Clinical Effects of Heliox Administration for Acute Bronchiolitis in Young Infants*

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**Objective:** To assess the effect of heliox, a helium-oxygen mixture, on respiratory distress symptoms in young infants.

**Design:** Prospective, randomized, double-blind study.

**Setting:** Pediatric ICU (PICU) of a university hospital.

**Patients:** Twenty infants, all <3 months old, admitted to the PICU with moderate-to-severe acute respiratory syncytial virus bronchiolitis.

**Interventions:** All infants were randomly and blindly assigned to inhale either heliox or an air-oxygen mixture (airox) for 1 h under an oxyhood.

**Measurements and results:** After 1 h, the respiratory distress score was significantly lower in the heliox group compared with the airox group (3.05 vs 5.5, p < 0.01), with a significant reduction in accessory muscles use (p < 0.05) and expiratory wheezing (p < 0.01). In contrast, inspiratory breath sounds and cyanosis did not significantly differ between groups. The ex-premature infants of the heliox group had a higher respiratory distress score at baseline compared with the term infants of this group (5.8 vs 5.2, p < 0.05) and a comparable decrease in the score at 60 min.

**Conclusions:** In young infants, even those born prematurely, heliox breathing induced a rapid reduction in accessory muscles use and expiratory wheezing. Further studies are needed to confirm the decreased respiratory muscle work of breathing during heliox inhalation in this population.

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**Key words:** bronchiolitis; helium; infant; randomized controlled trial; respiratory syncytial virus infections; respiratory therapy

**Abbreviations:** ANOVA = analysis of variance; FIO₂ = fractional inspired oxygen; MABP = mean arterial BP; m-WCAS = modified Wood clinical asthma score; PICU = pediatric ICU; RSV = respiratory syncytial virus; SpO₂ = oxygen saturation by pulse oximetry

Respiratory syncytial virus (RSV) bronchiolitis is the leading cause of hospitalization among infants in developed countries. Although most cases are relatively mild and respond to supportive care only, admission to an ICU for evolving respiratory distress is required in 2 to 6% of the cases and occurs more frequently in ex-premature infants. RSV bronchiolitis induces airways obstruction, and no therapy in current use has demonstrated the ability to rapidly reduce the obstruction, which causes an increased load on the respiratory muscles. Indeed,
pulmonary function testing in these patients shows a marked increase in the work of breathing, mainly due to the rise in intrathoracic pressure swings generated by the respiratory muscles. This can lead to muscle fatigue and respiratory failure if the work of breathing necessary to ensure adequate alveolar ventilation exceeds the capacity of the respiratory muscles. Young infants tolerate respiratory loads poorly and are particularly susceptible to fatigue because of the immature pattern of fiber types in these muscles.

Helium-oxygen mixtures have been proposed in the treatment of disorders associated with increased airways resistance such as COPD, acute severe asthma in both adults and children, and upper airways obstruction. Despite the controversial usefulness of heliox in these situations, particularly in asthma crisis, two studies have demonstrated the clinical benefits of helium-oxygen inhalation for infants < 2 years of age with acute bronchiolitis. The benefits of this gas mixture (heliox) have been attributed to its lower density, compared with air-oxygen mixtures, which decreases resistance to gas flow in turbulent conditions and consequently decreases the respiratory muscle work of breathing. The efficacy of heliox use in infants with acute bronchiolitis has never been investigated in a double-blind, randomized study and thus evidence to support its use is still limited. Yet further study of heliox use is warranted, especially in younger infants who are particularly susceptible to respiratory muscle overload. The purpose of the present study was thus to determine whether heliox clinically improves infants < 3 months old with RSV bronchiolitis, including ex-premature infants. For this purpose, we designed a randomized, double-blind, controlled study of infants admitted to the pediatric ICU (PICU) with moderate-to-severe acute RSV bronchiolitis.

**Materials and Methods**

**Patients**

Infants < 3 months who had been hospitalized in the PICU at the University Hospital Arnaud de Villeneuve for respiratory distress were considered for inclusion in this study. Once enzyme immunoassay of a nasopharyngeal swab specimen confirmed the diagnosis of RSV-positive bronchiolitis, venous perfusion was started and the children received an air-oxygen mixture delivered through an oxyhood to maintain oxygen saturation by pulse oximetry (SpO2) ≥ 90%. All treatment, including bronchodilators, corticoids, and kinesitherapy, was stopped.

The infants were monitored and respiratory distress was evaluated using the modified Wood clinical asthma score (m-WCAS) by one of the two investigators who were not clinically in charge of the cases but who were experienced with the scoring system (Table 1). This scale has been used in previous studies of bronchiolitis and includes a “mild” category of 0.5 points to better define the clinical response to helium-oxygen inhalation. To standardize our scoring, accessory muscles recruitment and expiratory wheezing were assessed using a visual analog scale, similar to that used for pain measurement. This scale is presented as a 200-mm horizontal line that is read from left (absence of the clinical sign) to right (maximal severity of the clinical sign). At each scoring session, the investigator thus assessed the infant, located these two parameters on the 200-mm line with a pen, and then measured the distance from the left extremity to each point. For both accessory muscles recruitment and expiratory wheezing, a distance < 5 cm was considered as “none,” a distance ≥ 5 cm but < 10 cm was considered as “mild,” a distance ≥ 10 cm but < 15 cm was considered as “moderate,” and a distance ≥ 15 cm was considered as “maximal” or “marked.” Good agreement (k = 0.8) between the two observers was noted regarding five infants admitted for bronchiolitis before the trial began.

If both SpO2 and the asthma score remained stable for 15 min, arterial blood gases were measured. The criteria for inclusion were the following: (1) PaCO2 > 42 mm Hg; (2) diagnosis of RSV bronchiolitis determined by enzyme immunoassay of a nasopharyngeal swab specimen; (3) no underlying cardiopulmonary disease, pneumothorax on chest radiograph, or corticosteroid or bronchodilator treatment within 2 h of study enrollment; (4) an m-WCAS > 5, indicating severe respiratory distress; and (5) signed authorization from the parents.

**Study Design**

This prospective study was randomized and double blinded. The infants meeting all the inclusion criteria were randomly assigned to one of the two groups: group A (revealed at the end of the study as the airox-treated group), or group B (revealed at the end of the study as the heliox-treated group). The study lasted 3 years until 20 children were included, and during this time none the parents and only one investigator knew which group was receiving airox or heliox treatment. After enrollment in group A or B, the patients received the corresponding gas mixture through a hood, delivered by a double flowmeter system (Fig 1).

The gas mixture flow was maintained constant throughout the study at 7 L/min, and the fractional inspired oxygen (FiO2) under the hood was first adjusted to 0.40. If SpO2 was < 90%, the

<table>
<thead>
<tr>
<th>Variables</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
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<tr>
<td>Cyanosis</td>
<td>None</td>
<td>In room air (&lt; 94% SpO2)</td>
<td>In 0.40 FiO2 (&lt; 94% SpO2)</td>
<td></td>
</tr>
<tr>
<td>Inspiratory breath sounds</td>
<td>None</td>
<td>Unequal</td>
<td>Decreased/absent</td>
<td></td>
</tr>
<tr>
<td>Accessory muscles use</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Expiratory wheezing</td>
<td>None</td>
<td>Moderate</td>
<td>Maximal</td>
<td></td>
</tr>
<tr>
<td>Cerebral function</td>
<td>Normal</td>
<td>Depressed/agitated</td>
<td>Coma</td>
<td></td>
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</table>

Table 1—m-WCAS
patient was excluded from the study. If \( \text{SpO}_2 \) was \( \geq 90\% \), the child was monitored continuously, and respiratory rate, heart rate, mean arterial BP (MABP), \( \text{SpO}_2 \), and the m-WCAS were recorded at time 0, time 0 + 30 min, and time 0 + 60 min. To assess cyanosis with the m-WCAS, \( \text{FiO}_2 \) was fixed at 0.21. If \( \text{SpO}_2 \) was \( > 94\% \), the score 0 was attributed to this parameter; if \( \text{SpO}_2 \) was \( \leq 94\% \), \( \text{FiO}_2 \) was fixed at 0.40 and cyanosis was scored as defined in Table 1. One to 2 min were usually required for the gas mixture under the hood to equilibrate to the new target \( \text{FiO}_2 \). The cumulative time necessary for these \( \text{FiO}_2 \) changes was not \( > 6 \) min and was not included in the study period because the 30-min intervals before and after T30 were strictly timed. After 1 h, gas delivery (A or B) was stopped. Fifteen minutes later, the m-WCAS was again determined and if it was equal to or lower than the value at time 0 + 60 min, the weaning was considered a success. If not, the gas delivery was restarted, and weaning was attempted 3 h later in the same conditions; this procedure was continued until success.

**Gas Delivery System**

The gas mixtures were stocked in tanks marked only “A” or “B.” Until the end of the study, only the principal investigator, who did not participate in the study, knew that A contained 21% oxygen/79% nitrogen and B contained 21% oxygen/79% helium. The delivery system, as illustrated in Figure 1, consisted of two standard pressure-compensated flowmeters calibrated with air for gas A and gas B. Blinding was accomplished by placing the two flowmeters in a box, each connected to one of the two gas tanks in such a way that the investigator had to select the output corresponding to group A or B and regulate the flow without knowing the nature of the gas mixture. Oxygen through another flowmeter was delivered through a 7-L oxyhood (Oxydom; Nasco; Sydney, Australia) in parallel with the gas mixture and was under the control of an oxygen analyzer directly connected through an orifice on the top of the hood to monitor \( \text{FiO}_2 \) during the study period.

**Statistical Analysis**

Data are presented as mean \( \pm \) SE. The differences between the airox and heliox groups for each parameter were assessed by independent sample \( t \) tests. Repeated-measures analysis of variance was used to compare changes in parameters over the course of the 1-h study period. Statistical significance was indicated by \( p < 0.05 \). All statistical analysis was performed using software (Prism 3; Graphpad; San Diego, CA).

**Ethical Considerations**

Informed written consent was obtained from the parents of all infants. This study protocol was approved by the University Hospital Human Subjects Committee of Montpellier.

**Results**

Thirty-one infants with the diagnosis of respiratory distress attributable to RSV bronchiolitis were admitted to the PICU during the study period, from November 1999 to March 2002. Among them, 11 (1 preterm and 10 full term) were excluded for clinical scores \( < 5 \). Twenty infants were thus randomized into the two groups, with 10 in each group. For 16 infants, the first symptoms of the disease had been observed in the 72 h preceding inclusion. Ten of these children had been born before 36 completed weeks of gestation, with a mean gestational age of 34.3 \( \pm \) 1.4 weeks and a mean birth weight of 2,137 \( \pm \) 185 g. The age, weight, clinical score, respiratory and heart rates, MABP, \( \text{FiO}_2 \) and arterial blood gases at the time of enrollment in the study were comparable between the two groups (Table 2). One infant randomized into the control group was excluded for an oxygen hemoglobin saturation \( < 90\% \) that persisted under the maximum 40% \( \text{FiO}_2 \) authorized by the protocol. In accordance with the protocol criteria, none of the patients had received systemic corticosteroids or nebulized bronchodilators in the 2 h prior to study enrollment.

The m-WCAS (Fig 2) improved only in the heliox group, with a mean decrease between baseline and 60 min of 2.35 \( \pm \) 0.35, vs 0.05 \( \pm \) 0.01 in the control group (\( p < 0.01 \), by two-way analysis of variance [ANOVA]). The analysis of the different components of the score showed that this decrease was associated with decreased accessory muscles use and expiratory

![Figure 1. Gas delivery system.](Image)

**Table 2—Group Characteristics After Randomization***

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Heliox (n = 10)</th>
<th>Airox (n = 9)</th>
</tr>
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<tbody>
<tr>
<td>Age, d</td>
<td>29 ( \pm ) 5</td>
<td>34 ( \pm ) 9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>3.5 ( \pm ) 0.46</td>
<td>3.83 ( \pm ) 0.24</td>
</tr>
<tr>
<td>Clinical score</td>
<td>5.4 ( \pm ) 0.2</td>
<td>5.6 ( \pm ) 0.2</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>59.4 ( \pm ) 6.4</td>
<td>64.9 ( \pm ) 5.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>152 ( \pm ) 14.9</td>
<td>144 ( \pm ) 8.5</td>
</tr>
<tr>
<td>( \text{FiO}_2 ) %</td>
<td>31.4 ( \pm ) 4.0</td>
<td>34.0 ( \pm ) 2.6</td>
</tr>
<tr>
<td>( P_{O_2} ), mm Hg</td>
<td>50.7 ( \pm ) 5.0</td>
<td>64.3 ( \pm ) 8.1</td>
</tr>
<tr>
<td>( P_{CO_2} ), mm Hg</td>
<td>56.5 ( \pm ) 4.9</td>
<td>53.6 ( \pm ) 2.3</td>
</tr>
<tr>
<td>pH</td>
<td>7.30 ( \pm ) 0.02</td>
<td>7.33 ( \pm ) 0.06</td>
</tr>
<tr>
<td>MABP, mm Hg</td>
<td>61.4 ( \pm ) 5.7</td>
<td>64.7 ( \pm ) 4.8</td>
</tr>
</tbody>
</table>

*Values are expressed as mean \( \pm \) SD.
wheezing (p < 0.05 and p < 0.01, respectively, by two-way ANOVA; Fig 3, 4). Conversely, a comparable increase in the cerebral score (p < 0.01, by two-way ANOVA; Fig 5), and no significant variation in inspiratory breath sounds or cyanosis was observed in the two groups. Heart rate, FiO2, transcutaneous PO2, and MABP did not vary in either group throughout the study. At 60 min, a mean increase of 6 ± 2 respirations per minute (revolutions/min) with a decrease of 2.2 ± 0.8 mm Hg in the transcutaneous PCO2 was observed in the whole population. The differences, however, were not significant between groups.

Five infants born prematurely were assigned to the heliox group. These infants had a higher m-WCAS on admission than the heliox term infants (5.8 ± 0.2 vs 5.2 ± 0.2, p < 0.05) and a comparable decrease in the score between baseline and 60 min (Fig 6).

After 1 h, the rate of successful weaning at the first attempt was 7/9 infants in the airox group vs 4/10 in the heliox group (p < .01). The mean duration of the gas mixture administration was 3.6 ± 1.8 h in the airox group vs 13.0 ± 3.8 h in the heliox group (p < 0.05). During the PICU stay, supplemental oxygen to maintain SpO2 > 90% was necessary during a comparable period of 3.2 ± 0.36 days in the airox group vs 3.5 ± 0.07 days in the heliox group. One infant in each group required endotracheal intubation for respiratory failure, 10 h following randomization for the infant included in the control group and 4 h for the infant in the heliox group.
To our knowledge, the effect of heliox therapy on the clinical asthma scores of infants with acute bronchiolitis has never been investigated through a randomized double-blind study. Hollman et al20 investigated the effect of a 20-min crossover from heliox to airox or vice versa on m-WCAS. In their study, however, the more severely affected patients were treated with helium-oxygen at presentation to avert potential intubation. Although studies in children with severe asthma11 or croup14,16 have suggested that heliox inhalation may avoid mechanical ventilation, this has never been demonstrated for infants with acute bronchiolitis. Thus, only the least affected patients admitted to the PICU, ie, those with clinical scores < 5, were excluded from our study. The greater severity of our population probably explains the magnitude of the decrease in m-WCAS that we observed compared with that observed in the study of Hollman et al,20 in which it reached only 0.46 for an initial score of 3.04 in their randomized patients. Furthermore, our population was more homogeneous with regard to the baseline scores, with a narrower range in both groups. Despite these patient characteristics, one infant in each group had to be intubated within the 12 h following randomization. The infant enrolled in the heliox group needed ventilatory assistance 4 h after weaning from the gas mixture for recurring incidents of apnea, while ARDS developed in the infant enrolled in the airox group, requiring artificial ventilation 10 h after his inclusion in the protocol. These observations highlight some of the circumstances of respiratory failure that are usually not improved with heliox and that can lead to mechanical ventilation in acute RSV bronchiolitis. Nevertheless, the primary goal of this study was to assess change in the m-WCAS after heliox inhalation and, because of the low number of patients, we cannot unambiguously conclude that heliox was ineffective in preventing endotracheal intubation in acute RSV bronchiolitis.

In the study of Martinon-Torres et al,21 a nonre-breather reservoir facemask was judged to be better adapted for delivering heliox but, in the authors’ opinion, the mask hindered adequate blinding. We preferred to deliver heliox in an oxygen hood because infants < 3 months old are almost always resistant to a facemask. Moreover, our double flowmeter gas delivery system was compatible with the double-blind design of the study. We are aware that the hood may not be optimal for heliox delivery because the helium tends to concentrate at the top of it, which potentially increases the density of the mixture inhaled by the infant.23 Previous clinical studies,16,24 however, have shown the efficacy of helium-oxygen mixtures in upper airways obstruction even in patients subjected to the hood, suggesting that the activation of a dyspneic infant under the hood probably modifies the gas distribution in the device. In our study, excessive activity was manifested in both groups by comparable increases in the cerebral function scores. The infants became more consistently excited after inclusion in the study, whereas before randomization agitation was seldom noted or present only when the infant was disturbed. In our opinion, this effect of the oxymask on the infants’ behavior was the probable explanation for the persistence of tachypnea and tachycardia in the heliox-treated patients even though their m-WCAS improved, as demonstrated by the reduction in accessory muscles use and wheezing. Our study in fact underlines the interest of separately analyzing the different components of the m-WCAS, as the improved respiratory status of children receiving heliox could be hidden by poor tolerance of the hood. Future studies could evaluate whether the use of more voluminous walls would still be appropriate for helium-oxygen delivery and better tolerated by these infants.

Despite the recommendations of the French Pediatric Society for the management of a first episode of RSV bronchiolitis, 20% of our patients had received nebulized β-adrenergic agents 4 to 6 h before study enrollment. For several reasons, however, we believe that these medications were unlikely to have influenced the baseline data or the final results. First, the bronchodilator effect after salbutamol inhalation generally lasts up to 2 to 4 h, meaning that this effect had vanished by the time the infants were included in the study. Second, the effectiveness of β-adrenergic bronchodilators, especially for young infants hospitalized with acute RSV bronchiolitis, is very uncertain. Poor aerosol deposition has been demonstrated in these patients25 and could explain the conflicting short-term effects of these agents on clinical scores and pulmonary mechanics. Third, the patients treated with salbutamol inhalation before inclusion were distributed almost equally in both
treatment \( (n = 3) \) and control \( (n = 2) \) groups. Fourth, and probably the major argument, was a comparable m-WCAS in the two groups at randomization.

A turbulent flow is the predominate feature in patients with major airways obstruction, such as an upper airways obstacle, asthma, or COPD. Airways resistance to such a flow is directly proportional to the density of the inspired gas and is reduced by the substitution of nitrogen by helium in heliox, which produces a mixture of lower density than air. The airways obstruction in acute RSV bronchiolitis is secondary to bronchial smooth-muscle constriction, mucosal edema, and plugging of the airways by mucous and cellular debris, and the obstruction predominates in the peripheral airways or bronchi. Thus, this lower respiratory tract infection should theoretically affect the laminar flow, independent of density changes. Two previous studies, however, demonstrated improved m-WCAS with heliox therapy in children with acute bronchiolitis, suggesting that our understanding of the flow characteristics associated with this condition is imprecise. The majority of our patients were included soon after disease onset, at a stage when mucosal edema significantly decreases nasal and upper airways calibers and turbulent gas flow probably originates. This contribution of upper airways inflammation to the disease process has been highlighted by the efficacy of epinephrine on respiratory distress scores and airways resistance, which mainly reflects upper airways patency. In our patients, the most obvious benefits of heliox were the sharp reduction in accessory muscles recruitment and expiratory wheezing. These two components of the m-WCAS are closely related to the work of breathing, which makes them particularly susceptible to modification by helium-oxygen inhalation. In order to improve the sensitivity of this score to the potential respiratory benefits of heliox, Hollman et al. added a “mild” category of 0.5 points for each of these parameters. However, we believe that these two clinical parameters should be evaluated with a standardized methodology to decrease intrinsic variability as much as possible. Analog scaling undoubtedly provided a simple tool to achieve this. In fact, the change in these two parameters was the deciding factor in the improved scores with heliox, despite the unfavorable evolution in cerebral function and the questions raised about the sensitivity of the two other components of the score. Even in the presence of distal airways obstruction, there is no theoretical reason for the lack of improvement in inspiratory breath sounds, notably vesicular murmur, because heliox permits a higher flow rate whenever laminar flow conditions predominate. Our failure to identify any modification in these sounds was nevertheless striking and may suggest, once again, the interest of a “mild” category as proposed by Martinon-Torres et al. Cyanosis remained stable with no significant variation in \( \text{SpO}_2 \) or \( F\text{O}_2 \) in either group, suggesting no effect on the ventilation/perfusion ratio in all patients. Conversely, \( \text{PCO}_2 \) tended to decrease, probably because of the increased ventilation associated in part with the agitation of the infants once they were settled under the hood. Although heliox may favor carbon dioxide diffusion because of its lower density, the difference between groups was too narrow to propose such a mechanism.

Of the infants admitted to the PICU with bronchiolitis during the study period, 26% had been born prematurely. Ninety percent of these infants reached scores compatible with inclusion compared with 57% of the term infants, confirming the influence of premature birth on the occurrence of more severe forms of RSV infection. These infants were born between 33 and 36 weeks of gestation and had no underlying cardiopulmonary disease, nor had they received bronchodilators or oxygen. This subgroup had not received the prophylactic RSV antibodies that are systematically administered to all preterms born before 32 weeks of gestation and all infants with congenital heart disease. This policy is recommended by the French Pediatric Society and has been in practice in our center, the regional reference center for preterm care, since October 1999. In spite of relatively mild prematurity, these infants had the highest baseline scores and benefited the most from the heliox therapy. The correlation between disease severity on admission and improvement with heliox has already been observed but never specifically in association with prematurity, although none of the cited studies clearly mentioned the exclusion of premature infants. Yet in this population, the markedly smaller airways diameter may predispose to greater obstruction during acute bronchiolitis, which is more likely to result in an increased work of breathing, muscle fatigue and ultimately respiratory failure. In an observational study, bronchiolitis was found to be the most common cause of acute respiratory failure in large pediatric referral centers in North American PICU. Future studies are required to confirm the interest of heliox, notably its ability to avoid endotracheal intubation in this specific population.

**Conclusion**

Our study showed that heliox rapidly and markedly improved the respiratory distress score of infants with moderate to severe bronchiolitis. Heliox
breathing reduced accessory muscles use and expiratory wheezing. These results were confirmed in the infants born prematurely, suggesting that heliox may be of particular interest in this target population. Further studies are needed to confirm the decreased respiratory muscle work of breathing during heliox inhalation and to establish the benefits, such as preventing endotracheal intubation and improving patient outcome, of reducing respiratory muscle overload with this gas mixture in young infants with acute RSV bronchiolitis.

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REFERENCES