Review

Hypoxaemic rescue therapies in acute respiratory distress syndrome: Why, when, what and which one?

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A B S T R A C T

Acute respiratory distress syndrome (ARDS) is an inflammatory condition of the lungs which can result in refractory and life-threatening hypoxaemic respiratory failure. The risk factors for the development of ARDS are many but include trauma, multiple blood transfusions, burns and major surgery, therefore this condition is not uncommon in the severely injured patient. When ARDS is severe, high-inspired oxygen concentrations are frequently required to minimise hypoxaemia. In these situations clinicians commonly utilise interventions termed ‘hypoxaemic rescue therapies’ in an attempt to improve oxygenation, as without these, conventional mechanical ventilation can be associated with high mortality. However, their lack of efficacy on mortality when used prophylactically in generalised ARDS cohorts has resulted in their use being confined to clinical trials and the subset of ARDS patients with refractory hypoxaemia.

First line hypoxaemic rescue therapies include inhaled nitric oxide, prone positioning, alveolar recruitment manoeuvres and high frequency oscillatory ventilation, which have all shown to be effective in improving oxygenation. In situations where these first line rescue therapies are inadequate extra-corporeal membrane oxygenation has emerged as a lifesaving second line rescue therapy. Rescue therapies in critically ill patients with traumatic injuries presents specific challenges and requires careful assessment of both the short and longer term benefits, therapeutic limitations, and specific adverse effects before their use.

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Is refractory hypoxaemia in acute respiratory distress syndrome (ARDS) a clinical problem?

ARDS is common and deadly

Acute respiratory distress syndrome (ARDS) is an inflammatory disorder of the lung parenchyma.\(^1\,^2\) ARDS results in impaired gas exchange and hypoxaemic respiratory failure, which can be refractory and life threatening.\(^1\,^2\) There are many clinical conditions associated with the development of ARDS in the critically ill including major trauma, blood transfusions, burns, sepsis, pneumonia, aspiration of gastric contents.\(^3\) The incidence of ARDS has been reported in various studies to range from 28 to 82 cases per 100,000\(^4\)–\(^7\). One large multi-centre trauma cohort in the USA had 5% of patients develop ARDS.\(^8\) In this study, injury severity, thoracic injury, poly-trauma, pneumonia and receiving more than 5 units of fresh frozen plasma were independent predictors of developing ARDS.\(^8\) The combination of the clinical frequency of ARDS in the trauma intensive care unit (ICU) with an in-hospital mortality rate up to 40%, makes ARDS a significant factor associated not only with mortality and morbidity, but also an increased rate of complications, prolonged duration of mechanical ventilation, with increased length of ICU and hospital stay and an ever growing use of expensive therapies (including hypoxaemic rescue therapies).\(^5\,^7\,^9\)–\(^13\)

Classification and mechanism of hypoxaemia and multi-organ failure in ARDS

ARDS is a syndrome defined by clinical criteria (acute onset, hypoxaemia (PaO\(_2\)/FiO\(_2\) < 200 mmHg on PEEP > 5 cm H\(_2\)O), bilateral infiltrates on chest radiograph without elevation of left atrial pressure).\(^14\) While the alveolar consolidation and resulting ventilation/perfusion mismatch in ARDS is the predominant mechanism for arterial hypoxaemia, it is important to note that other potential factors (e.g. impaired right ventricular performance) may also play a role. Computed tomography (CT) images in ARDS demonstrate that the apparently homogeneous lung infiltrate seen on antero–posterior chest X-ray (CXR) is actually heterogeneous, with 3 functionally distinct zones during tidal ventilation (see Fig. 1),\(^15\) dependent on gravitational forces.

Alveoli in the most dependent lung region remain collapsed throughout tidal ventilation, despite high positive end expiratory pressure (PEEP) levels, resulting in chronic collapse injury.\(^15\) An intermediate lung region that collapses and re-expands with each breath results in shear stress-induced injury (atelectrauma).\(^17\) Alveoli in the least dependent lung regions remain inflated throughout tidal ventilation, and are at risk of over-inflation lung injury (volutrauma) by excessive tidal volumes and plateau airway pressures.\(^18\,^19\) These repetitive mechanical insults promote a deleterious pulmonary and systemic inflammatory injury, called biautrauma.\(^20\) Interestingly, ARDS patients who die often succumb to multiple organ failure contributed to by the ongoing ventilator induced injury promoting such biautrauma.\(^1\,^13\)

A better understanding of the pathophysiology of ARDS has established that while mechanical ventilation is a lifesaving intervention, it has the potential to not only worsen pulmonary injury and augment non-pulmonary organ failure and increase mortality. These insights also explain the previous findings that strategies which used high intensity mechanical ventilation to maintain adequate systemic oxygenation concentration through the use of high volumes and pressure, demonstrated high rates of non-pulmonary associated mortality.\(^21\,^22\) Therefore clinicians often attempt to minimise the ‘intensity’ of mechanical ventilation, an approach that frequently involves the use of rescue therapies to maintain adequate gas exchange (i.e. preventing severe hypoxaemia). The use of rescue therapies requires an assessment that the benefits outweigh the risks for that patient.\(^23\) This is particularly important in

Fig. 1. (A) CT of supine ARDS patient (left, reproduced with permission) showing atelectasis and oedema in the dependent lung regions and (B) supine chest radiograph of a patient with ARDS.
ARDS + severe hypoxemia

Protective lung ventilation applied (Vt ≤ 6 ml/kg and Pplat ≤ 30 cmH2O) → No → Severe hypoxemia remains → No

Check the cardiovascular status (at least clinical exam and transthoracic echocardiography) → Yes

Left heart failure with increase in left atrial pressure → No → Manage diuretics and other heart failure therapies → Yes → Severe hypoxemia remains → No

Low PvO2 Hypovolemia Hypotension → Yes → Manage with fluid resuscitation and vasoactive drugs → No

Low Pplat Severe hypoxemia remains → No

Right heart failure Pulmonary hypertension Intra-cardiac shunt (require transesophageal echocardiography) → Yes → May guide the choice of a rescue therapy and/or a specific treatment → No

Sedation Neuromuscular blockades Fever reduction Use of a closed system Avoid useless endotracheal

Severe hypoxemia remains → No

REFRACTORY HYPOXEMIA
A rescue therapy is justified → Yes

Vt = Tidal Volume
Pplat = Plateau pressure

Fig. 2. Flow chart of suggested optimal patient management for severe ARDS with severe hypoxaemia prior to a rescue therapy being commenced. ECMO: extracorporeal membrane oxygenation; HFOV: high frequency oscillatory ventilation; iNO: inhaled nitric oxide; PEEP: positive end expiratory pressure.
patients with trauma who present with multiple complex injuries. Many of these injuries may tilt the potential balance more towards risk than benefit for a particular rescue therapy, therefore care is required in the selection of the most appropriate rescue therapies for traumatically injured ARDS patient with refractory hypoxaemia.

When to consider using a rescue therapy for severe hypoxia?

Is there a physiological basis for an oxygenation target?

Tissue related hypoxic injury is the result of hypoxaemia, hypoperfusion and cytokine-mediated mitochondrial dysfunction, termed cytopathic hypoxia. Interestingly recent evidence suggests that organ dysfunction in the critically ill may be more related to the derailment of the metabolic processes of cells to use available oxygen rather than the lack of available oxygen. This is further highlighted by the finding that at the mitochondrial level, a PaO2 as low as 5 mmHg is enough to fuel the reactions in normal individuals.

Oxygen might be part of the problem and not part of the answer—threshold of oxygen toxicity

While oxygen is necessary for our life, too much oxygen is toxic. Animal experiments have clearly demonstrated that exposure to FIO2 of 1.00 induced death in many animal species in 3–5 days. In humans, the time spent with a FIO2 higher than 0.6 is higher in ARDS patients with severe airspace enlargement at post mortem.

What is the correct oxygenation target in ARDS patients?

While a high PaO2 is not a major concern in the context of ARDS, it seems reasonable to avoid high FIO2 as oxygenation improves. Several recent papers have highlighted the risk of high PaO2 in cardiac arrest patients and in traumatic brain injury and even in the general population. It seems prudent to target the minimally safe PaO2 in our patients as soon as possible.

So how low should you go? There are many different opinions regarding the optimal threshold of oxygen saturation and PaO2. Most would agree with targets of 94–98% saturation for healthy subjects and between 88 and 92% and a PaO2 > 55–60 mmHg in the context of ARDS. There is growing interest in permissive hypoxia, a tolerance of even lower oxygenation targets to permit less injurious and intensive ventilation strategies, this is controversial and needs to be carefully considered in certain patient populations, for example acute traumatic brain injury where it is contra-indicated.

However, most studies in a general ARDS population and many clinicians define refractory hypoxia (and suggest the need for hypoxaemic rescue therapies) as either (i) a PaO2/FIO2 ratio < 100 or (ii) a SaO2 < 88% or (iii) a PaO2 < 60 mmHg with a plateau airway pressure > 30 cm H2O with a FIO2 > 0.8. The question of the minimal safe PaO2 in the context of TBI is less clear. Many clinicians are conservative and tolerate higher FIO2 and PaO2 above 70 mmHg in this context, while others target PaO2 of 60 or lower, often with additional cerebral oxygen monitoring (i.e. LiCoX). Before the addition of a hypoxaemic rescue therapy to the treatment bundle it is wise to confirm that current care is optimal to minimise lung injury and to maximise outcomes (Fig. 2).

How would an ideal hypoxaemic rescue therapy perform?

It is useful to consider how an ideal hypoxaemic rescue therapy might perform, as this may then provide a ‘yard stick’ by which to compare the pros and cons of current available alternatives. The ideal hypoxaemic rescue therapy would (i) have the ability to rapidly and effectively improve oxygenation, (ii) facilitate the use of low pressure and low volume protective lung ventilation strategies to minimise additional lung injury, (iii) be inexpensive, (iv) be simple, widely available and require minimal staff training to use, (v) be non-invasive, and (vi) have no short term or long-term adverse effects. Ideally it should not only increase oxygenation but also improve survival and the quality of life of long-term survivors (see Table 1). A rescue therapy needs to be considered safe and effective despite the complex issues of the patient. In particular, chest injuries and brain injuries in the traumatically injured cohort augment the potential for adverse effects of some rescue therapies.

First line hypoxaemic rescue therapy options

Inhaled nitric oxide

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator. Its administration via the inhaled route results in delivery to only the alveoli that receive alveolar ventilation and also minimises systemic effects (i.e. hypotension). By selectively dilating the pulmonary vasculature of these areas of ventilated lung, iNO improves ventilation perfusion matching and reduces

<table>
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<th>Table 1</th>
<th>Overview of the advantages and disadvantages of each rescue therapy for hypoxia.</th>
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<td>Rescue therapy</td>
<td>Advantages</td>
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<td>Management of pulmonary hypertension</td>
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<tr>
<td>Prone positioning</td>
<td>Cheap</td>
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<tr>
<td>RMs and PEEP titration</td>
<td>Readily available</td>
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<td>HFOV</td>
<td>Reduced driving pressure of the lungs</td>
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<td>ECMO</td>
<td>Management of air leaks</td>
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ECMO: extracorporeal membrane oxygenation; HFOV: high frequency oscillatory ventilator; N/S: not significant; PaO2/FIO2: ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; RMs: recruitment manoeuvres.

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pulmonary shunt. This effect frequently results in both improved oxygenation and decreased pulmonary artery pressure.36,37 iNO has also been suggested to have anti-inflammatory effects, however the clinical implications of these are as yet uncertain.38,39 However, iNO carries a risk of increased oxidative stress in red blood cells and the development of methaemoglobinemia,40 a complication which may aggravate the systemic delivery of oxygen. Patients treated with iNO therefore require careful monitoring of arterial blood for development of this side effect but this is seldom a clinical problem.

Several randomised controlled trials in ARDS patients have reported that while prophylactic iNO resulted in improvements in oxygenation over a period of 24–48 h (tachyphylaxis presumably develops thereafter), long term clinical outcomes were not improved.41,42 Individual study findings are supported by two systematic reviews of prophylactic iNO in ARDS that report no difference in survival or ventilator-free days between treatment and placebo groups.43,44 Furthermore, it may be that the greatest benefit is achieved in the most severe subset of ARDS patients and that this benefit is not detected in studies selecting all ARDS patients. Furthermore, the limited pharmacokinetic studies in ARDS make it difficult to make firm recommendations about the optimal dose of iNO,45 however, most would commence at 5 ppm (parts per million) and titrate up to 40 ppm to achieve optimal effect. Our experience suggests that an optimal effect on oxygenation can usually be achieved with lower doses (5–10 ppm), whereas optimal effect on pulmonary artery pressure may require higher doses (up to 40 ppm). Future studies are required to assess the response of different doses of iNO and the true effect of iNO in the presence of higher levels of PEEP.

Long term outcomes (to one-year) and hospital costs have also been assessed in a RCT of 385 adults with ARDS randomised to 5 ppm iNO or placebo.41 There were no differences between the groups for survival, hospital costs from enrolment to discharge or in length of hospital stay.

Clinical use of inhaled nitric oxide in the trauma patient

Given the substantial cost of iNO, and the absence of clear evidence of benefit, the routine use of iNO in ARDS cannot be currently justified. However, the current evidence suggests that while iNO will not improve survival or long term outcomes in patients with ARDS, it may be an effective short term rescue therapy for patients with very severe refractory hypoxaemia. This may be of clinical value (i) while waiting to establish another longer acting hypoxaemic rescue therapy (i.e. HFOV or ECMO, Fig. 3), (ii) allowing time for other interventions to take effect (i.e. diuretics, antibiotics) or even (iii) as an additional rescue therapy (i.e. add iNO to prone45).

Prone positioning

Patients with severe trauma and ARDS often spend prolonged time in the supine position, this tends to increase atelectasis and consolidation in the gravitational-dependent lung regions. In addition, the inflammatory pulmonary oedema that occurs during ARDS increases lung weight collapsing the dorsal regions of the lungs under the weight of the ventral regions, resulting in increased dorsal atelectasis.46 As the dependent posterior lung segments account for a large proportion of the lungs this may cause significant shunt which contributes to hypoxaemia. Prone positioning shifts the gravitational forces and reduces the cardiac compression of the lungs. The ventral regions become dependent and collapse under the weight of the dorsal regions, which inflate to a different extent. Because of their shape, a higher percentage of the lungs’ alveolar units are open to ventilation in the prone position than in the supine position.47 Therefore, in the prone position, air is distributed more homogeneously throughout the lungs, and stress and strain are decreased.48 This protective ventilator effect could potentially minimise the systemic inflammatory response and improve outcomes. Improved lung recruitment and ventilation-perfusion matching may occur, particularly if the prone position is maintained for a long period of time49.

Other potential benefits of prone positioning include enhanced drainage of secretions from the posterior lung segments, decreased alveolar overdistension and reduced ventilator induced lung injury.46,50

The process of prone positioning requires consideration of safety precautions. Extra staff are required, the position of the endotracheal tube and other lines must be securely maintained and the patient must receive constant monitoring for the development of pressure injuries.51 In a recent meta-analysis, prone positioning increased the risk of pressure ulcers, endotracheal tube obstruction and chest tube removal.52 One trial found increased risk of unplanned extubation and unplanned removal of venous or arterial catheters.53 There are several additional limitations to the use of prone positioning. Patients with ARDS as a result of severe traumatic injuries may not be suitable for the prone position due to unstable fractures of the face, spine or pelvis, external fixation or traumatic brain injuries. There may be
limitations due to wounds, skin grafts or orthopaedic management. However, several studies have examined prone ventilation in trauma cohorts and have found that it improves oxygenation without a significant increase in complications in carefully selected patients.54–56

The recent PROSEVA trial (NCT00527813) has reported a 28 day survival benefit with prone positioning for more than 16 h per day in patients with severe ARDS (PaO2/FiO2 < 150) compared to standard protective lung ventilation in the supine, semi-recumbent position. Previously, multi-centre randomised controlled trials49,57,58 and systematic reviews59–62 had failed to demonstrate that prone positioning leads to a survival benefit in a diverse patient population defined as having ARDS and ALI. Five randomised controlled trials have shown improved oxygenation with no survival benefit.49,53,57,58,63 The oxygenation was improved for up to 10 days in patients with prone positioning.59 However a recent pooled data meta-analysis suggested that patients with severe ARDS (defined as PaO2/FiO2 < 100 mmHg) may have a survival benefit when prone positioning is used.52

The optimal duration of prone positioning is yet to be determined however at least 16 h per day should be used (ref. PROSEVA). A study by Mancebo et al. investigated the use of prolonged ventilation.49 The investigators randomised 136 patients, 76 patients to receive prone ventilation for 20 h per day and showed prone positioning was used for a mean of 17 h per day for a mean 10 days with a possible trend towards a survival benefit (P = 0.12). There were a total of 28 complications, most of which were reversible. The authors concluded that prone positioning was safe and feasible and may reduce mortality when applied early in the course of ARDS and for prolonged periods of the day.

Clinical use of prone positioning in trauma patients with ARDS

Investigation of the survival benefits associated with prone positioning will require future studies to be designed with careful consideration of the use of the technique, the study population, the timing of the intervention and the duration of the intervention. At present the evidence suggests that the routine use of this technique is not justified, but that it may have a survival benefit in the subset of patients with severe hypoxaemic ARDS, and hence have a role as a rescue therapy. The use of this therapy in trauma patients could be considered only in the absence of exclusions.

Table 2
Clinical considerations for the application of rescue therapies.

<table>
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<tr>
<th>Rescue therapy</th>
<th>Benefit</th>
<th>Difficulties and complications</th>
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<tbody>
<tr>
<td>Nitric oxide</td>
<td>Right ventricular failure</td>
<td>Methaemaglobinaemia, renal failure, platelet inhibition</td>
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<tr>
<td>Prone positioning</td>
<td></td>
<td>Unstable or painful fractures (face, spine, chest)</td>
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<td>External fixation of fractures</td>
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<td>Facial injury</td>
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<td>Internal trauma</td>
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<td></td>
<td></td>
<td>Pneumothorax or air leaks</td>
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<tr>
<td>RMs and PEEP titration</td>
<td>Immobile patients (unable to turn)</td>
<td>Chest trauma</td>
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<tr>
<td></td>
<td></td>
<td>Right ventricular failure</td>
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<tr>
<td></td>
<td></td>
<td>Large amount of sputum</td>
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<tr>
<td>HFOV</td>
<td>Pneumothorax or air leaks</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Presence of ICC</td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>When other rescue therapies fail</td>
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</table>

ECMO: extracorporeal membrane oxygenation; HFOV: high frequency oscillatory ventilator; ICC: intercostal catheter; PEEP: positive end expiratory pressure; RMs: recruitment manoeuvres.

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(such as unstable spinal fractures, external fixation see Table 2) and only when the treating team are familiar with this intervention in order to minimise the risk of complications.

**Recruitment manoeuvres and PEEP titration**

Clinicians frequently use moderately high positive end-expiratory pressure (PEEP), defined as 10–16 cm H₂O as part of an open ventilation strategy to improve alveolar recruitment in patients with ARDS. 32,64 PEEP aims to reverse the pulmonary shunt due to increased lung collapse resulting from pulmonary inflammation in ARDS. High PEEP aims to maintain functional residual capacity and improve oxygenation. Three randomised controlled trials of open lung ventilation strategies that included high PEEP however did not demonstrate an improvement in survival. 10,32,65 However, in two of these trials there were improvements in important secondary outcomes including the rate of refractory hypoxaemia, 10 use of rescue therapies10,32 and the number of ventilator free days. 32

A systematic review on the clinical utility of high PEEP in ARDS and acute lung injury (ALI) has suggested that the randomised trials in this area have been underpowered to detect a small but potentially clinically important effect on reducing mortality associated with ARDS. 64,65 Importantly this meta-analysis did show an improved survival in the subgroup of patients with ARDS (as opposed to the less severe ALI) however the best strategy to determine optimal PEEP has not yet been established. 66–68

The role of recruitment manoeuvres (RM) in ARDS, usually as part of an open lung ventilation strategy, is controversial. A large randomised controlled trial that included high PEEP and a RM of sustained static lung inflation to pressures of 40 cm H₂O for 40 s failed to improve patient survival but reduced the use of rescue therapies and refractory hypoxaemia. 10 A Cochrane review of the effects of RMs, that identified seven relevant randomised trials, concluded that RMs transiently improved oxygenation in patients with ARDS and ALI without adverse effects of barotrauma or hypotension. 69 This and another meta-analysis both concluded that there was no evidence of outcome benefit but that there was insufficient data to exclude a beneficial effect. 69,70

In clinical studies there was substantial heterogeneity in methods used to deliver RMs, including peak pressure, time at maximum pressure, concurrent ventilator strategies and end PEEP levels. The most common RM used in protective ventilation strategies was a static RM of 40 cm H₂O pressure for 40 s. However this RM method can be uncomfortable, may induce circulatory depression and has not been associated with improved outcomes in patients with ARDS. 69 The lack of long term benefit from a static RM in patients with ARDS may have been because the static RM was not performed for an adequate time or with sufficient pressure to open collapsed alveoli this patient group. 69 Other recruitment techniques, such as a “staircase” recruitment manoeuvre, have been used in pilot randomised controlled trials and been shown to be safe and effective in improving oxygenation and lung compliance. 71

Protective mechanical ventilation strategies, including low tidal volume, limitation of plateau pressure and PEEP, have shown reductions in mortality and are now widely accepted. 72–76

**Clinical use of recruitment manoeuvres and PEEP titration in trauma patients with ARDS**

Current evidence suggests that high PEEP regimes may have a survival benefit in patients with severe ARDS but there is insufficient evidence to establish the long term effects of recruitment manoeuvres. 64,69,70 Although it is unclear whether recruitment manoeuvres have a long term effect in patients with ARDS, they may be used for patients with severe refractory hypoxaemia to improve oxygenation, reduce the use of alternate rescue therapies and potentially reduce ventilator free days. This concept is controversial, and novel trials are underway to assess the effect of open ventilation strategies using a combination of staircase recruitment manoeuvres, PEEP titration and permissive hypercapnia on survival and duration of mechanical ventilation.

While some studies demonstrate that recruitment manoeuvres are efficacious post traumatic injury, 77 there is substantial controversy surrounding their use in the trauma patients with ARDS where the use of high PEEP and recruitment manoeuvres may increase barotrauma in the presence of chest injuries. Two systematic reviews of RMs have shown no substantial increased risk of barotrauma in general ARDS populations 69,70 however this may not be the case in patients with fractured ribs or lung contusions. It is also important to note that high PEEP and RMs can cause systemic hypotension which may be exacerbated in patients with hypovolemia and significant haemorrhage. In this case, rapid diagnosis of bleeding and minimally invasive management of blood loss is crucial. 78 Furthermore, some strategies, which incorporate high levels of PEEP, minimise tidal volume in an attempt to limit airway pressures. This approach is frequently accompanied by increases in carbon dioxide, so called permissive hypercapnia. While this approach is safe in most ARDS patients, those who also have a co-existent traumatic brain injury are likely to be at risk of hypercapnia induced increased intracranial pressures. 79 Although head injury is an exclusion criteria in most recruitment trials, in our experience, when intracranial pressure monitoring present with controlled pressures, recruitment manoeuvres can be done with minimal elevation of intracranial pressure.

Recruitment manoeuvres and PEEP titration are inexpensive, readily available and in our experience should be considered prior to other expensive or invasive rescue therapies in patients with refractory hypoxaemia (Fig. 3).

**High frequency oscillatory ventilation (HFOV)**

High-frequency oscillatory ventilation (HFOV) is an alternative mode of ventilation which requires the use of a specific designed ventilator, the oscillator. The principle of HFOV is to deliver a continuous distending mean airway pressure (mPaw), around which oscillations of predefined amplitude (∆P) are actively superimposed at a high frequency (usually between 3 and 15 Hz) by using a motorised diaphragm. These pressure oscillations result in very small tidal volumes (1–4 ml/kg), usually smaller than the anatomical dead space. Furthermore, the pressure oscillations that are imposed into the proximal airways are highly attenuated (damped) by the time they reach the alveoli. Given this, new gas exchange mechanisms have been described during HFOV, which characterise oxygenation and carbon dioxide clearance. 80,81 Practically, oxygenation can be improved by either increasing the mPaw or the F(IO2). In theory, HFOV has the potential to reach the goals of an ‘ideal’ protective lung ventilation approach i.e. mean airway pressure can be set at a higher level than the PEEP level during conventional ventilation, potentially providing better alveolar recruitment. Furthermore, the very low pressure swings that reach the alveoli may limit volutrauma as well as the repetitive intra-tidal opening and closing of unstable lung units (atelectrauma), especially if the prior recruitment is optimal. To date, there is only limited clinical evidence on which to base these assertions, and a round table consensus/discussion was used to publish recent guidelines and protocol for use of HFOV. 72

HFOV usually requires heavy sedation and the use of neuromuscular blockers to avoid ventilator asynchrony and these
are a significant limitation. The first randomised controlled trial comparing HFOV with conventional ventilation in ARDS found a trend towards less mortality with the use of HFOV (37% vs. 52%; \( P = 0.10 \)). However this study was designed to demonstrate the equivalence of HFOV to conventional mechanical ventilation with respect to safety and was not powered to detect any difference in mortality. Furthermore the tidal volume in the conventional mechanical ventilation arm was set between 6 and 10 ml/kg of the actual body weight, a setting that is associated with a poor outcome as compared with a protective ventilation strategy using a low tidal volume (6 ml/kg of the predicted body weight).\(^1\)

To date, randomised trials that have compared HFOV with protective ventilation strategies have been underpowered to show a difference in mortality.\(^2\)\(^,\)\(^3\) Both observational and randomised trials have indicated that HFOV is safe and effective in improving oxygenation.\(^3\)\(^-\)\(^\text{6}\) A recent systematic review and meta-analysis has shown that HFOV improves oxygenation and reduces the risk of treatment failure (refractory hypoxaemia, hypercapnia, hypotension, or barotrauma) as well as hospital or 30 days mortality compared with conventional mechanical ventilation in patients with ARDS.\(^7\)\(^,\)\(^8\) The potential benefit of the routine use of HFOV as a ventilation strategy during ARDS has not been determined but ongoing clinical trials may provide further information in the future (ISRCTN10416500, NCT01167621).

**Clinical use of HFOV trauma of patients**

Limitations of HFOV include the expense of a separate ventilator to deliver HFOV, the need for specific training in the use of HFOV and circuit set-up, impaired clearance of pulmonary secretions and the need for heavy sedation and neuromuscular blockade. The ideal timing for the use of HFOV is uncertain. More data is required about the use of HFOV in combination with other rescue therapies. It is possible that synergies exist when other rescue therapies (i.e. prone and iNO) are combined with HFOV.\(^8\)\(^6\)\(^,\)\(^8\)\(^9\)

HFOV might be an ideal rescue therapy to be used with chest trauma, including patients with blunt trauma, significant barotrauma and air leaks from intercostal catheters. In a retrospective trauma case series in the USA, HFOV was used in 24 patients with ARDS to improve oxygenation.\(^9\)\(^0\) Of this cohort 79% had sustained blunt trauma. Severity of injury and number of organs failing were predictors of survival, but improved oxygenation was not. HFOV was found to be safe in patients with ARDS as a result of trauma to improve oxygenation, but survival was likely related to the severity of the initial injury and unlikely to be affected by the use of HFOV.

Currently the place of oscillation in the rescue of hypoxaemic ARDS patients is unclear but it is usually commenced after other rescue therapies have been unsuccessful (iNO, RMs, PEEP). Depending on local experience and training many centres would then choose between prone positioning and oscillation as an additional rescue at this point. Although there is some evidence that oscillation when prone may also be efficacious, future studies are required to determine the true clinical place of such a strategy.

**Extra-corporal membrane oxygenation (ECMO)**

Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) (see Fig. 4) is an alternative form of lung support that can provide non-pulmonary oxygen delivery and carbon dioxide removal and may also facilitate lung protective ventilation in ARDS.

Australian and New Zealand intensive care units have demonstrated a high utilisation and high success with ECMO for severe ARDS associated with H1N1 influenza.\(^9\)\(^1\)

ECMO has been used for over 44 years as a rescue therapy for severe acute respiratory failure that is refractory to mechanical ventilation.\(^9\)\(^2\) In the 1970s and 1980s, uncontrolled observational reports suggested clinical benefits with the use of extracorporeal support, but these were not realised in subsequent randomised controlled trials (RCTs).\(^9\)\(^3\)

The most recently published ECMO RCT is the CESAR (conventional ventilation or ECMO for severe adult respiratory failure) study.\(^1\)\(^1\) This study was conducted in the United Kingdom (UK) and was a pragmatic trial designed to assess the clinical efficacy of the UK model of ECMO provision which included transfer to a specialist ARDS management hospital. CESAR is, to date, the largest prospective adult ECMO trial conducted, with 103 referring hospitals and 180 patients randomly assigned to either to be referred for consideration for ECMO or receive conventional mechanical respiratory support. ECMO was provided at a single highly ECMO-experienced centre while the standard care was conducted at less specialised centres. The primary endpoint of the study was survival at 6 months or presence of severe disability. The study also evaluated 6 month quality-of-life; mental and emotional state, and sleep quality. The intention-to-treat analysis demonstrated that significantly more patients allocated to consideration for treatment including ECMO survived to 6 months without disability when compared with those allocated to conventional management (relative risk [RR], 0.69 [95% CI, 0.55–0.87]; \( P = 0.03 \)). Though a relatively large treatment effect is evident, the sample size (smaller than initially planned) appears to have limited the precision of the result. Only 8% of patients in the study had ARDS as a result of traumatic injuries or major surgery, thereby limiting inferences to this population. However, the major limitation of the trial was that it was not designed to specifically test the clinical efficacy of ECMO alone for respiratory failure – rather it was an evaluation of a pathway for care of patients with severe respiratory failure, which often included ECMO as part of the package. Only 75% of patients in the treatment arm actually received ECMO. Reasonable concerns with regard to the basis of the efficacy, the quality of respiratory care in the control arm and the generalisability of the findings outside the UK have been raised.\(^9\)\(^4\) The precise contribution of ECMO to the observed beneficial treatment effect remains debatable in view of possible differences in mechanical ventilation between study groups and the 75% use of ECMO in the treatment arm. Mean health-care costs per patient were more than twice as high for patients allocated to consideration for treatment by ECMO than for those allocated to conventional management. No significant differences were recorded between groups for any of the 6 month follow-up assessments.

ECMO is a complex intervention and historically it has been difficult to unequivocally ascertain its true clinical efficacy in the management of severe ARDS. The Réseau Européen de recherche en Ventilation Artificielle (REVA or Network for Mechanical Ventilation) programme will conduct an international clinical trial titled EOLIA (ECMO to rescue lung injury in severe ARDS) to determine the effectiveness of ECMO support in preventing death from severe ARDS. In this trial, 331 patients with severe ARDS will be randomised to receive either optimal conventional mechanical ventilation, or ultra protective lung ventilation facilitated by ECMO delivered by specialised ECMO centres.

**Clinical use of ECMO in trauma patients with ARDS**

The use of ECMO is frequently accompanied by systemic anti-coagulation to prevent thrombosis of the extracorporeal circuit. Haemorrhage is a major complication of ECMO and can be devastating either due to site (i.e. intracerebral bleed) or due to inability to surgically correct (i.e. massive GI bleed). While trauma patients are at excessively high risk of bleeding various strategies have been used (i.e. no systemic anti-coagulation, initial
heparin free ECMO or low dose anti-coagulation) have been used to facilitate the use of ECMO in this ARDS sub-population.95 Despite these high risks some patients have been successfully treated with ECMO as a rescue therapy.96,97 While there is currently little experience in the use of ECMO in trauma it could be considered in extremis as a useful hypoxaemic rescue therapy in adequately experienced centres.

Conclusion

Severe hypoxic respiratory failure is common in the severely injured patients, and the associated mortality is high. There are a number of potential rescue therapies which the clinician may deploy in an attempt to maintain gas exchange at minimally safe levels. These include first line therapies, such as potential rescue therapies (iNO, prone positioning, RM, PEEP and HFOV). These first line therapies are often sufficient to prevent critical hypoxia, to allow 'protective' ventilation and to minimise organ failure. More recently ECMO has been adopted as a second line therapy when these first line therapies have been ineffective. While ECMO is invasive, it has proven itself very useful in correcting hypoxaemia in ARDS and the information to date suggests that it is associated with improved rates of survival. However, not all of the rescue therapies available for ARDS patients are safe and appropriate for use in patients with traumatic injuries and attention needs to be directed to the contraindications of specific rescue therapies, for example prone ventilation with unstable facial fractures or the use of external fixators. The clinical choice of which hypoxaemic rescue therapy to use in the traumatically injured ARDS patient is a careful balance between the benefits and risks of each intervention for that patient and the local expertise and training.

Conflict of interest statement

There are no conflicts of interest to disclose.

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