Rescue therapies for acute respiratory distress syndrome: what to try first?

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Purpose of review
Severe respiratory failure due to the acute respiratory distress syndrome (ARDS) might require rescue therapy measures beyond even extended standard care to ensure adequate oxygenation and survival. This review provides a summary and assessment of treatment options that can be beneficial when the standard approach fails.

Recent findings
'Life-threatening' conditions or refractory hypoxemia during mechanical ventilation are more a matter of personal rating than an objective diagnosis based on defined and/or unanimously agreed thresholds that would mandate the use of rescue therapies. Although the outcome might vary with different rescue procedures, most of them will improve oxygenation. Prone positioning maintains a predominant role as rescue therapy in severe hypoxemia and does not only improve oxygenation in but also survival of ARDS patients. Recruitment maneuvers can have temporary positive effects. Inhaled nitric oxide, as well as high-frequency oscillatory ventilation might acutely improve oxygenation and can be used as a 'bridge' to alternative rescue therapies, but neither provides any survival advantage by itself and might even be detrimental. Although increasingly employed in other than the rescue indication, extracorporeal membrane oxygenation should still primarily be used in patients who do not respond to differentiated mechanical ventilation, which includes a careful evaluation of nonextracorporeal membrane oxygenation rescue therapies that might be combined in order to overcome the life-threatening situation. Early involvement of an ARDS or extracorporeal membrane oxygenation center should be considered to ensure optimal care.

Summary
A well timed, multimodal approach is required for patients with ARDS suffering from life-threatening hypoxemia. Understanding the limits of each type of rescue measure is of vital importance.

Keywords
acute respiratory distress syndrome, extracorporeal membrane oxygenation, high-frequency oscillatory ventilation, prone position, rescue therapy, severe hypoxemia

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is characterized by hypoxemia refractory to oxygen therapy, noncardiogenic pulmonary edema, bilateral chest X-ray opacities and reduced lung compliance. It can be categorized into three levels of severity [1], but the spectrum of therapeutic measures being applied does not clearly correspond to the level of severity. Mechanical ventilation combined with the application of positive end-expiratory pressure (PEEP) is the mainstay of ARDS therapy used for organ support to gain time for recovery from ARDS. Depending on the impairment of oxygenation, PEEP and FiO_2 are increased to stabilize alveolar space and to maintain adequate pulmonary gas exchange. The most common stepwise approach in adjusting PEEP and FiO_2 consists in the use of the ARDSnet protocol which aims at maintenance of PaO_2 in the range of 55–80 mmHg [2]. If this target cannot be obtained by a conventional approach, basically two options remain:

(1) Escalation of ventilator settings
(2) Alternative adjunctive measures.

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KEY POINTS

- The definition of 'rescue therapy' in ARDS depends on the definition of 'life-threatening' hypoxemia.
- Although not fully supported by evidence, some rescue methods have recently stepped out from being only a rescue maneuver into the light of standard care in severe ARDS.
- Prone positioning is the most effective way to improve oxygenation through enhancement of the VA/Q ratio and represents the first line rescue measure.
- ECMO is effective and should be applied to patients not responding to other rescue measures.

Both concepts must be evaluated in the light of potential benefits and risks. Escalating mechanical ventilation has its limits, because mechanical ventilation itself is associated with harmful side-effects and may exacerbate the lung injury. If adequate oxygenation cannot be achieved while remaining within the limits of lung protective ventilation, alternative or adjunctive measures are required to rescue the patient.

DEFINITION OF RESCUE PROCEDURES IN ACUTE RESPIRATORY DISTRESS SYNDROME

'Rescue' or 'salvage' therapy is, by common definition, the treatment of a probably life-threatening event of acute onset in a patient already undergoing standard or advanced therapy for a certain pathology. It is a final 'rescue' attempt to prevent severe complications or death from hypoxemia. In severe ARDS, heavy, edematous lungs have to be moved, and mechanical ventilation should therefore be seen as *standard* and not *rescue therapy* despite its representing a rescue measure for the failing respiratory system. Rescue therapy in ARDS is the expeditious application of an effective treatment that will rapidly improve oxygenation while accepting its higher 'price' in terms of increased risk compared with standard care. A salvage or rescue therapy usually carries the risk of, sometimes severe, side-effects or complications.

The following assumptions can be made with regards to conditions that require a rescue procedure in ARDS patients:

(1) **Relevance**: rescue therapies for ARDS must be justified and consequently require defined thresholds that characterize or clearly define the status and modalities under which the therapy is to be applied.

(2) **Timing**: a rescue intervention is required timely or even immediately in order to resolve an otherwise potentially deleterious clinical situation.

CLINICAL STATUS THAT REQUIRES A RESCUE PROCEDURE

Hypoxemia or hypercapnia – what requires definitive rescue procedures in acute respiratory distress syndrome?

Severe hypoxemia is the most frequent life-threatening and acute-onset event in a patient who is already undergoing advanced therapy. Severe hypercapnia, on the other hand, although possibly deleterious in principle, usually underlies a different time course. We thus did not consider hypercapnia as a trigger for a rescue approach in the context of this review.

Three main characteristics of the lung (small size, high weight and inhomogeneity) [3] contribute to hypoxemia in ARDS to different extents through one common pathway, that is the increase of ventilation-perfusion (VA/Q) mismatch. This mechanism, which increases in importance when moving from nondependent to dependent lung regions, accounts for the different degrees of venous admixture ranging from regions with low VA/Q to those with complete shunt (VA/Q = 0) [4]. This is partially counteracted by the reduction of blood flow to hypoventilated regions by hypoxic vasoconstriction of the pulmonary capillaries [5]. Other pathological vascular phenomena, such as microthrombi, are usually also present and may play an additional, relevant role in the genesis of hypoxemia.

Severe hypoxemia and hypoxia in acute respiratory distress syndrome – when is it time to rescue?

The severity of the oxygenation impairment is part of the Berlin definition of ARDS (mild: PaO_2/FiO_2 <300 mmHg, moderate: PaO_2/FiO_2 <200 mmHg severe: PaO_2/FiO_2 <100 mmHg) [1], but a clear cut-off that defines severe or life-threatening hypoxemia is an ongoing matter of debate [6▪]. The individual level at which hypoxia induces severe tissue hypoxia with irreversible cell damage is unknown. Tissue oxygenation depends on three key factors: oxygen blood content, oxygen delivery, and oxygen extraction rate. The latter two are difficult to determine. Although some methods for determining oxygen delivery to the tissues are promising [7], one cannot precisely judge whether an imbalance between oxygen demands and oxygen delivery actually exists and, if so, to what degree. The so-called 'oxygen delivery controversy', struggles between the extremes of 'permissive hypoxemia' and a 'normoxemic target' strategy [8,9]. A recent study by Mikkelsen *et al.* [10] on long-term outcomes of ARDS suggests that a lower PaO_2 could be associated with a poorer cognitive status at 12 months. The same group defined 'refractory hypoxemia' as a PaO_2 less than 55 mmHg, and tried to challenge the traditional PaO_2 target of 55–80 mmHg, used in many ARDS trials [2] by proposing a 'normoxemic target' of 85–110 mmHg, in order to mitigate the risk of long-term cognitive impairment [11]. A systematic review of 1651 studies failed to identify any relevant studies evaluating permissive hypoxemia versus normoxemia in mechanically ventilated, critically ill patients [12]. Another proposed strategy is based on the precise control of arterial oxygenation, that is trying to avoid both hypoxemia and hyperoxemia by delivering oxygen based on individually tailored narrow oxygenation targets [13]. Although the current practice usually leans towards hyperoxemia, Martin and Grocott [13] noticed that 'permissive hypoxemia' is not yet supported by sufficient clinical evidence. Without tackling this dignified debate we took for the purpose of this review the liberty to define a PaO_2/FiO_2 less than 60 mmHg as the 'alarm bell' that should make every clinician at the bedside aware of the clear and present danger of acutely life threatening or irreversible long-term consequences.

Rescue therapies in acute respiratory distress syndrome

Before considering any rescue procedure (Table 1 and Fig. 1), potentially reversible causes of hypoxemia should be carefully looked for and dealt with. These include pleural effusions, fluid overload, abdominal hypertension, or pulmonary embolism.

Table 1. Methods referred to as rescue therapy (PaO_2/FiO_2 ratio <60 mmHg) in comparison to accepted care for severe ARDS. Of note: Rescue therapy is often studied and provided outside the context of a sole and probably limited 'rescue' maneuver. A method accepted when facing a clinical situation that is deleterious might not be accepted in a less vital situation where complications and long-term outcome should be considered

Method	Rescue therapy $PaO_2/FiO_2 \leq 60$ mmHg	Standard care for severe ARDS $PaO_2/FiO_2 \leq 150$ mmHg	Expected effect/relevance in severe ARDS $PaO_2/FiO_2 \leq 150$ mmHg	PaO_2/FiO_2 cut-off in most recent study (RCT)
Prone positioning	Recommended first line	Might be considered	Oxygenation: ↑↑ Mortality reduction	<150 mmHg [14]
Recruitment maneuver	Might be considered	Not generally recommended	Oxygenation: ↑ Mortality: ?	≤200 mmHg [15]
iNO	Might be considered	Not generally recommended	Oxygenation: Transient ↑ Mortality: ∅ reduction	≤250 mmHg [16]
High PEEP strategy	Recommended first line	Not generally recommended	Oxygenation: ↑ Mortality: ?	≤250 mmHg [17]
IRV	Might be considered, PEEP-strategy is preferred	Not generally recommended	Oxygenation: ↑ Mortality: ∅ reduction	<200 mmHg [18][a]
ECMO	Recommended second line	Might be considered second line	Oxygenation: ↑↑↑ Mortality: ?	Combined, Murray score >3.0 [19]
HFOV	Might be considered, especially if ECMO is not available	Not recommended	Oxygenation: ↑ Mortality: ∅ reduction	≤200 mmHg [20,21]

[a]Restrospective study, no RCTs in ARDS available. ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; IRV, inversed ratio ventilation; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial.

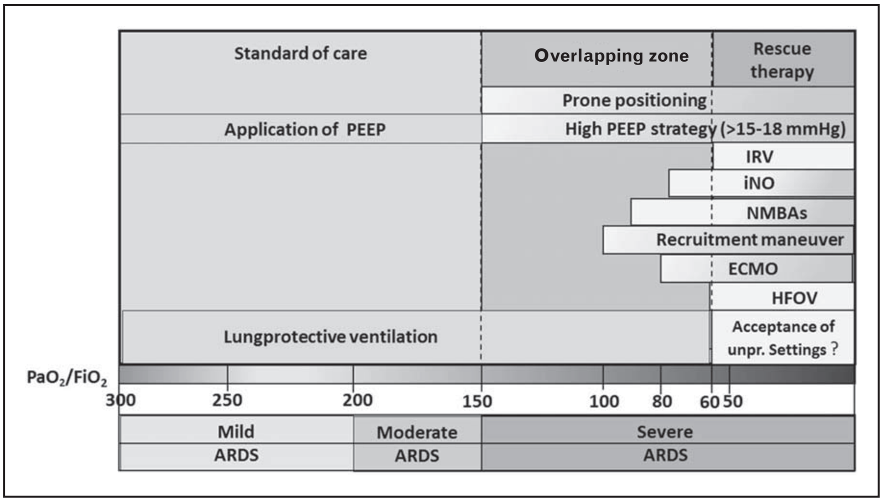

FIGURE 1. Rescue therapies (PaO_2/FiO_2 ratio <60 mmHg) interventions in ARDS. While application as a true rescue procedure might be considered for most interventions, the general use as a standard of care in severe ARDS should be applied with caution. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; IRV, inversed ratio ventilation; NMBAs, neuromuscular blocking agents; PEEP, positive end-expiratory pressure; RCT, randomized controlled trial.

Re-assessment of adequate positive end-expiratory pressure

Before implementing a rescue therapy, one must assess whether one can improve the ventilation and perfusion match by adjusting positive end-expiratory pressure (PEEP), increasing functional residual capacity (FRC) by alveolar recruitment measures, or redistributing extravascular lung water. Although the debate on 'best PEEP' lies outside the scope of this review, some aspects can be summarized.

Cyclic opening and closing of alveoli has been described as a possible source of ventilator-induced lung injury (VILI) [22,23], and consequently the 'opening and keeping open' approach ('open lung strategy') has been proposed. However, impact and validity still have to be demonstrated. PEEP is certainly beneficial for oxygenation. However, three main trials published between 2004 and 2008 [17,24,25] have shown no clear survival advantage for the high PEEP strategy. The basis for determining the 'best PEEP' is the quantification of recruitment [26]. Many techniques have been proposed such as ultrasonography [27], electric impedance tomography [28], respiratory mechanics measurements [29], nitrogen washout techniques [30], and quantitative CT scan [29], but none has yet gained general consensus or become routinely used in the clinical setting [31].

Thus although an individualized PEEP setting is preferred, in our opinion, in the event of life-threatening hypoxemia, the most useful instrument for verifying the clinical plausibility of the applied PEEP is the PEEP table developed by the ARDSnet [24]. Although being far from a perfect tool, it can at least help to acutely recognize patients with a dangerous 'PEEP-undertreatment'. Setting of high PEEP levels (>15–18 mmHg) should be accompanied by thorough hemodynamic assessment and might additionally be justified by transpulmonary pressure measurements and assessment of physiological dead space by volumetric capnography [32,33].

Unconventional 'nonprotective' settings of mechanical ventilation

It is common sense that lung protective ventilator settings should be used, irrespective of the severity of ARDS. Following this concept, tidal volume, and plateau, peek, and delta pressures should be kept within the narrow limits recently associated with improved outcome and lower incidence of development of VILI [34▪].

However, taking into account the mechanical power applied to the lung, keeping the above-mentioned variables within the defined limits would not necessarily mean that the patient is ventilated in a lung protective manner [35▪▪].

When considering a rescue procedure, the question arises of how long we should allow or accept ventilator settings outside the lung protective limits to be applied. The question of when and for how long 'nonprotective' ventilator settings might be acceptable before using an alternative rescue measure depends greatly on the invasiveness of the rescue procedure and the dynamics of the worsening of the pulmonary situation.

Inverse ratio ventilation

The application of inverse ratio ventilation (IRV) with a high inspiration-to-expiration ratio (I : E) (e.g., an inspiratory to expiratory time ratio of 2 : 1) has been suggested in order to increase mean airway pressure, shorten expiratory time, and thus to facilitate recruitment and stabilization of the alveolar space.

A recent study retrospectively assessed the feasibility of IRV as a rescue therapy in life-threatening gas exchange failure in 116 patients with ARDS [18]. Accordingly, IRV provided acceptable oxygenation without acute major complications; however, settings outside the box of 'protective ventilation' were applied. Due to the uncontrolled study design this study does not provide strong support for the use of IRV. In line with a recent review [6■] that was coauthored by two of the authors of this article, we follow the assumption that 'the overall results on the effect of IRV are conflicting and that the application and adjustment of an extrinsic PEEP offers a more physiological approach, that maintains a controlled and constant level'. However as a sole rescue maneuver (PaO_2/FiO_2 <60 mmHg) as defined in this review, the effect of increasing inspiratory time might be considered.

High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV) has been used as an alternative to conventional mechanical ventilation in patients with severe ARDS. However, judging from the results of two recent, large randomized, controlled trials, HFOV cannot at present be recommended as standard of care for the treatment of severe ARDS [20,21].

A recent systematic review which analyzed data from 10 RCTs [36] demonstrated that the overall effects of HFOV on oxygenation, mortality rate and adverse clinical outcomes are unpredictable and inhomogeneous. Since respiratory frequency is a relevant factor in the power transmitted to the lungs [35■■], negative side-effects of this approach seem likely. However, to the best of knowledge of the authors, there are currently no data available on the role of HFOV applied for a short period as a rescue therapy in patients with life-threatening hypoxemia. It might therefore still be considered as a rescue therapy in a desperate clinical situation.

Recruitment maneuvers

Recruitment maneuvers were already among the first recommendations because they had been shown to improve oxygenation in heavy, edematous lungs [37]. Since then, the concept of recruitment maneuvers has been closely related to that of PEEP, since both act in synergy in the 'open lung strategy' and were often combined and integrated in complex ventilator strategies [17]. Due to this tight connection it is difficult to isolate the effects of recruitment maneuvers from those of the complete ventilator strategy and to confirm their usefulness and eventual benefits in terms of survival. Despite its many limitations, a recent meta-analysis showed a trend towards reduced mortality with the use of recruitment maneuvers (6% difference). However, regarding the need for subsequent rescue therapies, there was not any significant difference between the patients who initially received recruitment maneuvers and those who did not [38].

If regarded as a pure rescue measure aimed at temporarily improving oxygenation in order to gain time while the subsequent rescue plan is being defined, recruitment maneuvers may be of vital significance. If, however, intended as a 'one-stop shop' rescue maneuver, they can even be dangerous, since they may only cure 'numbers' (i.e., PaO_2 and saturation), and needlessly delay further escalation of treatment.

Prone positioning

In the past 40 years, prone positioning has evolved into a therapeutic cornerstone for patients with severe ARDS, and has therefore definitively left the area of a pure rescue measure in a desperate clinical situation. The key mechanism by which prone positioning improves oxygenation is by counteracting gravitational forces and increasing lung homogeneity [3,39,40]. Although an improvement of oxygenation has been consistently shown [41,42], benefits in survival have been proposed for the most severe cases [43]. Moreover, it can also reduce the incidence of ventilator-induced lung injury [44]. Recently, the PROSEVA trial [14] demonstrated a survival advantage for patients treated by prone positioning. Two systematic reviews [45,46] confirmed a survival benefit in severe ARDS. Prone positioning should be offered as soon as possible, but not only to patients requiring rescue therapy for severe hypoxemia. It should also be considered for those patients with a PaO_2/FiO_2 less than 150 mmHg after adjustments of PEEP that there are no known contraindications [6■]. In these patients, a prior assessment of the recruitment potential to identify those patients that will likely not benefit from 'proning' might help to avoid the potential risks of an intervention that has a high probability of being ineffective. We are convinced that as a rescue therapy the benefits of 'proning' clearly overweigh the possible risks, especially if performed in centers with well-trained staff.

Inhaled nitric oxide

Inhaled nitric oxide (iNO) acts as local vasodilator of capillary vessels in well-aerated alveoli, thus improving the ventilation-perfusion match in the ARDS lung. Through this mechanism it can also reduce pulmonary vascular resistance and improve right ventricular output [47,48]. The most recent data show that iNO is not an adequate therapy in ARDS patients, since it produces only transient improvements in oxygenation with no reduction in mortality, and it may even be harmful with possible kidney injury [49–51]. Nevertheless, in a recent worldwide survey of ARDS care [34▪], 13% of the patients with severe ARDS were treated with local vasodilators. As a rescue measure it might temporarily improve oxygenation [48], and bridge the time until further rescue therapies can be established.

In fact, some centers report the successful use of iNO as an adjunctive therapy to increase the safety of severe hypoxemic patients during transport to an ECMO center, thus avoiding the need for cannulation in remote hospitals and subsequent transport with on-going extracorporeal circulation [52▪,53].

Neuromuscular blocking agents

A relevant outcome improvement was shown using neuromuscular relaxation with cisatracurium for 48 h [54]. The trial compared early cisatracurium infusions to placebo in 340 patients with moderate–severe ARDS and showed an improved adjusted survival rate in the cisatracurium group (hazard ratio 0.68; 95% CI 0.48–0.98). The study raises some concerns with regard to the study protocol and the chosen mode of mechanical ventilation [55]. There is a experimental evidence that ineffective ventilation or poor patient–ventilator interaction might have injurious effects in ARDS patients, especially in patients with a persistent high inspiratory effort [56–58]. However, the benefits that are related to modern concepts of sedation [59–61] and the physiological advantages of spontaneous breathing [62] should carefully be weighed against the benefit from deep sedation, paralysis and controlled mechanical ventilation. The use of neuromuscular blocking agents is suggested as a rescue measure, while we propose their use as a standard therapy only after assessment of respiratory drive (e.g., by esophageal pressure measurements) [32].

RESCUE THERAPY AIMED AT EXTERNALLY OXYGENATING THE BLOOD

Extracorporeal membrane oxygenation

If attempts to optimize the VA/Q ratio fail to alleviate the hypoxemia, extracorporeal oxygenation represents the last option to rescue and stabilize the patient in order to 'buy' time for lung recovery.

As with other rescue therapies that promise substantial outcome improvement, ECMO therapy recently stepped from the status of a pure rescue intervention into the light of standard care in severe ARDS [63▪▪]. However, evidence supporting this approach is lacking, and randomized clinical trials in this field are very difficult to perform [64]. From the available literature it might be assumed that ECMO helps to save the lives of at least some very critically ill patients [19,65–69]. Indications and contraindications for ECMO have already been widely discussed elsewhere [70,71,72▪] and are the topic of other articles in this issue of this journal.

HIERARCHY AND COMBINATION OF RESCUE THERAPIES

On the basis of the current evidence, we propose a hierarchy of steps that takes the invasiveness and availability of the measures into account. In this context, the necessity of referral to an ARDS center should be constantly re-assessed since timing is crucial, particularly in patients with rapid clinical deterioration. The combination of various rescue interventions has not been studied in a structured manner, but it seems feasible to combine them (Fig. 1). As an example, the combination of prone positioning and ECMO has been recently studied in three trials. In a study on 12 ECMO patients treated with a total of 74 sessions of prone position, safety of the procedure and some benefits in terms of oxygenation were shown [73]. Guervilly *et al.* [74] reported significant improvements in oxygenation and no major adverse events in 15 patients 'proned' during the ECMO. In another study in 17 patients on ECMO (total of 27 sessions of prone positioning), a clear benefit in terms of oxygenation and lung compliance and the absence of serious adverse events were demonstrated [75]. Being a sort of 'rescue of the rescue', prone positioning during ECMO may help to achieve sufficient oxygenation in the very critical patient and can contribute to lung healing through the above-mentioned mechanisms and by protecting from VILI.

CONCLUSION

Rescue therapies for ARDS are not clearly defined and range from escalating standard procedures to interventions that are exclusively accepted in patients in whom all conventional approaches have failed. Regardless of the cut-off or the definition of 'life-threatening' hypoxemia, early identification of patients with a high probability of requiring a rescue therapy is important. In this context, early consultation of an ARDS or ECMO center is suggested. Prone positioning is the therapy that showed convincing evidence of improved survival and should be applied as a first line measure in patients with severe hypoxemia. Other rescue treatments, such as recruitment maneuvers and iNO may play a role as a bridge to the commencement of external oxygenation, external oxygen supply. However, in patients in whom these interventions fail, ECMO remains the only option to ensure oxygenation. Although there are no data on the exact sequence in which the rescue treatments should be initiated, based on the current evidence we think that ECMO should generally be the second line option when all else has failed.

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Conflicts of interest

T.T. has no conflict of interest. Within the last 36 months, O.M. gave lectures on mechanical ventilation and hemodynamic monitoring at regional workshops and received speaker's honoraria from Pulsion Medical, HillRom and Maquet Critical Care. M.Q. consults for companies related to the field of Critical Care such as Maquet Critical Care, Novalung, CareFusion, Gambro, Sphere Medical and receive(s)d honoraria for these consultancies. He is a member of the international steering committee of the INTEREST trail, sponsored by Faron Pharm.

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