

# Heliox-Driven Albuterol Nebulization for Asthma Exacerbations: An Overview

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### Summary

**Our understanding of albuterol nebulization driven by helium-oxygen mixture (heliox) has matured with recent advances in clinical therapy, delivery systems, and understanding of dosing; this has led to substantial improvements in delivery as well as refinements of research protocols for asthma exacerbations. This review begins with heliox inhalation therapy and then addresses heliox as a driving gas for nebulization. Technical considerations are reviewed, including optimal gas mixtures, flow-rate adjustment factors, and nebulizer setup. Key words: heliox, asthma, albuterol, radionuclide, nebulizer.** [Respir Care 2006;51(6):613–618. © 2006 Daedalus Enterprises]

## Introduction

The clinical use of helium-oxygen mixture (heliox) was first described by Barach in 1935 as a therapy for asthma

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exacerbations. Barach found that heliox relieved dyspnea in patients with severe asthma and upper-airway obstruction.<sup>1</sup> Later investigators also examined the utility of heliox for asthma exacerbations.<sup>2–4</sup> Heliox is a low-density gas mixture that improves ventilation,<sup>5–6</sup> respiratory acidosis, and oxygenation, and decreases  $P_{aCO_2}$  during severe asthma exacerbations.<sup>2,7</sup>

Traditionally,  $\beta_2$  agonist bronchodilators have been nebulized with air or oxygen. However, in recent years heliox-driven  $\beta_2$  agonist nebulization has gained wider use and may be cost-effective in ICU settings.<sup>8</sup> This use has increased in both emergency departments and intensive care units, where patients are often seen during severe asthma exacerbations.

Heliox has the potential benefit of being able to carry aerosols deeper (than air or oxygen) into the distal airways during severe airway obstruction,<sup>9,10</sup> which might translate to higher deposition at the  $\beta_2$  agonist site of action in the distal lung and, therefore, greater bronchodilation.

Heliox-driven  $\beta_2$  agonist nebulization therapy has some disadvantages and limitations. One is that a hypoxic patient may require a higher fraction of inspired oxygen ( $F_{IO_2}$ ) than the 20% or 30% oxygen in the standard available heliox mixtures of 80% helium/20% oxygen (80:20 heliox) or 70:30 heliox.<sup>11</sup> This can be addressed by adding oxygen to the inhaled gas to increase the  $F_{IO_2}$ , which decreases the percentage of helium in the mixture and might mean less distal aerosol deposition, but this lower-percentage-of-helium mixture might still benefit the hypoxic patient (see below). A second disadvantage is that heliox-driven  $\beta_2$  agonist nebulizer systems might initially be considered complicated and confusing by health-care providers. As with any new therapy and technology, there is a learning and optimization period.

This paper reviews the history of heliox therapy for asthma exacerbations, evaluates published adult and pediatric radionuclide studies of heliox-driven nebulization, and discusses the adult and pediatric clinical studies of heliox-driven  $\beta_2$  agonist nebulization therapy and the controversies concerning optimal flow rate and nebulizer setup.

### Heliox Inhalation Therapy

Helium has a long history of safe use in respiratory medicine, and it is the principle inert gas used in deep-sea dives to > 150 feet.<sup>12</sup> Despite its demonstrated safety and the fact that Barach used the same mixture for patients with asthma in 1935,<sup>1</sup> heliox is not considered one of the main treatment adjuncts for pediatric patients with status asthmaticus. Several reports have described heliox benefits in adults. Gluck et al reported 7 intubated adults who had improved ventilation and decreased respiratory acidosis with 60:40 heliox.<sup>13</sup> According to Shiue and Gluck, 10 adult patients with status asthmaticus treated in the emergency department with heliox had substantial reversal of acidosis, none required intubation, and most sensed immediate reduction in shortness of breath with heliox.<sup>5</sup> Kass and Terregino reported that heliox rapidly improved ventilation in 23 asthmatic patients.<sup>3</sup>

For severe asthma, 2 recent pediatric trials found different results with heliox. Kudukis et al assessed 18 children who were being treated with continuous albuterol, and randomized them to 15 min of either 80:20 heliox or room air.<sup>14</sup> They found significantly better improvement in pulsus paradoxus, peak flow, and dyspnea in the heliox group.

Carter et al assessed pulmonary function in 11 children who had been hospitalized for asthma and were randomized to 70:30 heliox or room air.<sup>6</sup> There was no difference in forced expiratory volume in the first second, and peak flow was only slightly better in the heliox group. One possible explanation for the difference between the latter 2 studies was that the severity of illness in the patients in the

Carter et al study<sup>6</sup> was probably less than that of the patients in the Kudukis et al study,<sup>14</sup> as all of the patients in the Carter et al study were well enough to perform pulmonary function tests. In contrast, 3 patients in the Kudukis et al study were being prepared for intubation,<sup>14</sup> which was apparently averted by heliox administration. Of note, both of these pediatric studies had the important limitation that the therapies prior to the initiation of heliox were different.

Most studies of heliox use during asthma exacerbations have evaluated helium as a means of decreasing airway resistance, improving flow, and averting respiratory failure or facilitating mechanical ventilation. The outcome measures in those studies included peak expiratory flow, pulsus paradoxus,<sup>4</sup> peak airway pressure during mechanical ventilation,<sup>2</sup>  $P_{aCO_2}$ , pH while the patient was actively breathing heliox,<sup>5,13</sup> and ventilatory variables.<sup>3</sup> These studies examined the value of heliox for temporizing respiratory distress; they did not use heliox to drive albuterol nebulization.

### Mechanisms of Improved Aerosol Delivery

Helium is a biologically inert gas that has no bronchodilating or anti-inflammatory properties. It has a lower density than air and oxygen, and that lower density has several theoretical benefits for patients with airway disease.<sup>15</sup> The lower density of heliox provides higher flow with a given pressure, in turbulent or near-turbulent flows (ie, lower resistance). Heliox also provides higher flow through obstructed airways.<sup>16</sup> Less momentum loss in the high-resistance upper airways and through obstructed regions probably provides better ventilation of and aerosol delivery to the smaller airways and alveoli.<sup>17</sup>

Another theory contends that the lower density of heliox prevents the transition from laminar to turbulent flow. Nonturbulent flow would also have less resistance in the lung. Turbulence in the flow may also affect aerosol deposition, though this has not been proven.<sup>15</sup>

Higher minute volume is attainable with heliox, which might increase aerosol delivery to the lung periphery.<sup>17,18</sup> Heliox aerosol-delivery systems suffer less particle-impaction drug loss within the delivery system, thus increasing the dose available to the lungs.<sup>17,19</sup>

### Radionuclide Studies

In 1993, using an inhaled radionuclide deposition study, Anderson et al were among the first to observe the benefit of heliox as a driving gas for pulmonary aerosol deposition.<sup>9</sup> They concluded that heliox was significantly more effective than air in depositing 3.6- $\mu$ m particles in alveolar regions, and that improvement was more pronounced in asthmatic subjects than in healthy subjects.

Subsequently, Darquenne and Prisk used a radionuclide approach to compare upper-respiratory-tract deposition with 80:20 heliox versus air.<sup>20</sup> They concluded that heliox might reduce deposition in the upper respiratory tract and increase deposition in the distal airways and alveoli. That might partly explain the higher peripheral lung deposition in the other radionuclide studies.

Piva et al recently published radionuclide data from pediatric asthma patients. They found better pulmonary aerosol delivery with 80:20 heliox than with oxygen.<sup>10</sup> They concluded that heliox has a strong and pronounced effect in patients with severe lower-airway obstruction, and that increased aerosol delivery to distal airways may improve drug deposition and more rapidly resolve acute bronchospasm.

### Heliox as a Driving Gas for Nebulization

#### Adult Studies

Recently, heliox has been studied as the driving gas for nebulizing  $\beta_2$  agonist bronchodilator in the treatment of asthma exacerbations in both adult and pediatric patients (Table 1).<sup>21–29</sup> These studies have had different results, possibly due to differences in methods, severity of the

asthma exacerbations, aerosol delivery technique, patient characteristics, and duration of therapy.

In 2002, Henderson and colleagues studied 205 adult patients with mild-to-moderate asthma.<sup>25</sup> A 70:30 heliox mixture used to drive albuterol nebulization conferred no clinical benefit. This lack of effect may have been due to several limitations, and, as Kress et al noted, Henderson et al did not thoroughly describe their heliox-delivery system.<sup>21(25)</sup> Corcoran and Gamard pointed out the importance of using a closed system with a large-volume nebulizer and reservoir to prevent entrainment of room air, which dilutes the helium concentration.<sup>17</sup> Similarly, Rose et al studied 36 patients and found no difference in peak expiratory flow, forced expiratory volume in the first second, respiratory rate, or oxygen saturation after 2 hours of continuous heliox administration.<sup>27</sup> However, that study was limited by an inadequate sample size.

In contrast, in 2002 Kress et al studied 45 adult asthmatics and found that albuterol nebulized with heliox improved spirometry values more than did albuterol nebulized with oxygen.<sup>21</sup> They hypothesized that the difference was due to better distal-airway albuterol deposition with the heliox.

Similarly, in 2005, Lee et al found in a study with 80 adult asthmatics that spirometry values were significantly

Table 1. Clinical Studies of Heliox As the Driving Gas for Asthma Medications

First Author	Year	Number of Subjects	Subject Ages (y)	Large-Volume Nebulizer or Reservoir Used	Primary Results
<u>Studies That Found Benefit From Heliox-Driven Nebulization</u>					
Kress <sup>21</sup>	2002	45	< 50	Yes	Better improvement in FEV <sub>1</sub> with heliox than with air.
Bag <sup>22</sup>	2002	31	18–44	Yes	Better improvement in FEV <sub>1</sub> , FVC, and PEF with heliox.
Sattonnet <sup>23</sup>	2004	205	Unknown	Unknown	Significant improvement in PEF at 20, 40, and 60 min with heliox; lower intubation rate with heliox.
Lee <sup>24</sup>	2005	80	> 18	Yes	More rapid and greater improvement in PEF with heliox than with oxygen. Older patients benefited from heliox.
Kim <sup>11</sup>	2005	30	2–18	Yes	Significant better clinical scores at 120, 180, and 240 min, and lower rate of hospital admission with heliox.
<u>Studies That Found Little or No Benefit From Heliox-Driven Nebulization</u>					
Henderson <sup>25</sup>	1999	205	18–65	Unknown	No differences in improvement of PEF or FEV <sub>1</sub> .
Dorfman <sup>26</sup>	2000	39	8–55	No*	No difference in PEF. More admissions in heliox group.
Rose <sup>27</sup>	2002	36	18–55	Yes	Improvement in Borg dyspnea score with heliox than with oxygen. No improvement in respiratory rate, oxygen saturation, PEF, or FEV <sub>1</sub> .
Lanoix <sup>28</sup>	2003	94	19–55	Unknown	No difference in PEF, FEV <sub>1</sub> , time to best PEF/FEV <sub>1</sub> , emergency-department stay, or admission rate.
Rivera <sup>29</sup>	2006	41	3–16	Unknown	No difference in clinical scores at 10 and 20 min. Trend toward significant difference at 20 min.

heliox = helium-oxygen mixture

FEV<sub>1</sub> = forced expiratory volume in the first second

FVC = forced vital capacity

PEF = peak expiratory flow

\* Study gas added to inhalation circuit at 10 L/min proximal to oxygen-driven nebulizer.

better with 80:20-heliox-driven (than with oxygen-driven) albuterol nebulization. They found that older patients got the most benefit from heliox-driven nebulization.<sup>24</sup>

Finally, in 2004, Sattouet et al reported on spirometry values from 205 adult asthmatic patients who received 65:35 heliox-driven albuterol.<sup>23</sup> This study was a randomized double-blind multicenter trial. They observed a significantly lower intubation rate in the heliox group than in the control group. That observation was the first of its kind, and it fits well with the clinical experience of heliox-driven albuterol as a potentially useful adjunct to avoid respiratory failure and intubation.

### Pediatric Studies

Kim et al recently published the first prospective randomized single-blind pediatric study of heliox-driven albuterol nebulization with moderately-to-severely ill pediatric asthmatic patients.<sup>11</sup> Including children younger than 6 years of age necessitated using the Pulmonary Index clinical score (as opposed to pulmonary function test results) as the primary outcome measure. We found that continuous heliox-driven nebulization of albuterol early in the course of emergency-department care substantially improved the Pulmonary Index score. We also observed a statistically significant difference between the heliox and control groups in the unblinded discharge rate at the 12-hour treatment point. A trend was also noted toward earlier emergency-department discharge in the heliox group (66%) than in the oxygen group (33%).

Rivera et al studied a similar pediatric asthmatic population, but they used a different clinical asthma score, the Modified Dyspnea Index.<sup>29</sup> They found no statistically significant differences in clinical asthma score at 10 min or 20 min after initiation of heliox-driven albuterol therapy, but, interestingly, they observed a trend toward significance at the 20-min time point.

It is important to note that the study by Kim et al<sup>11</sup> found significant differences in clinical asthma score between the heliox and oxygen groups after 2 hours of therapy, and these differences were increased and sustained at the 3-hour and 4-hour time points. The longer duration of heliox-driven albuterol therapy, as well as the greater number of observation time points, may have led to different findings between the Kim et al<sup>11</sup> and Rivera et al<sup>29</sup> studies.

### Technical Considerations

#### Optimal Gas Mixture

There have been considerable differences between the various clinical trials as to the optimal mixture of heliox.<sup>11,21,23–25,27,29</sup> The heliox mixtures have ranged from

65:35 to 80:20 heliox. Some investigators defined “heliox failure” as a patient requiring an  $F_{IO_2} > 0.5$ .<sup>11</sup>

The main drawback of 80:20 heliox is the potential for hypoxemia in patients with severe asthma exacerbations.<sup>11,21</sup> A simple solution is to add more oxygen to the inhaled gas,<sup>11</sup> but this decreases the helium concentration, making the inhaled gas denser, which might decrease peripheral aerosol delivery. However, recent studies suggest that a 65:35 heliox does offer clinical benefit. Our clinical experience has been that it is not unusual to see benefit with helium concentrations as low as 40–50%, and we subsequently increase the helium percentage as the patient’s hypoxemia and overall clinical status improve.

#### Flow Rate

There is debate as to the optimal flow rate for heliox-driven nebulization. In clinical studies the flow rates have ranged from 11 L/min to 16 L/min, which may be one explanation for the different results among the studies.<sup>11,21,23–25,27</sup> Hess et al found that the flow rate must be sufficient to generate an optimal-size respirable particle.<sup>30</sup> Corcoran and Gamard found, with a small-volume nebulizer, that 12 L/min of 70:30 heliox is needed to generate an equivalent mass of particles  $< 3 \mu\text{m}$ , compared to 10 L/min of oxygen.<sup>17</sup>

An important consideration is that a standard oxygen-calibrated ball-valve flow meter will underestimate heliox flow rate. Corcoran and Gamard found that 80:20 heliox requires a conversion factor of 1.8, and 70:30 heliox requires a conversion factor of 1.6, when measured with an oxygen-calibrated ball-valve flow meter.<sup>17</sup> For example, with 70:30 heliox delivered through an oxygen-calibrated flow meter, a reading of 10 L/min indicates an actual flow 16 L/min. This conversion factor is critical, because an unconverted, inaccurate flow may lead to poor generation of aerosol particles and, therefore, falsely negative clinical results.

#### Large-Volume Nebulizer and Reservoir

Use of a large-volume nebulizer and reservoir may be important when using heliox to deliver aerosol drugs (Fig. 1). Corcoran and Gamard noted that 5 out of 5 positive studies used the large-volume-nebulizer-with-reservoir approach for nebulizing albuterol with heliox,<sup>17</sup> and that a reservoir large enough to accommodate larger tidal volumes is useful during heliox nebulization. Larger patients such as teenagers and adults may have minute-ventilation requirements that exceed the output rate of small-volume nebulizers. To avoid entrainment of room air and consequent dilution of heliox mixtures, Corcoran and Gamard suggest using a large-volume nebulizer and a reservoir bag.

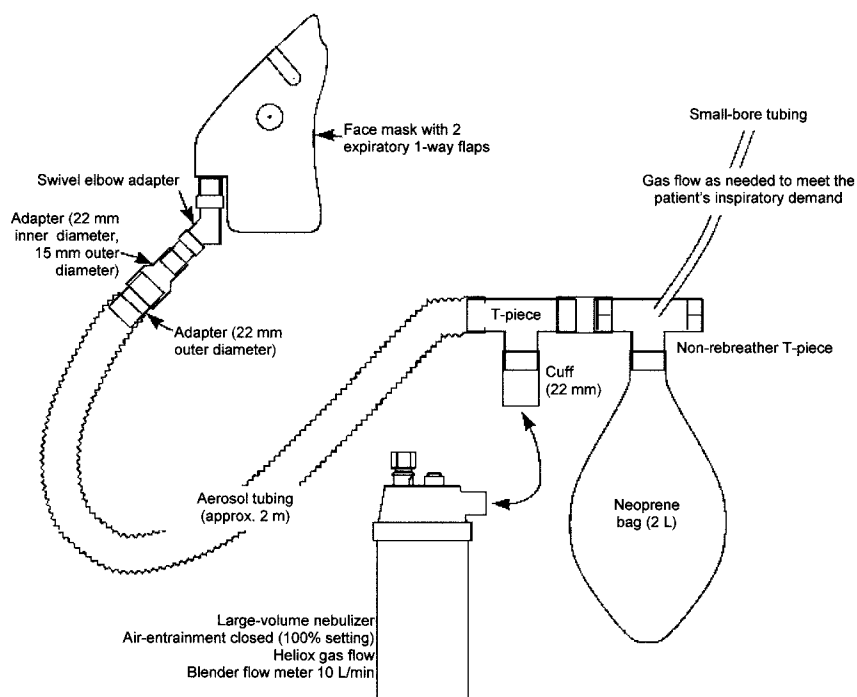


Fig. 1. Large-volume nebulizer circuit, with reservoir, for use with helium-oxygen mixture (heliox).

### Summary

Heliox-driven albuterol nebulization is generating increased interest, and most of the recent clinical adult and pediatric studies have found that heliox benefits patients in severe asthma exacerbations. Further studies are needed to determine the role of heliox-driven albuterol nebulization in the care of asthma exacerbations in the emergency department and intensive care unit.

The health-care provider faces several choices when a patient's asthma exacerbation does not respond well to conventional  $\beta_2$ -agonist and corticosteroid therapy. The options include heliox-driven albuterol therapy, parenteral  $\beta_2$ -agonist therapy, parenteral or inhaled magnesium therapy, and noninvasive positive-pressure ventilation. Larger studies are needed on emergency-department admission rates, intensive-care-unit and hospital stay, and intubation rate to determine the best approach for escalating care of patients suffering asthma exacerbations.

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