The Potential of Heliox as a Therapy for Acute Respiratory Distress Syndrome in Adults and Children: A Descriptive Review

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Key Words

Acute respiratory distress syndrome · Respiratory distress syndrome · Mechanical ventilation · Helium · Heliox · Intensive care medicine · Paediatric intensive care medicine · Lung injury

Abstract

Background: In neonatal respiratory distress syndrome (RDS) and acute RDS (ARDS) mechanical ventilation is often necessary to manage hypoxia, whilst protecting the lungs through lower volume ventilation and permissive hypercapnia. Mechanical ventilation can, however, induce or aggravate the lung injury caused by the respiratory distress. Helium, in a gas mixture with oxygen (heliox), has a low density and can reduce the flow in narrow airways and allow for lower driving pressures. **Objectives:** The aim of this study was to review preclinical and clinical studies of the use of heliox ventilation in acute lung injury associated with respiratory failure. **Methods:** A systematic search was executed in the PubMed and EMBASE databases, with search terms referring to ARDS or an acute lung injury condition associated with respiratory failure and the corresponding intervention. **Results:** A total of 576 papers were retrieved. After the majority had been excluded 20 papers remained, of which 6 articles

described animal models (3 paediatric; 3 adult animal models) and 14 were clinical studies, of which 12 described paediatric patient populations and 2 adult patient populations. In both paediatric and adult animal models, heliox improved gas exchange while allowing for less invasive ventilation in a wide variety of models using different ventilation modes. Clinical studies show a reduction in the work of breathing during heliox ventilation, with a concomitant increase in pH and decrease in PaCO₂ levels compared to oxygen ventilation. **Conclusions:** Although evidence so far is limited, there may be a rationale for heliox ventilation in ARDS as an intervention to improve ventilation and reduce the work of breathing.

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Introduction

Acute respiratory distress syndrome (ARDS) is a well-known entity in critically ill patients, with mortality rates of 20% among paediatric patients and 60% among the elderly [1–3]. Common features of ARDS are hypoxia and hypercapnia, the latter being due to increased dead space with a concomitant increased work of breathing, which is due to both obstructed airways with increased

airway resistance as well as to an increased need for CO₂ removal [4–6]. These processes occurring during ARDS frequently warrant mechanical ventilation. In neonates, ARDS is called neonatal RDS and the pathophysiology also includes a surfactant dysfunction [7, 8].

In both ARDS and neonatal RDS, mechanical ventilation is necessary but can induce or aggravate pulmonary damage. Overstretching of alveoli by application of high tidal volumes or high driving pressures and by repetitive opening and closing of the alveoli can all lead to ventilator-induced lung injury and a pro-inflammatory state [7, 9–11]. Mechanical and inflammatory processes most likely interact: a mechanically stressed lung may produce an inflammatory reaction. Conversely, inflammation renders the lung susceptible to mechanical stress [12].

It is well recognized that a limited tidal volume ventilation of 6 ml/kg is beneficial in ARDS [7, 13]. The use of even lower tidal volumes was found to confer additional protection in ARDS and neonatal RDS [7, 14]. In addition to limited tidal volumes, high airway pressures are also linearly associated with mortality [15, 16]. The application of relatively low plateau pressures (26–27 cm H₂O) can already generate an inflammatory response in the lung [10]. Despite recognition that the intensity of mechanical ventilation influences the outcome of ARDS, application of limited tidal volume ventilation and low driving pressures can often not be achieved [17]. Therefore, adjunctive therapies which allow for less invasive ventilation may be beneficial in ARDS.

Helium is an inert gas with a lower density than air, thus flow of helium through an airway is less turbulent, leading to lower resistance [18]. As a result, during heliox ventilation, lower driving pressures are necessary to distribute oxygen to the distal alveoli to improve oxygenation [18, 19]. Also, diffusion capacities of CO₂ are increased, further resulting in improved gas exchange [18]. Another potential benefit of helium is that it may have anti-inflammatory properties [20]. Helium has been used to reduce the work of breathing during exacerbations of asthma and COPD [19, 21–23]. Most of the data on the effect of heliox have been gathered within these patient populations, whilst most asthma studies have been conducted in the paediatric population. In ARDS, most data on helium ventilation are also derived from the paediatric population, which may be related to an increased airway resistance in neonates and children compared to adults. In light of the increasing awareness of the necessity to limit the intensity of mechanical ventilation [2, 10, 13–16], in this descriptive review we investigated whether he-

liox has a therapeutic potential in ARDS by summarising the results from preclinical and clinical studies on its use in ARDS.

Methods

A systematic search of the PubMed and EMBASE databases to identify all publications of studies focusing on the effect of heliox in ARDS was done by the same reviewer. The databases were searched up to January 2014.

The search included search terms referring to the condition ('lung injury'; 'acute lung injury'; 'acute respiratory distress syndrome'; 'ARDS, human'; 'lung injury'; 'ARDS'; 'respiratory distress syndrome'; 'respiratory failure'; 'hypoxia'; 'mechanical ventilation'; 'artificial respiration') as well as to the intervention ('helium'; 'heliox'). Retrieved papers were screened for relevance by reading of the abstract by 2 reviewers. The reference lists of selected articles were also screened for additional relevant papers.

Inclusion criteria for article selection of preclinical studies were the use of parameters for animal models of ARDS [24]. Inclusion criteria for the clinical studies were patient populations that were described as having acute respiratory failure with the need for respiratory support (for studies published prior to the existence of the ARDS consensus [25]), or use of the consensus criteria for ARDS [25]. Included titles were limited to the English language.

Results

Of 576 papers retrieved from PubMed or EMBASE, 556 articles were excluded based on no use of helium during mechanical ventilation, no original data or no ARDS/acute lung injury condition associated with respiratory failure, leaving 20 papers to be included and described in detail in this review (fig. 1). The level of evidence was graded using the Oxford Centre for Evidence-Based Medicine Levels of Evidence (version 2; <http://www.cebm.net/index.aspx?o=5653>). Risk of bias was not graded due to the descriptive nature of the papers, which also included a series of case reports.

The Effect of Heliox on Lung Mechanics and Inflammation in Animal Models of ARDS

We found 3 articles describing the effect of heliox on gas exchange in paediatric animal models and 3 studies using adult animal models.

Neonatal RDS Animal Models

In a study in neonatal piglets with ARDS induced by saline lavage, animals were ventilated with 40 or 60% helium balanced with oxygen in a high-frequency oscillatory ventilation (HFOV) mode with fixed mean airway

Fig. 1. The study selection process for the inclusion of articles in this review.

pressure, oscillation amplitude and frequency [26]. The ventilation settings were targeted to reach PaCO_2 levels of 55–80 mm Hg and a PaO_2 level above 100 mm Hg. Heliox resulted in decreased PaCO_2 levels, combined with a modest improved oxygenation, together with an increased tidal volume delivery, as measured by a pneumotachometer. As increased tidal volume delivery is unwanted in neonatal RDS, the effect of heliox on gas exchange was investigated while keeping the tidal volume constant. Swine with saline lavage-induced ARDS were

ventilated with 40% helium or 40% nitrogen while tidal volume was kept constant by adjusting the oscillation amplitude [27]. At a constant tidal volume, helium did not alter oxygenation. However, the oscillation amplitude did decrease significantly during heliox ventilation, which relates to a decrease in the peak inspiratory pressure (PIP).

Similar results were found during continuous positive airway pressure (CPAP) ventilation, using a neonatal pig model in which ARDS was induced by oleic acid [28]. Heliox significantly improved gas exchange, reduced the

need for oxygen and decreased PaCO₂ levels compared to animals ventilated with nitrogen. Besides improved gas exchange, heliox ventilation significantly decreased the respiratory rate, tidal volume, minute ventilation and airway resistance, while respiratory compliance increased. Also, heliox improved the amount of aerated lung as measured by histomorphometrical analyses, showing a significantly larger percentage of the gas exchange area relative to the parenchymal area. Interestingly, lung inflammation was also investigated in this model. In the lung tissue of animals ventilated for 4 h, levels of IL-8 and myeloperoxidase, both indicators of neutrophil activation, were lower in animals ventilated with heliox compared to animals ventilated with nitrogen. Thereby, heliox improved ventilation and reduced barotrauma, resulting in an attenuation of lung inflammation.

In summary, in paediatric animal models of ARDS ventilated in an HFOV mode, heliox improved gas exchange while allowing for less invasive ventilation, with a concomitant reduction in lung inflammation [26–28].

ARDS Animal Models

In an adult rabbit model of ARDS, lung injury was induced by oleic acid instillation [29]. Animals were ventilated with low bias flow oscillation with a CO₂ scrubber, which is a modified HFOV system to reduce gas utilisation. Animals were ventilated in cycles of 20 min, with a variable helium concentration (40–50–60–70%) balanced with oxygen. All heliox ventilation cycles were preceded by 20 min of ventilation with 40% oxygen and 60% nitrogen. After each cycle, a blood gas was drawn. All ventilator settings remained unaltered during the experiment. Ventilation with helium increased CO₂ clearance compared to nitrogen-ventilated animals, the magnitude of which correlated with the concentration of helium.

A study in an adult rat model of ARDS induced by saline lavage focused on the effect of helium on histopathological and immunohistochemical changes in lung tissue [30]. Male rats were ventilated in a pressure-controlled mode for 1 h with either heliox (50% helium, 50% oxygen) or 100% oxygen. After the intervention, rats continued to be ventilated for 2 h with 50% oxygen before they were sacrificed and lung tissue was harvested. The severity of pathological features (infiltration of neutrophils, presence of oedema and haemorrhage and hyaline membrane formation) was graded. Heliox ventilation resulted in a reduction of all these features compared to the control group. Also, myeloperoxidase and inducible nitric oxide synthase in lung tissue, which are activated by neutrophils or endothelial cells, respectively, were reduced due to he-

liox ventilation. This study suggests a possible role for heliox in attenuating lung inflammation that seems to be unrelated to less invasive mechanical ventilation settings. Of note, however, the control group in this study had hypoxia, which is known to induce inflammation [31, 32].

The effect of heliox on lung mechanics was studied in an adult rat model in which lung injury was provoked by injurious ventilator settings [33]. With tidal volumes of 15 ml/kg, rats were ventilated with either heliox (50% helium, 50% oxygen) or a standard gas mixture (50% oxygen, 50% air) for 4 h, while adjusting the respiratory rate to maintain normocapnia. Heliox ventilation significantly reduced minute volume ventilation, while maintaining a normal acid-base balance and adequate oxygenation. However, pulmonary protein levels and inflammatory cytokine levels were not affected by heliox ventilation.

Taken together, in animal experiments, heliox improved ventilation in ARDS models during pressure-controlled ventilation and spontaneous breathing. However, the effects of heliox on inflammation yield contrasting results [29, 30, 33].

The Effect of Heliox on Lung Mechanics and Gas Exchange in Clinical Studies

Clinical studies on the effect of heliox in ARDS patients are limited. We found 14 articles, of which 12 were in the paediatric patient population and 2 in the adult patient population. All trials had small patient numbers, as is shown in table 1 along with the level of evidence for each study.

Neonatal Clinical Studies on RDS

An important and much referred to study on the effect of helium on gas exchange was performed in premature newborn infants (weight <2,000 g) with neonatal RDS in need of mechanical ventilation before 24 h of life [34]. In this double-blind randomized study, 31 infants were mechanically ventilated in a volume-controlled mode with either 78% heliox or nitrox (78% nitrogen, 22% oxygen) for a maximum of 8 days, after which the ventilator was connected to the standard air-in-oxygen gas mixture again. Mechanical ventilation was targeted to maintain a transcutaneous PO₂ (TcPO₂) between 6 and 9 kPa and PaCO₂ levels between 5 and 8 kPa. The heliox group showed an improved TcPO₂/FiO₂ ratio after 2 days of ventilation compared to the nitrox group. After 4 days of ventilation, mean airway pressure and FiO₂ could significantly be reduced in the heliox group compared to the nitrox group. Complications due to neonatal RDS, including bronchopulmonary dysplasia (BPD) and death, were sig-

Table 1. Overview of clinical studies, with patient numbers and main outcome

First author	n	Study type	Patient population	Ventilation mode	Main outcome	Level of evidence
Elleau [34]	31	Randomized controlled trial	ARDS – infant	Volume controlled	↑ Transcutaneous PO ₂ /FiO ₂ ratio	1b
Colnaghi [36]	51	Randomized controlled trial	ARDS – infant	Nasal CPAP	↑ PaO ₂ /FiO ₂ ratio ↓ Need for intubation	1b
Migliori [37]	10	Observational intervention	ARDS – infant	SIMV	↓ Peak inspiratory pressures ↓ Work of breathing	2c
Szczapa [38]	8	Observational intervention	ARDS – infant	SIMV	↑ PaO ₂ /FiO ₂ ratio ↓ PaCO ₂ levels	2c
Winters [39]	5	Case report	ARDS – infant	HFOV	↓ PaCO ₂ levels	4
Gross [40]	10	Observational intervention	Bronchiolitis – infant	SIMV	= PaO ₂ /FiO ₂ ratio = PaCO ₂ levels	2c
Kneyber [41]	13	Observational intervention	Bronchiolitis – infant	Pressure controlled	↓ Airway resistance	2c
Paret [42]	1	Case report	Bronchiolitis – infant	Non-invasive pressure controlled (head hood)	↓ Need for intubation	4
Martinon-Torres [43]	15	Observational intervention	Bronchiolitis – infant	CPAP	↓ Need for intubation ↓ PaCO ₂ levels	2c
Liet [44]	39	Randomized controlled trial	Bronchiolitis – infant	Non-invasive pressure controlled (head hood)	= Need for intubation	1b
de Gamarra [46]	8	Observational intervention	Bronchopulmonary dysplasia – infant	Non-invasive pressure controlled (Plexiglas chamber)	↓ Transcutaneous PO ₂	2c
Szczapa [47]	15	Observational intervention	Bronchopulmonary dysplasia – infant	Volume controlled	↑ PaO ₂ /FiO ₂ ratio	2c
Pizov [48]	7	Observational intervention	Respiratory failure – adult	Tracheal insufflation	↓ PaCO ₂ levels ↓ Peak inspiratory pressures	2c
Kirby [49]	2	Case report	ARDS – adult	HFOV/BiPAP	↓ PaCO ₂ levels	4

nificantly higher in the nitrox group. Although the results suggest a beneficial effect of heliox on respiratory status, patient numbers in this study were small. Moreover, this study was carried out before surfactant was introduced as a therapeutic agent in infants with ARDS [35].

The effect of heliox in preterm born infants with neonatal RDS and ventilated with nasal CPAP was investigated in a randomized pilot study [36]. The intervention group (n = 27) received 80% heliox and the control group (n = 24) received nasal CPAP with medical air. After 12 h, heliox was replaced with medical air if nasal CPAP was still necessary. The main outcome was the requirement of mechanical ventilation within 7 days. Heliox significantly decreased the risk for intubation and need for surfactant therapy. A trend was seen towards improved gas exchange and shortened duration of nasal CPAP in favour of heliox ventilation.

The effect of heliox was studied in 10 preterm infants with neonatal RDS, who received long-term ventilation by synchronised intermittent mandatory ventilation (SIMV) [37]. Heliox (80% helium, 20% oxygen) replaced the air-in-oxygen gas mixture. PIPs were adjusted to keep tidal volumes constant. Ventilatory parameters and pulmonary mechanics were measured before, during and after 1 h of heliox therapy. During heliox ventilation, PIP, TcPCO₂ and the work of breathing were reduced, with a concomitant increase in TcPO₂ and minute ventilation. Infants who showed a reduction in peak pressures of at least 20% were extubated. After extubation, they received bilevel positive airway pressure (BiPAP) with heliox for another 3 h. Out of the 10 infants, 8 could be extubated. BiPAP did increase the need for FiO₂, but only 1 infant needed re-intubation after 5 h of ventilation with air-in-oxygen. Although the sample size was small and a control

group was lacking, these results show the ability of heliox to reduce the work of breathing and the need for invasive pressure support ventilation, while improving gas exchange.

In a pilot study in 8 newborns who were mechanically ventilated in a pressure-controlled SIMV mode because of respiratory failure due to meconium aspiration, 80% heliox was administered for 1 h [38]. There was a trend towards increased expiratory tidal volumes, minute ventilation and a peak expiratory flow rate during heliox ventilation. Heliox significantly reduced the alveolar-arterial oxygen tension and increased the $\text{PaO}_2/\text{FiO}_2$ ratio. Blood gas analysis showed a non-significant decrease in PaCO_2 levels with a concomitant increase in pH values. These beneficial effects of heliox were reversed after ventilation was switched back to an air-in-oxygen gas mixture.

These studies suggest that heliox improves gas exchange and allows for less invasive mechanical ventilation in the neonatal population. Most of the studies had outcomes focussed on lung mechanics, rendering the effect of heliox on clinically relevant outcomes unclear.

Paediatric Clinical Studies on ARDS

A summary of case reports reported the use of HFOV to administer heliox in 5 paediatric intensive care unit patients with hypoxemic respiratory failure and respiratory acidosis, caused by a variety of underlying pathologies [39]. The concentration of helium in the gas mixture differed from 20 to 65% and exposure time varied from 2 to 6.5 h. Despite this variation, in all patients the PaCO_2 levels dropped dramatically after the introduction of heliox compared to nitrogen-oxygen ventilation. Oxygenation remained adequate.

In paediatric patients, ARDS can also be triggered by bronchiolitis, which is caused by the respiratory syncytial virus (RSV). When bronchiolitis is severe, it can result in respiratory failure and the need for respiratory support. In mechanically ventilated children with bronchiolitis, the effect of stepwise increased percentages of helium in the ventilated gas mixture was investigated [40]. Ten infants were ventilated in SIMV mode, with a nitrox gas mixture (50% nitrogen, 50% oxygen). During the study protocol, heliox was administered for 15 min with a concentration of 50, 60 or 70% balanced with oxygen. Gas exchange was measured every 15 min, just before changing the gas mixture. In this setting, heliox did not alter the $\text{PaO}_2/\text{FiO}_2$ ratio or PaCO_2 levels compared to nitrox ventilation. These negative findings were ascribed to the relatively small CO_2 retention due to the SIMV mode used,

the small sample size, and to a possibly mild-to-moderate lung disease.

In another small study population, 13 infants with RSV infection were ventilated in a pressure-controlled ventilation mode, with 60% heliox for two periods of 30 min [41], interspersed with nitrox ventilation (60% nitrogen, 40% oxygen). During ventilation with heliox, the airway resistance was reduced without improving CO_2 elimination, PIP or end-expiratory lung volume. The effect on resistance reversed after switching back to nitrox ventilation.

A case report on a 4-month-old boy with RSV-induced bronchiolitis and respiratory failure described the effects of ventilation with 80% heliox via an oxyhood at 5 litres/min [42]. In this case, non-invasive heliox therapy avoided intubation and mechanical ventilation, as the respiratory rate and PaCO_2 levels dropped dramatically. Heliox therapy was continued for 48 h before the patient was weaned from the heliox gas mixture.

Non-invasive CPAP ventilation with 70% heliox has also been used long-term, for up to 14 days in infants with refractory acute bronchiolitis [43]. The clinical condition, oxygenation and gas exchange in 15 paediatric patients admitted to the intensive care unit were measured at baseline and during heliox therapy. Compared to baseline, heliox ventilation improved saturation, the respiratory rate and PaCO_2 levels.

These results were not confirmed in a randomized multicentre study in 39 infants investigating the effect of 78% heliox versus an air-oxygen mix (78% nitrogen, 22% oxygen) through a non-invasive inflatable head hood for at least 24 h [44]. Compared to air-oxygen, heliox did not generate any significant differences in the need for positive-pressure ventilation or gas exchange.

Taken together, the effects of heliox in RSV-induced ARDS are less apparent than in ARDS due to other causes. A possible explanation could be that RSV represents a relatively mild version of ARDS in paediatric patients [45].

Paediatric Clinical Studies on BPD

Respiratory distress is also common in paediatric patients suffering from BPD, which may be considered a more chronic form of neonatal RDS. The effect of heliox ventilation was studied in 2 groups of 4 neonates with or without BPD [46]. All infants were placed in a Plexiglas chamber, which was filled successively with an air-oxygen mix (78% nitrogen, 22% oxygen) and heliox (78% helium, 22% oxygen) for a maximum of 3 h. Spontaneous breathing of heliox resulted in acute hypoxia, with sig-

nificantly decreased TcPO₂ levels in the BPD group versus the control group, whereas TcPCO₂ was unaltered. These results limit the application of heliox in patients who are in need of higher oxygen demands.

In another study in 15 patients with respiratory failure due to BPD, 80% heliox was administered during mechanical ventilation for 1 h [47]. Compared to baseline, heliox increased the tidal volume, dynamic compliance and peak expiratory flow rate. The PaO₂/FiO₂ ratio improved during heliox ventilation, with a related decrease in the alveolar-arterial oxygen tension and oxygenation index. A non-significant decrease was seen in PaCO₂ levels, with an increase in pH. All these beneficial effects reversed after switching back to a normal gas mixture.

In summary, these clinical studies in paediatric patients suggest that heliox ventilation reduces the work of breathing and the need for mechanical ventilation, with the clearest effect in ARDS and least effect in RSV-induced respiratory failure. Due to small samples sizes, results were often non-significant.

Adult Clinical Studies on ARDS

Clinical studies of the effect of heliox in adult patients with ARDS are scarce. To reduce hypercapnia, tracheal gas insufflation with 100% oxygen or 100% helium was investigated in 7 mechanically ventilated patients with respiratory failure due to various aetiologies [48]. Tracheal insufflation was administered at 2, 4 and 6 litres/min for 15 min. Heliox decreased PaCO₂ levels with both gases. Compared to baseline, the maximum flow of helium resulted in a decrease in PIP. Overall, the efficiency of tracheal insufflation, calculated by dividing the PaCO₂ change by the change in PIP, improved with the use of helium.

In a summary of 2 case reports of patients with bronchiolitis obliterans syndrome and acute respiratory failure following lung transplantation, 60% heliox was administered either via BiPAP or HFOV [49]. Heliox ventilation increased pH and decreased PaCO₂ levels, and therefore respiratory status was improved.

Safety of Heliox Ventilation

There is extensive experience with heliox in asthma and COPD patients, and complications have not been reported [21, 50–55]. The lower density of helium causes inaccurately high readings from flow meters calibrated for air and/or oxygen [18, 22]. Therefore, the flow transducer within the ventilator needs adjustment to correctly measure the flow in order to prevent a discrepancy in

used tidal volumes and a misinterpreted improvement in CO₂ clearance.

The safety of heliox during mechanical ventilation in patients with acute respiratory failure is rarely described [23]. In paediatric patients, the frequency of complications was described, without any appreciable effect of heliox ventilation [34]. Another case report describes that heliox ventilation was safe during pregnancy [56]. It is of note, however, that the safety of heliox in various modes of ventilation has not been studied systematically.

The percentage of oxygen within the heliox mixture is a concern when ventilating severely hypoxic ARDS patients. The efficacy of heliox is proportional to the percentage used, which may not allow for sufficient FiO₂ in hypoxic patients. Of note, however, adverse outcome in ARDS may be more related to causes other than hypoxemia, including multiple organ failure and right ventricular failure.

Discussion and Conclusion

In general, both preclinical and clinical studies showed improved ventilation and gas exchange with heliox ventilation. Neonatal RDS animal models mostly used HFOV, in which heliox improved gas exchange while allowing for less invasive ventilation, with an associated decrease in lung inflammation. In adult animal ARDS models, heliox improved ventilation during both pressure-controlled ventilation and spontaneous breathing. The effects of heliox on inflammation show contrasting results, raising the question of whether heliox decreases inflammation by reducing the intensity of ventilation or if it also has a direct anti-inflammatory effect.

The effects of heliox on the intensity of mechanical ventilation are expected immediately following the application of heliox ventilation. In line with this, all clinical studies on ARDS showed promising effects of heliox on short-term outcomes, including minute volume ventilation, applied pressures and in most studies also gas exchange. In the paediatric patient studies, heliox ventilation was also found to influence relevant clinical outcomes, including reduced work of breathing and need for mechanical ventilation. In the adult clinical studies, heliox long-term outcomes have not been investigated.

Small patient numbers, differences in study designs, the aetiology of ARDS, the lack of original data and in the quality of the papers limit the interpretation of the existing data. Also, the effects of heliox in asthma and COPD are likely to be different to the effects in ARDS, which is

a limitation of this review. Also, it is clear that data on relevant outcome parameters are scarce. Therefore, any formal grading at this point seems inappropriate. We conclude that the summarized evidence in this review suggests that heliox improves gas exchange and may reduce the intensity of mechanical ventilation in ARDS on a short-term basis. However, data on clinical outcome are limited.

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