. There were concerns about prostacyclins' inhibitory effects on platelet aggregation [82]. However, studies that have utilized prostacyclins in ARDS have not reported major bleeding events [83]. Thus, inhaled pulmonary vasodilators though not supported for routine use based on existing evidence, may be considered as adjunctive therapy in severe ARDS especially if associated with pre-existing pulmonary hypertension [4,79].

7. Extra- corporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) has been used successfully in patients with severe acute respiratory distress syndrome (ARDS) since 1972 [84]. There has been a marked increase in the number of patients receiving extracorporeal support for respiratory failure especially after the H1N1 influenza pandemic [85]. In patients with moderate-severe ARDS, and refractory hypoxemia on LPV, when part of the gas exchange can be taken over by veno-venous ECMO (VV-ECMO), tidal volumes and plateau pressures can be substantially reduced on the ventilator to provide time for recovery of the injured lungs.

In 2009, a UK based multicenter trial Conventional Ventilation or ECMO for severe adult respiratory failure (CESAR) [86] randomized 180 adult patients in 1:1 ratio with severe but reversible respiratory failure to receive ECMO (n = 90) or conventional management (n = 90). Patients randomized to ECMO were transferred to a single specialized ECMO center, while patients randomized to conventional mechanical ventilation remained at their local hospital. Only 68 of the 90 (75%) patients randomized to the ECMO group, actually received ECMO. Patients were maintained on lung protective ventilation while on VV ECMO which was continued until lung recovery, or until apparently irreversible multi-organ failure. The study found an absolute mortality reduction by 16% without severe disability in the ECMO group (63% survivors in ECMO group vs. 47% in non ECMO group). But the CESAR study had several weaknesses -which include a) Absence of standardized ventilation protocol in conventional ventilation arm b) Among those referred to ECMO centers, only 75% received ECMO and c) Significantly higher percentage of patients in the ECMO group received LPV, as compared to conventional management arm. In fact, if one only considers the mortality of those patients who actually received ECMO and compare it to those who were managed with conventional ventilation regardless of location, there is no significant difference in survival (51.5% ECMO vs. 56.9% conventional ventilation) Thus, it is unclear whether the improvement in survival was attributable to ECMO or to better care and adherence to LPV in specialized centers [86].

The 2009 H1N1 pandemic stimulated the use of ECMO for severe ARDS in various parts of the world- and demonstrated survival rates

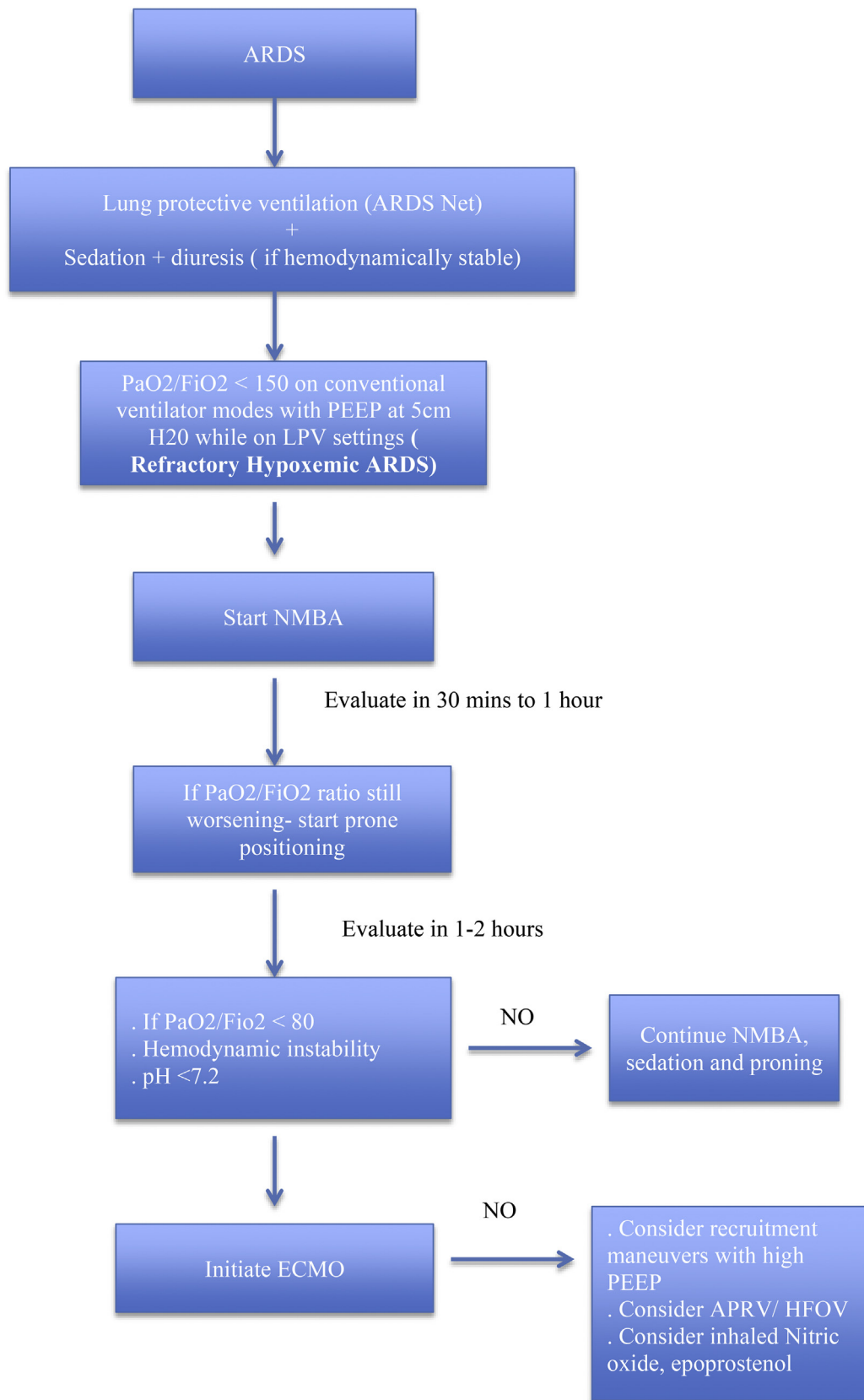


Fig. 1. Proposed flow chart of management of refractory hypoxemia in moderate-to severe ARDS.

between 68 and 77%. However, all of the reported case series were uncontrolled and shared the same shortcomings of the CESAR trial and whether improvement in survival could be attributed to ECMO or better care with lung protective ventilation/rescue strategies in specialized hospitals is unclear [87–89].

The authors of a recently published evidence based clinical practice guidelines state that additional evidence is necessary to make a definitive recommendation for or against the use of ECMO in severe ARDS [28]. To date, there are no well-defined clinical criteria to determine the specific patient population that would benefit from the use of ECMO over conventional therapy. In a recently concluded randomized controlled trial- the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA trial)- early use of ECMO within 7 days for severe ARDS (defined as Pao₂:Fio₂ ratio < 50 for more than 3 h; or PaO₂/Fio₂ ratio < 80 for 6 h) was compared with conventional treatment group (low tidal volume mechanical ventilation and on LPV settings). At 60 days, the ECMO group did not have a statistically significant mortality benefit compared with the control group. Notably though, 28% of patients in the control group crossed over to the ECMO group, possibly diluting the true effect of ECMO initiation in these patients. Hence the data is still inconclusive for clinical benefit from ECMO, although a trend towards decreased mortality and renal failure was observed in the arm with early institution of ECMO (within 7 days) [90].

8. Conclusions

Refractory hypoxemia in ARDS continues to pose a major treatment challenge and is associated with considerable mortality. Salvage therapies, with the exception of extra-corporeal membrane oxygenation and pulmonary vasodilators work on the physiological principles of opening up collapsed alveoli, with resultant reduction in shunt fractions and dead space, thus improving lung compliance and alveolar recruitment and consequently ventilation–perfusion ratios [91–94].

In light of the present evidence suggesting a mortality benefit, we suggest proning and paralysis as first line therapy. There currently are no data to recommend which other salvage therapies should be initiated and the use of such measures is likely going to be dependent upon clinician familiarity, resource availability, patient risk and cost considerations [91]. Future research to identify mechanical or biological markers predicting response to these therapies may provide more targeted patient selection than simply hypoxemia [92–94]. A proposed flow chart is outlined below (Fig. 1).

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Author contributions

SVC, AK, KA: Performed literature search, design, and prepared the manuscript. **RA, MA, AM:** Supervised, critically reviewed, edited the manuscript and helped prepare the manuscript.

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Glossary

PEEP: Positive End Expiratory Pressure

V/Q ratio: Ventilation-perfusion ratio

TT: Endotracheal tube

NMBA: Neuromuscular Blocking Agents

NO: Nitric Oxide