Heliox Therapy in Bronchiolitis: Phase III Multicenter Double-Blind Randomized Controlled Trial
Mina M. Chowdhury, Sheila A. McKenzie, Christopher C. Pearson, Siobhan Carr, Caroline Pao, Arvind R. Shah, Elizabeth Reus, Joseph Eliahou, Fabiana Gordon, Hubert Bland and Parviz Habibi

*Pediatrics* 2013;131;661; originally published online March 18, 2013;
DOI: 10.1542/peds.2012-1317

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/131/4/661.full.html
**Heliox Therapy in Bronchiolitis: Phase III Multicenter Double-Blind Randomized Controlled Trial**

**AUTHORS:** Mina M. Chowdhury, MB, ChB, a Sheila A. McKenzie, FRCP, b Christopher C. Pearson, FRACP; c Siobhan Carr, FRCPCH; d Caroline Pao, MRCP; e Arvind R. Shah, FRCPCH; f Elizabeth Reus, MSc, g Joseph Eliahoo, PhD; h Fabiana Gordon, PhD; i Hubert Bland, MB, ChB, j and Parviz Habibi, PhD, FRCP, FRCPCH

1 Department of Pediatrics, Wright Fleming Institute, Imperial College, London, United Kingdom; 2 Department of Pediatrics, Royal London Hospital Whitechapel, London, United Kingdom; 3 Department of Pediatrics, Women’s and Children’s Hospital, North Adelaide, Australia; 4 Department of Pediatrics, North Middlesex University Hospital, London, United Kingdom; 5 Statistical Advisory Service, Imperial College, London, United Kingdom; and 6 Surrey Clinical Research Centre, University of Surrey, Guildford, United Kingdom

**KEY WORDS**
randomized controlled trial, heliox, bronchiolitis

**ABBREVIATIONS**
Airox—mixture of 21% oxygen + 79% nitrogen
BREATHE—Bronchiolitis Randomized Controlled Trial Emergency-Assisted Therapy with Heliox—An Evaluation
CPAP—continuous positive airway pressure
FiO₂—fraction of inspired oxygen
FM—facemask
Heliox—mixture of 21% oxygen + 79% helium
LoT—length of treatment
NC—nasal cannula
RCT—randomized controlled trial
RSV—respiratory syncytial virus
SpO₂—percutaneous oxygen saturation

Dr Chowdhury and Dr Habibi designed the study and wrote the trial protocol and manuscript; Dr McKenzie, Dr Bland, Dr Carr; Dr Pao, Dr Shah, and Dr Pearson contributed to the study design and writing of manuscript; Dr Habibi was the chief investigator; Dr Chowdhury was the trial coordinating investigator; Dr McKenzie, Dr Carr; Dr Pao, Dr Shah, and Dr Pearson were principal investigators at collaborating centers; Dr Habibi, Dr Chowdhury, and Ms Reus coordinated study conduct and data collection at the centers and played a major role in supervision of the trial nurses involved in recruitment; and Dr Eliahoo and Dr Gordon performed the statistical analyses and contributed to the writing and approval of the final manuscript.

This trial has been registered at [http://www.controlled-trials.com/ISRCTN18238432](http://www.controlled-trials.com/ISRCTN18238432)

do:10.1542/peds.2012-1317

Accepted for publication Dec 18, 2012

Address correspondence to Parviz Habibi, PhD, FRCP, FRCPCH, Reader and Consultant in Pediatric Intensive Care and Respiratory Medicine, Wright Fleming Institute, Imperial College, Norfolk Place, London W2 1PG, United Kingdom. E-mail: p.habibi@imperial.ac.uk

(Continued on last page)

**WHAT’S KNOWN ON THIS SUBJECT:** Bronchiolitis, a leading cause of infant hospitalization, has few proven treatments. A few small studies have reported the beneficial effects of a mixture of 21% oxygen + 79% helium (Heliox). The 2010 Cochrane Review concluded that additional large randomized controlled trials were needed to determine the therapeutic role of Heliox in bronchiolitis.

**WHAT THIS STUDY ADDS:** TheBronchiolitis Randomized Controlled Trial Emergency-Assisted Therapy with Heliox—An Evaluation (BREATHE) trial is the largest multicenter randomized controlled trial to date to investigate the efficacy of Heliox in acute bronchiolitis. The delivery method for Heliox therapy was found to be crucial to its efficacy.

**abstract**

**BACKGROUND AND OBJECTIVE:** Supportive care remains the mainstay of therapy in bronchiolitis. Earlier studies suggest that helium-oxygen therapy may be beneficial, but evidence is limited. We aimed to compare efficacy of 2 treatment gases, Heliox and Airox (21% oxygen + 79% helium or nitrogen, respectively), on length of hospital treatment for bronchiolitis.

**METHODS:** This was a multicenter randomized blinded controlled trial of 319 bronchiolitic infant subjects randomly assigned to either gas; 281 subjects completed the study (140 Heliox, 141 Airox), whose data was analyzed. Treatment was delivered via facemask (nasal cannula, if the facemask intolerant) ± continuous positive airway pressure (CPAP). Severe bronchiolitics received CPAP from the start. Primary end point was length of treatment (LoT) required to alleviate hypoxia and respiratory distress. Secondary end-points were proportion of subjects needing CPAP; CPAP (LoT); and change in respiratory distress score.

**RESULTS:** Analysis by intention to treat (all subjects); median LoT (inter-quartile range, days): Heliox 1.90 (1.08–3.17), Airox 1.87 (1.11–3.34), P = .41. Facemask tolerant subgroup: Heliox 1.46 (0.85–1.95), Airox 2.01 (0.95–2.86), P = .03. Nasal cannula subgroup: Heliox 2.51 (1.21–4.32), Airox 2.81 (1.45–4.78), P = .53. Subgroup started on CPAP: Heliox 1.55 (1.38–2.01), Airox 2.26 (1.84–2.73), P = .02. Proportion of subjects needing CPAP: Heliox 17%, Airox 19%, O.R. 0.87 (0.47–1.60), P = .76. Heliox reduced respiratory distress score after 8 hours (mixed models estimate, −0.1298; P < .001). The effect was greater for facemask compared with nasal cannula (mixed models estimate, 0.085; P = .04).  

**CONCLUSIONS:** Heliox therapy does not reduce LoT unless given via a tight-fitting facemask or CPAP. Nasal cannula heliox therapy is ineffective. *Pediatrics* 2013;131:681–689
Acute viral bronchiolitis is a leading cause of infant hospitalization, with a rising incidence and health-economic burden in developed countries. In the United States, ~75,000 respiratory syncytial virus (RSV)-positive bronchiolitic infants are hospitalized each year. Stang et al estimated the annual cost burden of this to be between US$385 and $585 million. Although there are many treatments, few have a strong evidence base or have demonstrated a reduced length of hospital stay or need for respiratory support. With oxygen being the mainstay of therapy. A mixture of 21% oxygen + 79% helium (Heliox) is lighter than air or oxygen, promoting laminar flow in areas of turbulence or airway narrowing and thus may improve respiratory distress and wheezing. Heliox also reduces respiratory system resistance, has a higher binary diffusion coefficient for CO₂ and O₂ and therefore may enhance alveolar gas exchange and lung recruitment, and is an inert gas with an excellent safety profile. Heliox may therefore be a useful therapy in bronchiolitis that is associated with small airway inflammation causing increased respiratory system resistance and increased work of breathing. Since 1996 when Paret et al successfully treated a bronchiolitic infant in respiratory failure with Heliox, 9 studies (combined total of 172 infants) have investigated Heliox treatment in bronchiolitis. Six of these studies reported various clinical benefits, including improvement of hypercapnea and respiratory distress. These studies had small sample sizes, used different delivery methods for Heliox, and were not always blinded, and only 1 study assessed the effect of Heliox on length of treatment (LoT) or hospital stay. Furthermore, regardless of clinical efficacy, heliox must be cost-effective. The cost of a single bed day on a pediatric ward is $1947. Even reducing the hospital LoT by 0.5 days would save $974, which is equivalent to 14 cylinders of Heliox at a cost of $70 each. In our experience, only 3 to 5 cylinders per day are consumed during Heliox therapy, thus supporting our hypothesis that Heliox may be cost-effective if it reduces duration of hospital treatment. The 2010 Cochrane Review concluded that additional large randomized controlled trials (RCTs) were needed to investigate the delivery system for Heliox and determine its therapeutic role in bronchiolitis. We therefore report the largest phase III RCT, called Bronchiolitis Randomized Controlled Trial Emergency-Assisted Therapy with Heliox—An Evaluation (BREATHE). Results of this work have been previously published as an abstract.

METHODS

Setting

A prospective, double-blind RCT was carried out in the bronchiolitis seasons during 2005 to 2008 across 4 centers in the United Kingdom and Australia.

Participants

Pediatricians in the emergency departments or pediatric wards of participating hospitals, independent of the BREATHE study, assessed infants (or 12-month corrected age if premature). They clinically determined if the infants had a diagnosis of bronchiolitis (history of upper respiratory tract infection followed by wheezing, coughing, breathing difficulty, or chest crackles on auscultation) and if they needed hospitalization for respiratory distress or hypoxia (percutaneous oxygen saturation [SpO₂] < 93% in room air). Exclusion criteria were as follows: imminent intubation; SpO₂ < 93% despite 15 L/minute O₂ via non-rebreathing facemask (FM); tracheostomy; participation in another study in the previous 4 weeks; salbutamol, epinephrine, or ipratropium therapy within 1 hour or systemic steroids within 4 hours of entry into the study; and bronchiolitis readmission within 24 hours of exit from BREATHE. An independent data committee monitored safe conduct throughout the study. The trial was registered internationally and had independent ethics committee approval.

Interventions

Heliox or a mixture of 21% oxygen + 79% nitrogen (Airox), labeled as gas A or B, was the treatment or control intervention with additional oxygen titrated via Y-connection tubing, resulting in 2 gas mixes: A or B ± additional oxygen. Gas delivery was by a tight-fitting 3-valve, nonrebreathing facemask (FM; 1192; Intersurgical) or a nasal cannula (NC; BC 2745-20; Fisher & Paykel Healthcare) if the subject was FM intolerant. Gas A or B drove the continuous positive airway pressure (CPAP) device (EME infant flow driver; CareFusion).

Outcome Measures

The primary end point was the total LoT to alleviate hypoxia (SpO₂ ≥ 93% in room air) and respiratory distress (minimal work of breathing). LoT was calculated from the start to successful stop of the trial gas, as defined by clinical stability (minimal work of breathing and SpO₂ ≥ 93%) for 1 hour breathing room air. Minimal work of breathing was qualified as having a normal respiratory rate, no cyanosis, no nasal flaring, no tracheal tug or grunting, no head bobbing, and no use of accessory muscles except for mild intercostal recessions. Secondary end points were proportion of each treatment group needing CPAP and the change in respiratory distress over time measured by the Modified Wood’s Clinical Asthma Score (Table 1). We used a scoring tool to assess change in respiratory distress over time, similar to that used in previous heliox studies. The scoring tool was a modified version of the original Wood’s Clinical Asthma Score.
At each assessment period, the type of delivery (FM or NC) and FM tolerance was prospectively recorded on the trial clinical report forms to allow analysis of LoT in the FM and NC subgroups. We also recorded the duration of CPAP therapy (CPAP LoT) in a group of severe bronchiolitic subjects who were commenced on CPAP from the beginning of treatment to compare the impact of Heliox versus Airox on duration of CPAP. Management of bronchiolitis was standardized to a strict protocol across trial centers: gas A or B ± oxygen humidified via MR850 (Fisher & Paykel Healthcare), minimal handling, attention to hydration status, and careful airway toilet/suction. Intravenous fluids were preferred over nasogastric feeding in subjects with severe respiratory distress. Bronchodilator, epinephrine, or steroid use constituted failure was defined as hypoxia (SpO2 < 93%) despite oxygen >4 L/minute via FM or >2 L/minute via NC. CPAP was discontinued once subjects were weaned to 1 to 2 cmH2O pressure and were no longer hypoxic in fraction of inspired oxygen (FiO2) < 0.4 for 1 hour. CPAP failure was defined as hypoxia (SpO2 < 93%) despite 9 cmH2O pressure and FiO2 0.6, whereupon subjects exited the trial. Those subjects with severe bronchiolitis at presentation, who required immediate commencement of CPAP driven by gas A or B, followed the CPAP protocol (Fig 1).

### TABLE 1 Modified Wood’s Clinical Asthma Score

<table>
<thead>
<tr>
<th>SCORE</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO2</td>
<td>&lt;93% Room Air</td>
<td>&lt;94% Room Air</td>
<td>&lt;94% 40% FiO2</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>None</td>
<td>Any one of: Recessions, Head bobbing, Nasal flaring, Tracheal tug</td>
<td>All four of: Recessions, Head bobbing, Nasal flaring, Tracheal tug</td>
</tr>
<tr>
<td>Cerebral function</td>
<td>Normal</td>
<td>Depressed or Agitated</td>
<td>Coma</td>
</tr>
<tr>
<td>Breath sounds</td>
<td>Normal</td>
<td>Unequal</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td>Expiratory wheezing</td>
<td>None</td>
<td>Yes – In room air</td>
<td>Yes – In 40% FiO2</td>
</tr>
<tr>
<td>Accessory muscle use</td>
<td>NONE of: Recessions, Head bobbing, Nasal flaring, Tracheal tug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse oximetry</td>
<td>SpO2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maximum score = 11.

Sample size calculation (using nQuery Advisor v4.0) was based on an unpaired t test with 80% power for a 2-sided α of 5% to detect a 0.75-day LoT reduction. A baseline mean LoT for bronchiolitis of 2.7 days (SD = 2.3 days) was assumed. The calculation showed that 298 subjects would be needed to achieve a reduction in total LoT by 0.75 days. Three-quarters of a day duration was selected both from the point of view of feasibility of recruitment and also representing a clinically important threshold (eg, a 0.75-day LoT reduction in a center that treats 100 infants would save 75 bed-days and was considered a positive impact on health economics).

### Randomization and Blinding

After written informed consent was obtained from parents, patients were enrolled and allocated to Gas A or B by telephone using computer-stratified block-randomization. Parents/legal guardians and clinical/study personnel were blinded to randomization sequence and allocation. Randomization codes remained secure until the end of the trial. For blinding, identical cylinders marked Gas A or B and identical equipment and connections were used. The CPAP oxygen dial was blanked off and FiO2 was regulated by the LED display. The air inlet to the CPAP device was modified to deliver Gas A or B using identical connectors.

### Statistical Methods

The primary endpoint (LoT) was analyzed blind, for all subjects, based on intention to treat, in order to determine any difference in LoT between treatment groups known as gas A and gas B. Subgroup LoT data was analyzed for FM, NC subjects and for CPAP subjects who were severe enough to warrant CPAP from the start. The Mann-Whitney test was used to compare LoT between treatment groups (as data was skewed), with results summarized as medians with interquartile ranges.
FIGURE 1
BREATHE treatment protocol.
(IQR). Fisher’s exact test was used to compare proportions progressing to CPAP in the two groups. All analyses were two tailed with an alpha level set at 0.05. STATA 10 and SPSS 17 were used for analysis. Change in respiratory distress over time measured by MWCAS was analyzed for all subjects as well FM and RSV positive (RSV+) subgroups. Mixed Models methodology was used since it takes into account correlated measures (gas type, gender, birth gestation, age, weight, virus status, temperature, heart rate, respiratory rate, SpO2). Due to the nature of the data, the square root transformation of MWCAS was used as the dependant variable for the modelling. The modelling and estimation of the effects of interest was carried out by the PROC MIXED routine in SPSS version 17, with a significance level set at 5%.

RESULTS

Participant Flow, Recruitment, Baseline Characteristics, and Numbers Analyzed

Infants presenting with any respiratory signs or symptoms were screened between the period of 2005 to 2008. A total of 361 patients with clinically diagnosed bronchiolitis were considered for eligibility. Consent was obtained for 319 subjects who were randomized and enrolled into the study. The consort flowchart (Fig 2) shows that 3 subjects were excluded (2 withdrawal of consent and 1 screening failure); therefore, 316 subjects were allocated to treatments. An additional 35 subjects were excluded because of protocol violation, consent withdrawal, screening failure, hospital clinician’s decision, or premature disruption of therapy. Thus,
281 subjects (140 Heliox and 141 Airox) with similar baseline characteristics (Table 2) completed the study, and their data was analyzed. The results are summarized in Table 3. There were no hospital readmissions for subjects who had completed or exited the trial.

**Length of Treatment**

Analysis of data from all 281 subjects showed no difference in median LoT between treatment groups [Heliox 1.90 days (interquartile range 1.08–3.17) compared to Airox 1.87 days (interquartile range 1.11–3.34), \( P = .41 \). However, LoT was significantly reduced in favor of Heliox for FM-tolerant subjects [Heliox, 1.46 days (interquartile range 0.85–1.95); Airox, 2.01 days (interquartile range 0.93–2.86); \( P = .03 \)].

A more notable reduction in LoT was seen in RSV+ subjects [Heliox, 1.31 days (interquartile range 0.61–1.91); Airox, 2.18 days (interquartile range 1.40–2.95); \( P = .004 \)]. There was no difference in LoT for NC subjects [Heliox 2.51 days (interquartile range 1.24–4.32); Airox 2.81 days (interquartile range 1.45–4.78); \( P = .53 \)].

**Impact on Respiratory Distress**

Heliox reduced respiratory distress in all 281 subjects across all time points and statistically significant at 8 hours onwards. MWCA (mixed models estimate = −0.1298, 95% confidence interval −0.202 to −0.057, \( P < .001 \)). Regardless of gas type, FM was more effective than NC (mixed models estimate = 0.093, 95% confidence interval 0.005 to 0.181, \( P = .04 \)).

**Adverse Events**

Six subjects required intubation for different reasons. In one case there was CPAP equipment malfunction which precipitated emergency reduction in proportions requiring CPAP in favor of Heliox, at borderline significance [3 of 27 Heliox subjects (11%) vs 10 of 31 Airox subjects (32%); odds ratio 0.26 (0.07–1.02), \( P = .76 \)].

---

**Table 2: Baseline Characteristics of Subjects in the Study**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Units</th>
<th>Heliox (N = 140)</th>
<th>Airox (N = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td>male:female ratio</td>
<td>1:1.59</td>
</tr>
<tr>
<td>Gestation at birth</td>
<td>wk</td>
<td>39.0 (38.0–40.0)</td>
<td>40.0 (39.0–40.0)</td>
</tr>
<tr>
<td>Age at presentation</td>
<td>wk</td>
<td>10.90 (5.85–25.50)</td>
<td>17.70 (6.80–28.40)</td>
</tr>
<tr>
<td>Weight at presentation</td>
<td>kg</td>
<td>5.65 (4.34–7.70)</td>
<td>5.70 (4.40–7.70)</td>
</tr>
<tr>
<td>NPA+ at presentation</td>
<td></td>
<td>111 (79.3%)</td>
<td>116 (82.3%)</td>
</tr>
<tr>
<td>Temperature</td>
<td>°C</td>
<td>37.0 (37.0–38.0)</td>
<td>37.0 (37.0–38.0)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>beats per min</td>
<td>152.0 (136.0–165.0)</td>
<td>148.5 (135.5–168.0)</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>breaths per min</td>
<td>56.0 (44.0–62.0)</td>
<td>53.0 (47.0–63.5)</td>
</tr>
<tr>
<td>SpO2 in room air</td>
<td>%</td>
<td>92.0% (89.0–95.0)</td>
<td>91.0% (89.0–94.0)</td>
</tr>
<tr>
<td>Modified Wood’s Clinical</td>
<td></td>
<td>Maximum score of 11</td>
<td>3.0 (2.0–3.0)</td>
</tr>
</tbody>
</table>

Values are medians and IQRs. NPA, nasopharyngeal aspirate virus detection.

---

**Table 3: Summary of BREATHE Findings**

<table>
<thead>
<tr>
<th>Impact on LoT</th>
<th>Intervention</th>
<th>N</th>
<th>Mean LoT (95% Confidence Interval), days</th>
<th>Median LoT (Interquartile Range), days</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>Heliox</td>
<td>140</td>
<td>2.268 (1.993 to 2.544)</td>
<td>1.902 (1.083–2.173)</td>
<td>.41</td>
</tr>
<tr>
<td></td>
<td>Airox</td>
<td>141</td>
<td>2.487 (2.180 to 2.794)</td>
<td>1.865 (1.114–3.344)</td>
<td></td>
</tr>
<tr>
<td>NC (±CPAP)</td>
<td>Heliox</td>
<td>40</td>
<td>2.952 (2.355 to 3.568)</td>
<td>2.505 (1.210–4.315)</td>
<td>.53</td>
</tr>
<tr>
<td></td>
<td>Airox</td>
<td>47</td>
<td>3.296 (2.643 to 3.948)</td>
<td>2.810 (1.450–4.780)</td>
<td></td>
</tr>
<tr>
<td>FM (±CPAP)</td>
<td>Heliox</td>
<td>44</td>
<td>1.538 (1.234 to 1.841)</td>
<td>1.464 (0.852–1.947)</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>Airox</td>
<td>40</td>
<td>2.236 (1.744 to 2.728)</td>
<td>2.006 (0.926–2.853)</td>
<td></td>
</tr>
<tr>
<td>FM (±CPAP), RSV+</td>
<td>Heliox</td>
<td>27</td>
<td>1.411 (0.982 to 1.841)</td>
<td>1.310 (0.608–1.906)</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td>Airox</td>
<td>31</td>
<td>2.456 (1.688 to 3.044)</td>
<td>2.179 (1.396–2.951)</td>
<td></td>
</tr>
<tr>
<td>CPAP LoT</td>
<td>Heliox</td>
<td>9</td>
<td>1.619 (1.301 to 1.934)</td>
<td>1.552 (1.380–2.013)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Airox</td>
<td>12</td>
<td>2.380 (1.773 to 2.986)</td>
<td>2.258 (1.844–2.727)</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of cases needing CPAP

| All cases | Heliox | 24/140 | 17% | 0.87 | .78 |
|           | Airox  | 27/141 | 19% | (0.47–1.60) |       |
| FM, RSV+  | Heliox | 3/27   | 11% | 0.26 | .07 |
|           | Airox  | 10/31  | 32% | (0.07–1.02) |       |

Impact on MWCA

<table>
<thead>
<tr>
<th>Results are Heliox effect relative to Airox over time</th>
<th>Comparison</th>
<th>Estimate of Fixed Effects (95% Confidence Interval)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>All patients</td>
<td>−0.1298 (−0.202 to −0.057)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FM relative to NC</td>
<td>FM relative to NC</td>
<td>0.003 (0.005 to 0.181)</td>
<td>.04</td>
</tr>
</tbody>
</table>
intubation. Two subjects suffered recurrent apnoeas immediately following enrolment (i.e. screening failure). One subject due to receive CPAP was intubated and transferred out because no high dependency bed available while one subject was intubated because of delay in high dependency bed availability. One subject had a previously undetected patent ductus arteriosus and was therefore referred to the cardiologists.

**DISCUSSION**

Bronchiolitis is a leading cause of infant hospitalization worldwide yet, to date, oxygen and supportive care are the mainstay of treatment for the vast majority of patients. The excellent safety profile and unique physical properties of Heliox position it as a potentially useful therapy for acute bronchiolitis. The BREATHE study found the delivery method of Heliox to be crucial to its efficacy: it was only beneficial if given by a tight-fitting FM or by CPAP. Thus, if delivered effectively, Heliox therapy significantly reduced length of hospital treatment at different points of care (ward, PICU). The BREATHE study was powered to detect a 0.75-day reduction in LoT. However, the statistically significant finding of a 0.55-day reduction in LoT in FM-tolerant patients is still a clinically useful finding, given the very significant pressure on hospital beds every winter imposed by bronchiolitis. Furthermore, given the need to justify the health-economic cost of Heliox, the results of the subgroup analysis support the rational use of Heliox in RSV+ patients who showed a greater reduction in LoT (0.87 day).

Heliox rapidly reduced respiratory distress, making it a potentially useful stabilization tool in emergency care. The effect was greater when considering RSV+ subjects (archetypical bronchiolitis), consistent with Martinon-Torres’ findings on his group of RSV+ subjects. However, the authors of that study found Heliox shortened the length of hospital stay. Because many other variables can affect the length of hospital stay, we chose to measure total LoT as the primary end point, because it is directly linked to therapy.

We found Heliox conferred no benefit over oxygen when delivered by NC at a flow rate of ≤3 L/minute. We believe the difference in efficacy between FM and NC is caused by several factors. A tight-fitting FM is used in clinical situations when the highest FiO2 needs to be delivered with minimal air entrainment. Delivering a high concentration of helium must also be very important for Heliox therapy, and our previous findings also provide support for use of the nonrebreathing FM. The use of an NC is subject to significant air entrainment, and thus variable FiO2, as demonstrated by Sung et al. The disadvantages of the NC would be magnified when using Heliox, a much lighter gas. Furthermore, in small infants, nasal prongs may also increase resistance to nasal airflow and work of breathing. It is not surprising therefore that NC therapy with Heliox at conventional flow rates is ineffective.

The BREATHE study was the only RCT thus far to investigate the rate of CPAP use in bronchiolitis. However, the observed 66% reduction only reached borderline statistical significance, which may be because of the relatively small number of CPAP subjects (n = 58). Martinon-Torres et al in their Heliox-CPAP study demonstrated a reduction in work of breathing and improved CO2 clearance. The BREATHE study also enabled assessment of the impact of Heliox on CPAP efficacy. We analyzed data for subjects who were started on CPAP from the beginning of the trial because their pathophysiology had not yet been altered by previous therapy. We found that CPAP duration was significantly reduced if Heliox was the driving gas for CPAP. The numbers of subjects totaled only 21, so we cannot draw any strong conclusions. However, if the finding of reduced treatment time was to be replicated in a larger CPAP study, this would represent a significant health-economic benefit for using Heliox to drive CPAP in cases of severe bronchiolitis. We did not select patients based on clinical severity but screened consecutive infants presenting with any respiratory signs or symptoms and found 361 patients with clinically diagnosed bronchiolitis. We could not rule out the possibility that some patients may have had asthma. However, any cases of asthma-bronchiolitis overlap would have been balanced out between the 2 treatment groups through the process of randomization. Virus detection from nasopharyngeal aspirate was carried out by the hospitals on 281 of the enrolled patients. We found 227 of 281 (≈80%) were virus positive, with RSV accounting for the vast majority. The centers routinely assayed only for RSV, para-influenza, adenovirus, Flu A/B, and rhinovirus. Therefore, the 80% virus positive rate (Table 2) was most likely an underestimate and we are confident that our clinical selection criteria captured mostly viral bronchiolitis.

The BREATHE study is the largest phase III, multicenter, double-blinded RCT of Heliox in bronchiolitis. It attempted to resolve the challenges of blinding. The use of special hosing material, identical in appearance for Heliox and Airox en-
study, we chose it as the delivery interface because it is readily available, and others\textsuperscript{13,16} had reported effective Heliox delivery by FM. Our previous research\textsuperscript{28,29} also found that a tight-fitting 3-valve, nonrebreathing FM would deliver the highest concentration of oxygen and helium. However, FMs are generally poorly tolerated in young children, and this was also our experience. To maximize FM compliance in their study, Martinón-Torres et al\textsuperscript{16} used swaddling to comfortably restrain subjects with the FM held against the face by soft elasticized tube netting applied over the head. We used a bonnet to allow a tighter-fitting 3-valve, nonrebreathing FM to deliver the highest concentration of oxygen and helium. However, FMs are generally poorly tolerated in young children, and this was also our experience. To maximize FM compliance in our study, Martinón-Torres et al\textsuperscript{16} used swaddling to comfortably restrain subjects with the FM held against the face by soft elasticized tube netting applied over the head. We used a bonnet to allow a tighter-fitting FM and help prevent the elastic band from slipping down, used swaddling, and encouraged staff and mothers to maximize compliance. Despite our best efforts, many subjects did not tolerate the FM, and it proved impossible to apply it continuously. Mask intolerance was highlighted after recruitment of the first few subjects into the trial when we found nursing staff wishing to use an NC, the commonly used mode of oxygen delivery for infants. It was considered unethical to withhold a trial gas treatment if subjects had already started to improve. We therefore considered delivery of trial gas via NC because Williams et al\textsuperscript{31} successfully used NC with Heliox in infants, and oxygen is already conventionally administered via NC. Therefore, NC was included as a protocol amendment for subjects who were FM intolerant.

We prospectively studied a cohort of clinically diagnosed bronchiolitic infants, regardless of severity and viral etiology, enabling us to identify a treatment for bronchiolitis that can be used across different modalities (FM and CPAP) and points of care (emergency department, ward, and PICU). Nonetheless, this approach to recruitment resulted in a smaller proportion of severe cases, making it difficult to conclusively study outcomes such as CPAP. The latter is very important because CPAP compared with standard treatment has been shown to improve ventilation, with a reduction in hypercapnea,\textsuperscript{32} with growing consensus that CPAP therapy prevents deterioration and need for mechanical ventilation.

We did not collate data on length of stay but rather focused on length of treatment. The study was powered for the latter because LoT was a clear and definitive endpoint in the disease process. The BREATHE study was not powered to investigate intubation rates, which would also have been informative. Only 8 of 316 (2.8%) needed intubation. Therefore, a much larger sample size or a moderate number of a more selected severe group of patients would be needed to investigate the impact of Heliox on intubation rates. The BREATHE protocol (part B, not yet carried out) had originally been designed to investigate intubation rate in a more severe subgroup of bronchiolitics (defined as already requiring CPAP). A baseline figure of 35% was assumed for the bronchiolitis intubation rate (defined as CPAP failure) derived from data for our PICU at St Mary's hospital. The power calculation showed that a total of 86 severe bronchiolitics on CPAP would need to be recruited to detect a reduction in the intubation rate from 35% to 10% with 80% power.

The BREATHE study has highlighted the need to review our approach to respiratory care in general: use of FM has tolerance issues, and NC (at conventional flow rates) has limited efficacy. Although NC delivery of Heliox at flow rates <3 L/minute was ineffective, we theorize that at higher flow rates (tolerated based on our anecdotal experience), Heliox therapy by nasal cannula may be effective. A well-designed RCT comparing 3-valve nonrebreathing FM versus high-flow NC therapy is needed to identify the optimal method of delivery. Furthermore, a sufficiently powered RCT of Heliox-driven versus conventional Airox-driven CPAP would determine whether Heliox reduces the need for mechanical ventilation.

In the meantime, the clinical practice recommendations arising from the BREATHE study findings are as follows:

- Heliox therapy should be started for bronchiolitic infants who require hospital admission for treatment of hypoxemia or respiratory distress.
- If the use of Heliox therapy needs to be rationalized, it could be targeted to those who are RSV positive.
- Heliox therapy should only be delivered via a tight-fitting nonrebreathing FM or CPAP, as per the protocol outlined in the BREATHE study.

CONCLUSIONS

The BREATHE study showed that the delivery method of Heliox is critical to its efficacy. Heliox is effective if delivered via a tight-fitting nonrebreathing FM or CPAP but not via a NC at conventional flow rates. With effective delivery, Heliox reduces the LoT, alleviates respiratory distress, improves CPAP efficacy, and may reduce the need for CPAP. A more acceptable patient interface for effective delivery remains the challenge for industry if Heliox is to be more widely used in pediatric respiratory care.

ACKNOWLEDGMENTS

We thank the patients, families, and nursing, medical, and other healthcare staff across all the hospitals, whose cooperation and support allowed us to undertake the BREATHE trial. We especially thank the BREATHE team members whose meticulous attention to trial conduct ensured the rigor of this study.
REFERENCES


17. Martín-Torres F, Rodríguez-Núñez A, Martín-Sánchez JM. Nasal continuous positive airway pressure with heliox in infants with acute bronchiolitis. Respir Med. 2006;100(8):1458–1462


(Continued from first page)
**Heliox Therapy in Bronchiolitis: Phase III Multicenter Double-Blind Randomized Controlled Trial**

Mina M. Chowdhury, Sheila A. McKenzie, Christopher C. Pearson, Siobhan Carr, Caroline Pao, Arvind R. Shah, Elizabeth Reus, Joseph Eliahoo, Fabiana Gordon, Hubert Bland and Parviz Habibi

*Pediatrics* 2013;131:661; originally published online March 18, 2013; DOI: 10.1542/peds.2012-1317

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/131/4/661.full.html">http://pediatrics.aappublications.org/content/131/4/661.full.html</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 29 articles, 4 of which can be accessed free at: <a href="http://pediatrics.aappublications.org/content/131/4/661.full.html#ref-list-1">http://pediatrics.aappublications.org/content/131/4/661.full.html#ref-list-1</a></td>
</tr>
<tr>
<td>Citations</td>
<td>This article has been cited by 1 HighWire-hosted articles: <a href="http://pediatrics.aappublications.org/content/131/4/661.full.html#related-urls">http://pediatrics.aappublications.org/content/131/4/661.full.html#related-urls</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): <strong>Respiratory Tract</strong> <a href="http://pediatrics.aappublications.org/cgi/collection/respiratory_tract">http://pediatrics.aappublications.org/cgi/collection/respiratory_tract</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://pediatrics.aappublications.org/site/misc/Permissions.xhtml">http://pediatrics.aappublications.org/site/misc/Permissions.xhtml</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://pediatrics.aappublications.org/site/misc/reprints.xhtml">http://pediatrics.aappublications.org/site/misc/reprints.xhtml</a></td>
</tr>
</tbody>
</table>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.