Potential therapeutic strategies aimed at reducing the intensity of mechanical ventilation in ARDS
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The potential of heliox as a therapy for acute respiratory distress syndrome in adults and children: a descriptive review

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Submitted
Abstract

Introduction: In neonatal respiratory distress syndrome (RDS) and acute respiratory distress syndrome (ARDS) mechanical ventilation is often necessary to prevent hypoxia and 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. Also diffusion capacities of CO₂ can improve with heliox ventilation. We reviewed preclinical and clinical studies of the use of heliox ventilation in ARDS like syndromes.

Methods: A systematic search was executed in the PubMed and EMBASE database, with search terms referring to ARDS or an ARDS like condition and the intervention.

Results: 576 Papers were retrieved of which the majority were excluded, resulting in 20 papers 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 work of breathing during heliox ventilation, with a concomitant increase in pH and decrease in PaCO₂ levels, compared to oxygen ventilation.

Conclusion: Although the evidence so far is limited, there may be a rationale for heliox ventilation in ARDS as an intervention to improve ventilation and reduce work of breathing.
Introduction

Acute respiratory distress syndrome (ARDS) is a common entity in critically ill patients, with a staggering mortality of 20% among paediatric patients and 60% among the elderly. Common features of ARDS are hypoxia and hypercapnia with a concomitant increased work of breathing, the latter due to both obstructed airways with increased airway resistance as well as to an increased need for CO₂ removal. These processes occurring during ARDS frequently warrant mechanical ventilation.

Pathophysiology of neonatal respiratory distress syndrome (RDS) includes a surfactant dysfunction. In both ARDS and neonatal RDS, mechanical ventilation 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. 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.

It is well recognized that limited tidal volume ventilation of 6 ml/kg is beneficial in both neonatal RDS and ARDS. Use of even lower tidal volumes was found to confer additional protection in ARDS and neonatal RDS. In addition to limited tidal volumes, also airway pressures are linearly associated with mortality. Application of relatively low plateau pressures (26–27 cm H₂O) can already generate an inflammatory response in the lung. Despite recognition that intensity of mechanical ventilation influences outcome of ARDS, application of limited tidal volume ventilation and low driving pressures can often not be achieved. Thereby, 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. As a result, during heliox ventilation, lower driving pressures are necessary to distribute oxygen to the distal alveoli to improve oxygenation. Also, diffusion capacities of CO₂ are increased, further resulting in improved gas exchange. Another potential benefit of helium is that it may have anti-inflammatory properties. Helium has been used to reduce the work of breathing during exacerbations of asthma and COPD, mostly in the paediatric population. Also in
ARDS, most data on helium ventilation are 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 intensity of mechanical ventilation, we have summarized results from preclinical and clinical studies, which have explored the potential therapeutic use of heliox in ARDS in this descriptive review.

**Methods**

We performed a systematic search in the PubMed and EMBASE database to identify all publications of studies focusing on the effect of Heliox in ARDS. The databases were searched until 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").

For preclinical studies, parameters described for animal models of ARDS were used to select articles. In the clinical studies we accepted patient populations who were described as having acute respiratory failure with the need for respiratory support. Since the search gathered articles dating back to 1989, it was not always possible to use consensus criteria for ARDS. Titles were limited to English language. Retrieved papers were screened on relevance by reading of the abstract. The reference lists of selected articles were screened for additional relevant papers.

**Results**

Of 576 papers retrieved from Medline or EMBASE, 556 articles were excluded based on no use of helium during mechanical ventilation, no original data, or no ARDS/ARDS like condition, leaving 20 papers included and described in detail in this review (Figure 1).

*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 pressure, oscillation amplitude and frequency. The ventilation settings were targeted to reach PaCO₂ levels of 55-80 mmHg and a PaO₂ level above 100 mmHg. Heliox resulted in decreased PaCO₂ levels, combined with a modest improved oxygenation, together with an increased tidal volume delivery, as measured by 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. 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 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. Heliox significantly improved gas exchange, reduced the need for oxygen and decreased PaCO$_2$ levels compared to animals ventilated with nitrogen. Besides improved gas exchange, heliox ventilation significantly decreased 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, in this model also lung inflammation was investigated. In lung tissue of animals ventilated for 4 hours, levels of IL-8 and myeloperoxidase (MPO), both indicators of neutrophil activation, were lower in animals ventilated with heliox compared to animals ventilated with nitrogen. Thereby, heliox improved ventilation and reduced barotauma, resulting in an attenuation of lung inflammation.

In conclusion, in paediatric animal models of ARDS ventilated in a HFOV mode, heliox improved gas exchange while allowing for less invasive ventilation, with a concomitant reduction in lung inflammation.

**ARDS animal models**

In an adult rabbit model of ARDS, lung injury was induced by oleic acid instillation. Animals were ventilated with low bias flow oscillation with a CO$_2$ scrubber, which is a modified HFOV system to reduce gas utilization. Animals were ventilated in cycles of 20 minutes, with a variable helium concentration (40-50-60-70%) balanced with oxygen. All heliox ventilation cycles were preceded by 20 minutes 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 CO$_2$ 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, focussed on the effect of helium on histopathological and immunohistochemical changes in lung tissue. Male rats were ventilated in a pressure-controlled mode for one hour with either heliox (50% helium; 50% oxygen) or 100% oxygen. After the intervention, rats continued to be ventilated for 2 hours with 50% oxygen before they were scarified 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 MPO and inducible nitric oxide synthase in lung tissue, which are activated by respectively neutrophils or endothelial cells were reduced due to heliox 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 hyperoxia, which is known to induce inflammation.

The effect of heliox on lung mechanics was studied in an adult rat model, where lung injury was provoked by injurious ventilator settings. 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 hours, while adjusting 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. The effects of heliox on inflammation yield contrasting results.

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 (Table 1).

Neonatal clinical studies on RDS

An important and much referred study on the effect of helium on gas exchange was performed in premature newborn infants (weight <2000 g) with neonatal RDS in need of
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Table 1: Overview of clinical studies, with patient numbers and main outcome

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Number of patients</th>
<th>Study type</th>
<th>Patient population</th>
<th>Ventilation mode</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elleau (30)</td>
<td>N=31</td>
<td>Randomized controlled trial</td>
<td>ARDS - Infant</td>
<td>Volume controlled</td>
<td>↓ Transcutaneous (PO_2/FIO_2) ratio</td>
</tr>
<tr>
<td>Colnaghi (32)</td>
<td>N=51</td>
<td>Randomized controlled trial</td>
<td>ARDS - Infant</td>
<td>Nasal CPAP</td>
<td>↑ (PaO_2/FIO_2) ratio; ↓ need for intubation</td>
</tr>
<tr>
<td>Winters (33)</td>
<td>N=5</td>
<td>Case report</td>
<td>ARDS - Infant</td>
<td>HFOV</td>
<td>↓ (PaCO_2) levels</td>
</tr>
<tr>
<td>Migliori (34)</td>
<td>N=10</td>
<td>Observational intervention</td>
<td>ARDS - Infant</td>
<td>SIMV</td>
<td>↓ Peak Inspiratory pressures; ↓ Work of Breathing</td>
</tr>
<tr>
<td>Szczapa (35)</td>
<td>N=8</td>
<td>Observational intervention</td>
<td>ARDS - Infant</td>
<td>SIMV</td>
<td>↑ (PaO_2/FIO_2) ratio; ↓ (PaCO_2) levels</td>
</tr>
<tr>
<td>Gross (36)</td>
<td>N=10</td>
<td>Observational intervention</td>
<td>Bronchiolitis - Infant</td>
<td>SIMV</td>
<td>= (PaO_2/FIO_2) ratio; = (PaCO_2) levels</td>
</tr>
<tr>
<td>Kneyber (37)</td>
<td>N=13</td>
<td>Observational intervention</td>
<td>Bronchiolitis - Infant</td>
<td>Pressure controlled</td>
<td>↓ Airway resistance</td>
</tr>
<tr>
<td>Paret (38)</td>
<td>N=1</td>
<td>Case report</td>
<td>Bronchiolitis - Infant</td>
<td>Non Invasive Pressure controlled (Head hood)</td>
<td>↓ Need for intubation</td>
</tr>
<tr>
<td>Martinon-Torres (39)</td>
<td>N=15</td>
<td>Observational intervention</td>
<td>Bronchiolitis - Infant</td>
<td>CPAP</td>
<td>↓ Need for intubation; ↓ (PaCO_2) levels</td>
</tr>
<tr>
<td>Liet (40)</td>
<td>N=39</td>
<td>Randomized controlled trial</td>
<td>Bronchiolitis - Infant</td>
<td>Non Invasive Pressure controlled (Head hood)</td>
<td>= Need for intubation</td>
</tr>
<tr>
<td>de Gammara (42)</td>
<td>N=8</td>
<td>Observational intervention</td>
<td>Bronchopulmonary dysplasia - Infant</td>
<td>Non Invasive Pressure controlled (Plexiglas chamber)</td>
<td>↓ Transcutaneous (PO_2)</td>
</tr>
<tr>
<td>Szczapa (43)</td>
<td>N=15</td>
<td>Observational intervention</td>
<td>Bronchopulmonary dysplasia - Infant</td>
<td>Volume controlled</td>
<td>↑ (PaO_2/FIO_2) ratio</td>
</tr>
<tr>
<td>Pizov (44)</td>
<td>N=7</td>
<td>Observational intervention</td>
<td>Respiratory failure - Adult</td>
<td>Tracheal insufflation</td>
<td>↓ (PaCO_2) levels; ↓ Peak Inspiratory pressures</td>
</tr>
<tr>
<td>Kirby (45)</td>
<td>N=2</td>
<td>Case reports</td>
<td>ARDS - Adult</td>
<td>HFOV / BiPAP</td>
<td>↓ (PaCO_2) levels</td>
</tr>
</tbody>
</table>

BiPAP: Bilevel Positive Airway Pressure; HFOV: High Frequency Oscillatory Ventilation; SIMV: Synchronized Intermittent Mandatory Ventilation; Nasal CPAP: Nasal Continuous Positive Airway Pressure; CPAP: Continuous Positive Airway Pressure
mechanical ventilation before 24 hours of life. 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, where after the ventilator was connected to the standard air-in-oxygen gas mixture again. Mechanical ventilation was targeted to maintain a transcutaneous PO2 (TcPO2) between 6-9 kPa and PaCO2 levels between 5-8 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 and death, were significantly higher in the nitrox group. Although the results suggest a beneficial effect of heliox on respiratory status, patient numbers in this study are small. Moreover this study was carried out before surfactant was introduced as therapeutic agent in infants with ARDS.

The effect of heliox in preterm born infants with neonatal RDS and ventilated with nasal continuous positive airway pressure (CPAP) was investigated in a randomized pilot study. The intervention group (N=27) received 80% heliox and the control group (N=24) received nasal CPAP with medical air. After 12 hours, 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 were ventilated long-term by synchronized intermittent mandatory ventilation (SIMV). Heliox (80% helium; 20% oxygen) replaced the air-in-oxygen gas mixture. Peak inspiratory pressures were adjusted to keep tidal volumes constant. Before, during and after 1 hour of heliox therapy, ventilatory parameters and pulmonary mechanics were measured. During heliox ventilation, peak inspiratory pressure, TcPCO2 and 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 hours. 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 hours of ventilation with air-in-oxygen. Although the sample size is small and a control group is lacking, these results show the ability of heliox
to reduce work of breathing and the need for invasive pressure support ventilation, while
gas exchange improves.

In a pilot study in 8 new-borns who were mechanically ventilated in a pressure-controlled
SIMV mode because of respiratory failure due to meconium aspiration, 80% heliox was
administered for 1 hour. There was a trend towards increased expiratory tidal volumes,
minute ventilation and peak expiratory during heliox ventilation. Heliox significantly
reduced the alveolar-arterial oxygen tension and increased PaO2/FiO2 ratio. Blood gas
analysis showed a non-significant decrease in PaCO2 levels, with a concomitant increase in
pH values. These beneficial effects of heliox were reversed after ventilation was switched
back to air-in-oxygen gas mixture.

These studies suggest that heliox improves gas exchange and allows for less invasive
mechanical ventilation in the neonatal population. As most of the studies had outcomes
focussed on lung mechanics, the effect of heliox on clinically relevant outcomes is not
unequivocally proven, although a benefit towards prevention of intubation and less time
on the ventilator was observed.

*Paediatric clinical studies on ARDS*

A summary of case reports reported the use of HFOV to administer heliox in 5 paediatric
intensive care unit (ICU) patients with hypoxemic respiratory failure and respiratory
acidosis, caused by a variety of underlying pathology. The concentration of helium in
the gas mixture differed from 20 to 65% and exposure time varied from 2 to 6.5 hours.
Despite this variation, in all patients the PaCO2 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. 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 minutes with a concentration of respectively 50, 60 or 70% balanced with oxygen.
Gas exchange was measured every 15 minutes, just before changing the gas mixture.
In this setting, heliox did not alter PaO2/FiO2 ratio nor PaCO2 levels compared to nitrox ventilation. These negative findings were ascribed to the relatively small CO2 retention due to the used SIMV mode, 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 times 30 minutes 42, interspersed with nitrox ventilation (60% nitrogen; 40% oxygen). During ventilation with heliox, the airway resistance was reduced, without improving CO2 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 effects of ventilation with 80% heliox via an oxyhood at 5L/min 43. In this case, non-invasive heliox therapy avoided intubation and mechanical ventilation, as respiratory rate and PaCO2 levels dropped dramatically. Heliox therapy was continued for 48 hours 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 44. In 15 paediatric patients admitted to the ICU, clinical condition, oxygenation and gas exchange were measured at baseline and during heliox therapy. Compared to baseline, heliox ventilation improved saturation, respiratory rate and PaCO2 levels. These results were not confirmed in a randomized multicentre study in 39 infants investigating the effect of 78% heliox versus air-oxygen mix (78% nitrogen; 22% oxygen) through a non-invasive, inflatable head hood for at least 24 hours 45. Compared to air-oxygen, heliox did not generate any significant differences in the need for positive-pressure ventilation or gas exchange.

Taken together, 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 46.
Paediatric clinical studies on bronchopulmonary dysplasia

Respiratory distress is also common in paediatric patients suffering from bronchopulmonary dysplasia (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. All infants were placed in a plexiglas chamber, which was filled successively with air-oxygen mix (78% nitrogen; 22% oxygen) and heliox (78% helium; 22% oxygen) for a maximum of 3 hours. Spontaneously breathing of heliox resulted in acute hypoxia, with significantly decreased TcPO$_2$ levels in the BPD group versus the control group, whereas TcPCO$_2$ 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 hour. Compared to baseline, heliox increased tidal volume, dynamic compliance and peak expiratory flow rate. PaO$_2$/FiO$_2$ 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 PaCO$_2$ levels, with an increase in pH. All these beneficial effects reversed after switching back to a normal gas mixture.

In conclusion, these clinical studies in paediatric patients suggest that heliox ventilation reduces work of breathing and the need for mechanical ventilation, with the clearest effect in ARDS and less 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. Tracheal insufflation was administered at 2, 4 and 6L/min for 15 minutes. Heliox decreased PaCO$_2$ 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 PaCO$_2$ 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. 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. Complications have not been reported. The lower density of helium causes inaccurately high readings from flow meters calibrated for air and/or oxygen. Thereby, the flow transducer within the ventilator needs adjustment to correctly measure the flow. The safety of heliox during mechanical ventilation in patients with acute respiratory failure is rarely described. In paediatric patients, the frequency of complications was described, without any appreciable effect of heliox ventilation. Another case report describes that heliox ventilation was safe during pregnancy.

**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. However, the effects of heliox on inflammation show contrasting results, raising the question if heliox decreases inflammation by reducing the intensity of ventilation or whether it also has a direct anti-inflammatory effect.

Effects of heliox on intensity of mechanical ventilation are expected immediately following 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.

Taken together, the summarized evidence in this review suggests a rationale for heliox ventilation in ARDS. However, data on clinical outcome is limited.
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