ARDS: challenges in patient care and frontiers in research

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ABSTRACT   This review discusses the clinical challenges associated with ventilatory support and pharmacological interventions in patients with acute respiratory distress syndrome (ARDS). In addition, it discusses current scientific challenges facing researchers when planning and performing trials of ventilatory support or pharmacological interventions in these patients.

Noninvasive mechanical ventilation is used in some patients with ARDS. When intubated and mechanically ventilated, ARDS patients should be ventilated with low tidal volumes. A plateau pressure <30 cmH_2O is recommended in all patients. It is suggested that a plateau pressure <15 cmH_2O should be considered safe. Patient with moderate and severe ARDS should receive higher levels of positive end-expiratory pressure (PEEP). Rescue therapies include prone position and neuromuscular blocking agents. Extracorporeal support for decapneisation and oxygenation should only be considered when lung-protective ventilation is no longer possible, or in cases of refractory hypoxaemia, respectively. Tracheotomy is only recommended when prolonged mechanical ventilation is expected.

Of all tested pharmacological interventions for ARDS, only treatment with steroids is considered to have benefit.

Proper identification of phenotypes, known to respond differently to specific interventions, is increasingly considered important for clinical trials of interventions for ARDS. Such phenotypes could be defined based on clinical parameters, such as the arterial oxygen tension/inspiratory oxygen fraction ratio, but biological marker profiles could be more promising.

Introduction

Optimal care for patients with acute respiratory distress syndrome (ARDS) has changed noticeably over recent years. This holds particularly true for ventilatory support, essential in almost all ARDS patients, where the primary aim is to minimise the risk of harm from ventilation and gas exchange that is no longer adequate. While numerous pharmacological interventions targeting the underlying pathophysiological mechanisms of ARDS have been tested in clinical trials, none of them have been shown to improve outcome, despite promising findings in preceding investigations in animals.

This review focuses on current challenges in the ventilatory support of patients with ARDS. In addition, it provides an overview of successful and unsuccessful pharmacological interventions for ARDS (table 1). Subsequent recommendations and suggestions for daily care of ARDS patients are given, in line with previous international recommendations [1, 2].

The article ends with a discussion on the challenges facing researchers when planning and performing clinical trials of ventilatory support or pharmacological interventions in patients with ARDS.

Ventilatory support

Ventilatory management of critically ill patients, including those with ARDS, has changed dramatically over the past three decades [3]. The paradigm of ventilation in critically ill patients has shifted from one that targeted physiological, and at times even supraphysiological goals to one that merely accepts the pathophysiology, at least to a certain level, and aims to prevent further harm [4]. Indeed, the targets have changed from completely reducing atelectases and aiming at normal to high arterial oxygen levels and strictly normal arterial pH or carbon dioxide levels, to tolerating atelectases and accepting low arterial oxygen levels and even hypercapnia when the price of full compensation of blood acidosis becomes too high. Treatment goals such as "permissive atelectasis", "permissive hypercapnia" and even "permissive hypoxaemia" have been introduced as targets of ventilatory support. Together with the increased knowledge and understanding of how mechanical ventilation can harm the lungs, major effort has been put into preventing or shortening the use of mechanical ventilation as much as possible, and using settings that are considered to be "lung protective".

Noninvasive versus invasive mechanical ventilation in patients with ARDS

The main advantages of noninvasive over invasive mechanical ventilatory support are the reduced need for sedation and prevention of ventilator-associated pneumonia. Noninvasive mechanical ventilation can be interrupted easily, and thus has the potential to shorten the time the lungs are subjected to the harmful effects of mechanical support.

While noninvasive mechanical ventilatory support by face mask was found to affect neither intubation rates nor clinical outcomes in a randomised controlled trial (RCT) of 123 ARDS patients [5], helmet ventilation was found to reduce the need for intubation when compared to oxygen therapy in a multicentre RCT of 81 ARDS patients [6], and to reduce intubation rates and even to improve survival when compared to a face mask in a single-centre randomised clinical trial of 83 ARDS patients [7].

TABLE 1 Ventilatory and pharmacological management of acute respiratory distress syndrome (ARDS) per responsive phenotype

Intervention	Suggested/recommended	Responsive phenotype
NIV	Recommended	Early phase of respiratory failure, with rapid response after start of NIV
Tracheotomy	Suggested	Prolonged mechanical ventilation
Low tidal volumes	Recommended	All patients with ARDS
Plateau pressure <30 cmH$_2$O	Recommended	All patients with ARDS
Driving pressure <15 cmH$_2$O	Suggested	All patients with ARDS
High PEEP strategy	Recommended	P_{aO_2}/F_{IO_2} <200
Prone position	Recommended	P_{aO_2}/F_{IO_2} <150
Neuromuscular blocking agents	Recommended	P_{aO_2}/F_{IO_2} <150 and first 48 h of ARDS
Extracorporeal membrane oxygenation	Suggested	Patients requiring rescue therapy
Glucocorticosteroids	Suggested	No responsive phenotype identified

NIV: noninvasive ventilation; PEEP: positive end-expiratory pressure; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction.

Oxygen administered through a high-flow nasal cannula is suggested to be an attractive strategy as a first-line therapy to avoid intubation, seen in the results of a multicentre RCT in which 301 hypoxaemic patients without hypercapnia received either high-flow oxygen therapy, standard oxygen therapy delivered through a face mask or noninvasive positive-pressure ventilation [8], but the beneficial effects found thus far need to be confirmed.

When noninvasive mechanical ventilatory support is used, patients should be monitored closely [9], as it can fail, for example because of patient nonacceptance and technical issues, but also when the disease progresses with a worsening of gas exchange. Substantial clinical (respiratory rate) and laboratory (blood gas analyses) improvements must be seen within the first few hours, otherwise it is necessary to proceed with invasive ventilation. A prospective observational trial of 101 patients suggested that a rapid shallow breathing index >105 breaths·min^{-1}·L^{-1} [10] could be used to decide to intubate the patient. A prospective observational trial of 62 patients suggested that expired tidal volumes persistently >9.5 mL·kg^{-1} predicted body weight (PBW) predicts noninvasive ventilation failure [11].

Modes of invasive mechanical ventilatory support

Volume-controlled modes of mechanical ventilation allow for better measurement of respiratory mechanics and driving pressures and may have a potential advantage with regard to the prevention of volutrauma. In addition, in contrast to pressure-controlled modes of mechanical ventilation, volume-controlled modes do guarantee a predefined tidal volume. Conversely, pressure-controlled modes have the alleged advantage of a decelerating flow curve during inspiration. Despite these potential physiological considerations, there are no outcome advantages of using a pressure-controlled mode over a volume-controlled mode, or *vice versa*. Indeed, one systematic review and meta-analysis of 34 studies did not suggest differences in any clinical outcome [12]. However, the studies were small and varied considerably in quality, and were at high risk of bias.

Tracheotomy

Tracheotomy may increase patient comfort. Several RCTs, including a large trial of 909 patients who did not necessarily have ARDS showed that early tracheostomy (within 4 days of admission to critical care) was not associated with an improvement in mortality or morbidity [13]. However, one systematic review and meta-analysis of 12 investigations suggested that early tracheotomy could lead to more ventilator-free days, shorter stays in intensive care, shorter duration of sedation and reduced long-term mortality [14]. The optimal timing of tracheotomy in critically ill patients remains a topic of debate. Presently, tracheotomy is recommended only when prolonged mechanical ventilation is expected.

Tidal volume size and plateau pressure

One key causal factor of so-called ventilator-induced lung injury is damage to the lungs due to overdistension from the use of high tidal volumes and inappropriately high airway pressures.

Mechanical ventilation targeting a tidal volume of 6 mL·kg^{-1} PBW and plateau pressure <30 cmH$_2$O was found to reduce mortality and morbidity in the pivotal ARDS Network "ARMA" trial of 861 ARDS patients [15]. One important notion is that tidal volume size should be titrated according to PBW (based on height and sex) and not to actual body weight, a frequently missed issue [16]. However, setting a low tidal volume could still result in overdistension and lung stress if the amount of aerated lung tissue is or remains low, as shown in an observational study in 30 patients [17]. In this elegant study, pulmonary computed tomography scanning at end-expiration showed that limiting tidal volume to 6 mL·kg^{-1} PBW and plateau pressure to 30 cmH$_2$O may not be sufficient in patients characterised by large nonaerated parts. Either tidal volumes of <6 mL·kg^{-1} PBW [18] or higher positive end-expiratory pressures (PEEP) to recruit more lung tissue could be used [19]. Another approach is to adjust tidal volume to compliance by using the driving pressure (plateau pressure *minus* PEEP), aiming at a value <15 cmH$_2$O [20]. Notice that this last approach is based on evidence coming from an individual patient data meta-analysis of RCTs that did not test the role of driving pressure. Direct RCT evidence for this approach is lacking.

PEEP

Three large RCTs comparing high with low PEEP in ARDS patients, the ALVEOLI trial in 549 ARDS patients [21], the LOVS trial in 983 ARDS patients [22] and the EXPRESS trial in 767 ARDS patients [23] showed that a ventilation strategy using a high PEEP does not reduce mortality, despite improved lung function. One meta-analysis using individual patient data from these three RCTs showed ventilation with high PEEP to be associated with better survival [24]. However, it should be acknowledged that the mortality benefit of high PEEP was restricted to patients with moderate or severe ARDS, and ventilation with high PEEP was associated with prolonged duration of ventilation in patients with mild ARDS.

Ventilation with high PEEP balances between potential benefit (*i.e.* recruitment) and harm (*i.e.* overdistension), and individual responses to PEEP are very variable [25]. A test comparing several PEEP levels could help select the best PEEP level for an individual patient: PEEP titrations may be based on the extent of lung recruitability [26], changes in transpulmonary pressures [27] or more-easily captured changes in driving pressures [20].

Rescue therapies

Prone positioning results in redistribution of lung densities, with recruitment of the well perfused dorsal regions. Thus, prone positioning could result in a reduction in alveolar shunt and improved ventilation–perfusion matching. While several RCTs of prone positioning in ARDS patients failed to show improvements in outcome, one systematic review and meta-analysis of nine RCTs showed an association between prone positioning and mortality, although only in patients with an arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio <100 [28]. One multicentre, prospective RCT in 466 ARDS patients with a P_{aO_2}/F_{IO_2} <150, $F_{IO_2} \geqslant 0.6$ and PEEP $\geqslant 5$ cmH$_2$O showed that early application of prolonged prone positioning sessions significantly decreased 28-day and 90-day mortality [29]. Of note, not all patients may benefit from prone positioning, but it should always be considered in the early phase of severe ARDS [29]. Relative contraindications for prone positioning include open abdominal wounds, unstable pelvic fractures, instable spinal lesions and brain injury and the absence of staff well-trained in prone positioning.

Muscle paralysis with neuromuscular blocking agents may avoid dyssynchrony, prevent excessive transpulmonary pressures and breath stacking by inspiratory efforts [30] and derecruitment by expiratory efforts [31]. Neuromuscular blocking agents have been shown to benefit patients with ARDS [32], confirmed in a meta-analysis of three RCTs [33]. Muscle paralysis with neuromuscular blocking agents should probably be reserved for patients with the most severe forms of ARDS, and restricted to the acute phase and during the first 48 h.

Extracorporeal membrane oxygenation provides different degrees of carbon dioxide removal plus oxygenation, thus preventing in part harm caused by mechanical ventilatory support. This technique should only be used in the most severe cases of ARDS [34], and only by well-trained staff [35]. Extracorporeal carbon dioxide techniques have been used to allow mechanical ventilatory support at very low tidal volumes (3–4 mL·kg^{-1} PBW) [36, 37]. However, convincing evidence of the benefit of both techniques is absent and eagerly awaited. Trained staff and sufficient exposure could be critical for its safe use [35].

Pharmacological interventions

The initial or exudative phase of ARDS is characterised by a pro-inflammatory pulmonary response driven mainly by the innate immune system. The resulting unbalanced response leads to accumulation of protein-rich fluid in the alveolar space and the interstitium [38]. This process can be initiated by direct damage to the lung (*e.g.* pneumonia or aspiration) or as a consequence of endothelial damage and neutrophil activation (*e.g.* due to sepsis or blood transfusion). During the proliferative phase, repair mechanisms are activated in order to restore pulmonary function [39]. If repair is unsuccessful, for example due to continuing injury by mechanical ventilation or infection, lung tissue will become fibrotic. This phase in particular is associated with very high mortality rates [40].

Pharmacological interventions have mainly focused on dampening of the pro-inflammatory response in the initial phase of ARDS, reduction of pulmonary oedema or improvement of repair mechanisms. Besides treatment with glucocorticosteroids, none of the other pharmacological interventions tested so far in clinical trials showed a consistent reduction in morbidity and mortality [41].

Glucocorticosteroids

Glucocorticosteroids are effective in numerous inflammatory diseases across many fields in medicine. It seems plausible that high-dose glucocorticosteroids could improve outcomes in ARDS because of their pleiotropic anti-inflammatory action [42]. However, the evidence for benefit of glucocorticosteroids in ARDS is conflicting and the use of glucocorticosteroids in patients with ARDS remains controversial.

The latest individual data meta-analysis indicates an accelerated resolution of ARDS when patients are treated with a high dosage of glucocorticosteroids for a prolonged period of time [43]. Furthermore, methylprednisolone treatment has been found to be associated with shorter periods of need for invasive mechanical ventilation and lower mortality rates. Glucocorticosteroids have not been found to increase the risk of infections. These results are very encouraging, but should be seen in the light of the limitations of the original studies. There is clear need for additional clinical trials of glucocorticosteroids.

Salbutamol

Salbutamol was suggested to reduce pulmonary oedema through stimulation of the sodium–potassium pump (Na/K/ATPase) but the largest trial to date was stopped after the inclusion of 326 patients because an interim analysis suggested that the intervention might cause harm [44].

Surfactant

Administration of exogenous surfactants was found to improve oxygenation when results of all studies were pooled in a systematic review, but did not influence mortality and should therefore not be used in patients with ARDS [45].

N-acetylcysteine

N-acetylcysteine is the best-studied antioxidant in ARDS. It increases glutathione levels and was thought to reduce the oxidative pulmonary damage seen in patients with ARDS. A systematic review of several smaller clinical trials in patients with ARDS showed that infusion of N-acetylcysteine did not affect mortality [46].

Neutrophil esterase inhibitor

Neutrophil esterase seems to play a central role in the activation of neutrophils in the lung during the development of ARDS [47]. Sivelestat, a neutrophil esterase inhibitor, is used in the treatment of ARDS in Japan. However, pooled analysis of all available data showed no reduction in mortality, even when only studies performed in Japan were included [48].

Granulocyte-macrophage colony-stimulating factor

Granulocyte-macrophage colony-stimulating factor was tested as a treatment to promote resolution of lung injury, 3 days after patients fulfilled the ARDS criteria. A phase II study with 130 patients did not show any effect on length of stay or mortality [49].

Challenges in research in patients with ARDS

Many RCTs on mechanical ventilation and pharmacological treatment in ARDS have failed. Interestingly, all tested pharmacological interventions successfully passed preclinical studies in models of lung injury and even phase I/II clinical trials. These disappointing results contrast sharply with other fields of medicine, where up to one in every 10 drugs found to be beneficial and safe in preclinical investigations and phase I/II trials influence clinically relevant outcomes, are implemented in daily practice and included in recommendations in the guidelines [50]. Studies that show no benefit from the intervention could result from the selection of ineffective interventions and unresponsive patients for the intervention, as well as inadequate choices in trial design (for example, with regard to sample size and the end-points used [51]).

Ineffective interventions

Intervention efficacy is tested frequently in small-animal models for acute lung injury. Several factors, besides the fact that rodents may inherently respond differently to treatment, can prevent successful drug selection in preclinical studies.

Lung injury is experimentally evocated through "hits", which correspond to the many risk factors for ARDS (such as sepsis, trauma, pneumonia and aspiration). However, none of the small-animal models provide all the hallmarks of human ARDS [52, 53] and therefore, by definition, fail to represent the clinical scenario of ARDS. Besides, most experiments use young male rodents that almost never have comorbidities for the evaluation of new treatments for ARDS, while patient populations seen in intensive care units are elderly and frequently have concomitant diseases such as diabetes mellitus, chronic obstructive pulmonary disease or active cancer [54]. The few studies that compared elderly rodents to younger ones indeed found a difference in the biological response between these groups [55, 56].

The timing of the start of treatment is another factor that may limit the translation of positive results from preclinical experiments to clinical trials in humans. Interventions may only be effective when given preventively or early in the course of disease; ARDS patients have to be recognised and informed consent must be obtained from the legal representative before a drug can be administrated in a clinical trial. Together, these factors may, at least in part, explain the failed translation of preclinical results and we should put more effort in creating models that better reflect the clinical situation.

Balance between benefit and harm

A second challenge in clinical trials of ARDS treatments is the inherent biological heterogeneity. The biological heterogeneity directly relates to the ARDS definition, which is based on clinical criteria without a central, singular underlying pathophysiological mechanism [57]. A drug targeting a specific molecular

mechanism that is effective in part of the population might harm patients with a separate biological response. Therefore, the outcome of the study is highly dependent on the prevalence of patients that are responsive (*e.g.* in whom benefit outweighs harm) to the treatment in the included population. It is the premise of precision medicine to enrich this group as much as possible with patients with a responsive phenotype (also called predictive enrichment) [58]. The selection of the right patient for the right treatment is one the largest challenges for the coming decade [59, 60].

Exclusion of patients with a negative balance between benefit and harm

Patients with a particular phenotype that is responsive to a treatment can be identified through pathophysiological reasoning. An illustrative example is the application of prone positioning in patients with a P_{aO_2}/F_{IO_2} ratio <150 [61]. The physiological consequences of laying a patient in prone position include the recruitment of the dorsal parts of the lungs and derecruitment of the ventral parts of the lung [62, 63]. Because of the ventro–dorsal asymmetry of the thorax, prone positioning a patient with ARDS frequently results in an overall recruitment effect [63]. These phenomena can be utilised in patients with ARDS (see the section on mechanical ventilation) because it will improve gas exchange and reduce ventilator-induced lung injury [62]. However, this procedure is not without complications such as hypotension, pressure sores, accidental extubation and the complications of more sedation [64]. With the background knowledge that patients with lower P_{aO_2}/F_{IO_2} scores have an increased heterogeneity of ventilation in the lung and the most problems with gas exchange, this is the phenotype that is most likely to benefit from the intervention.

If we apply this reasoning to pharmacological interventions, we could aim to identify key mediators in the pathophysiology of ARDS and design drugs to target these mediators. Studies can be enriched through the selection of patients that have a higher expression of the targeted molecules. For example, a study investigating an antibody against interleukin-8 could choose to select patients based on high level of interleukin-8 in plasma, or, even better, locally in the lung. Patient selection based on the treatment mechanism is still not utilised sufficiently in intensive care medicine research and may improve the chances on finding effective pharmacological interventions for ARDS.

Better selection of phenotypes through an unbiased, data-driven approach

A second approach towards the definition of ARDS phenotypes is an unbiased, data-driven analysis of clinical or biological data. Although the case for the application of prone positioning in a patients with a clinical phenotype of a low P_{aO_2}/F_{IO_2} ratio seems logical with hindsight, almost all studies were designed to include all patients with ARDS. The low P_{aO_2}/F_{IO_2} ratio phenotype was recognised only after several RCTs were completed [28].

In essence, the data-driven approach recognises that we are inherently biased in our recognition of subgroups and it faces the problem of phenotype selection from the other direction, not initiated by pathophysiology, but by empirical evidence, which is later translated back to pathophysiology.

If we recognise the complexity of the biological processes that contribute to ARDS it seems overly simplistic and therefore unlikely that we would identify a single marker such as P_{aO_2}/F_{IO_2} ratio that is predictive of a specific, responsive phenotype. Over the past decades, vast improvements in bioanalytical assays and computing power have introduced the age of "omics" analyses. When more than one variable is considered to define a phenotype, a data-driven approach is even more warranted. Computer algorithms have no inherent struggles with highly dimensional datasets and we can utilise that capacity to reduce complex datasets to understandable proportions. The output of computer algorithms can serve as inputs
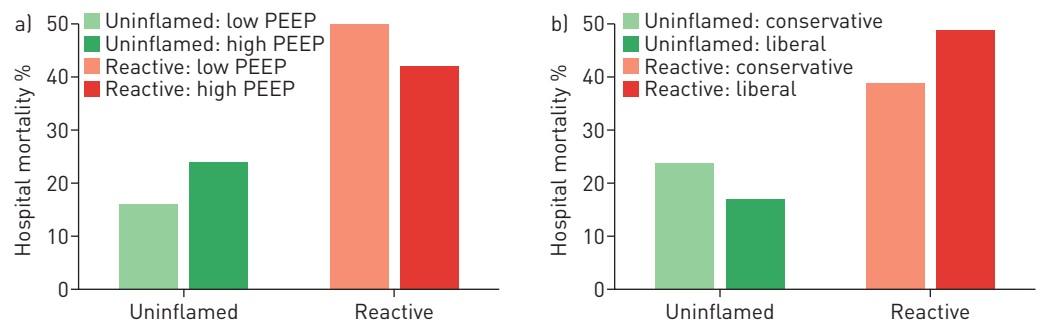

FIGURE 1 Differential response to treatment between two phenotypes of acute respiratory distress syndrome. a) High and low positive end-expiratory pressure (PEEP); b) conservative and liberal fluid management.

for clinicians and can guide them in making the right clinical decision. With unbiased cluster analysis, one of the most widely used algorithms for identifying patterns, researchers can identify patients who show similar biological "fingerprints", even though they might not look alike from a clinical perspective. This data-driven analysis limits the danger of self-fulfilling prophecies based on widely accepted paradigms and are hypothesis-generating.

Two landmark articles suggest that ARDS can be separated into at least two distinct phenotypes based on unbiased, data-driven analyses of clinical data and several plasma biomarkers of inflammation, coagulation and endothelial activation [65, 66]. One phenotype is characterised by a hyperinflammatory and hypercoagulatory state in the blood, while the other phenotype shows a hypo-inflammatory state and high bicarbonate levels [65, 66]. One of the major disadvantages of such a data-driven approach is the danger of over-fitting to the specific dataset. Importantly, very similar phenotypes were found independently in a group of ARDS patients that was separated in time and place, and analysed using an alternative approach [67]. Progress in the identification of specific phenotypes is not only seen in ARDS, but also in other problems frequently encountered in the intensive care unit, such as sepsis and failure to wean [68–70].

Implications for clinical practice in the future

Post hoc analysis of two multicentre RCTs indicate that the two above-described phenotypes show a differential response to a high (*versus* conventional) PEEP strategy and a conservative (*versus* liberal) fluid management. Fluid management was steered by a strict protocol relying on the central venous pressure or pulmonary artery occlusion pressure, need for vasopressors and an "effective circulation" (combination of cardiac index and physical examination) [71] resulting in the advice for vasopressor use, furosemide administration or fluid administration. The hyper-inflammatory phenotype seemed to benefit from a higher PEEP strategy and conservative fluid management, while the hypo-inflammatory phenotype did not seem to benefit and might even be harmed by the intervention (figure 1). Of course, *post hoc* analyses of RCTs do not provide definitive answers, as research questions are not stated beforehand and the randomisation process is disturbed, but it indicates that our simplistic views on the management of ARDS may need to be revised in the near future.

Conclusions

There are several ventilation-related interventions that have a strong potential to improve outcomes of patients with ARDS. Of all tested pharmacological interventions, only treatment with glucocorticosteroids may impact outcomes in these patients. We are in need of better-designed RCTs, not necessarily larger trials in the field of ARDS. We advocate a personalised approach to the treatment of ARDS patients, with the recognition of individual phenotypes to guide treatment decisions. The challenge in research is the identification of phenotypes of ARDS that benefit from specific treatments. Phenotypes might be defined based on clinical parameters (such as P_{aO_2}/F_{IO_2} ratio) or based on profiles of biological markers.

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