The Effect of Heliox in Acute Severe Asthma*

A Randomized Controlled Trial

Jonathan E. Kass, MD, FCCP; and Carol A. Terregino, MD

**Study objectives:** To evaluate the effect of heliox on airflow obstruction and dyspnea in patients with acute severe asthma.

**Design:** A prospective, randomized, controlled study.

**Setting:** A university hospital.

**Patients:** Twenty-three patients presenting to the emergency department with acute severe asthma were randomized to receive 70%/30% heliox or 30% oxygen.

**Measurements:** Peak expiratory flow (PEF), dyspnea score, heart rate, respiratory rate (RR), and BP were measured at baseline and 20, 120, 240, 360, and 480 min after starting the test gas. After baseline, the PEF was measured by using the gas that was randomized to the treatment program.

**Results:** In the first 20 min, there was a 58.4% increase in percent predicted PEF (%PEF) in the heliox group (p < 0.001), whereas there was only a 10.1% increase in %PEF for the oxygen group (p > 0.1). Eighty-two percent of the heliox group had > 25% improvement in %PEF at 20 min, whereas only 17% of the oxygen group did (p < 0.01). The next significant improvement in %PEF in the heliox group occurred at 480 min. At the end of the study in the heliox group, the PEF did not significantly (p > 0.1) change immediately after the heliox was discontinued (270.6 to 264.2 L/min). In the heliox group in the first 20 min, there was a significant decrease in dyspnea score and RR (p < 0.05), but there were no further significant improvements for the rest of the study.

In the oxygen group, no variables significantly improved until 360 min.

**Conclusion:** Heliox rapidly improves airflow obstruction and dyspnea in patients with acute severe asthma and may be useful as a therapeutic bridge until the corticosteroid effect occurs.

(CHEST 1999; 116:296–300)

**Key words:** asthma; heliox; helium; status asthmaticus

**Abbreviations:** Fio₂ = inspired oxygen fraction; PEF = peak expiratory flow; %PEF = percent predicted PEF; RR = respiratory rate

Although helium was first used by Barach to treat asthma in 1935,¹ it did not gain widespread acceptance. Only recently has the use of helium-oxygen (heliox) mixtures in the treatment of acute severe asthma been rediscovered.²–⁶ Heliox has been shown to quickly improve ventilation in nonintubated and intubated patients with acute severe asthma and respiratory acidosis²–⁴ and to lower airway pressures in intubated patients.³ It has also been shown to rapidly decrease airway resistance and dyspnea in nonintubated patients with severe asthma.⁵

Because heliox has not been tested in a randomized controlled study, its efficacy has been questioned. The possibility has been raised that concomitant conventional treatment for asthma may explain its beneficial effects.⁷ In one review, it has been relegated to the group of unproved alternative therapies for acute severe asthma.⁸ The optimal duration of heliox therapy for acute severe asthma is not known. It has been postulated to be 6 to 12 h,⁴ which is the reported range of time for the effect of IV corticosteroids to occur.⁹

Because patients with acute asthma report less dyspnea with heliox,⁵ the purpose of our study was to assess in a randomized, controlled fashion whether this subjective response was associated with an acute improvement in airflow obstruction as measured by

*From the Division of Pulmonary and Critical Care Medicine (Dr. Kass), and the Department of Emergency Medicine (Dr. Terregino), Cooper Hospital/University Medical Center, UMDNJ/Ro[...](http://publications.chestnet.org/pdff accessed ashx?url=/data/journals/chest/21930/ on 04/29/2017)
peak expiratory flow (PEF), and whether the effect of heliox is maintained during the subsequent 8-h period.

Materials and Methods

The study was reviewed and approved by our Institutional Review Committee. We enrolled 23 adult subjects who presented with acute severe asthma to the Cooper Hospital/University Medical Center Emergency Department from 1992 to 1995. Patients between 18 and 50 years of age were eligible if they had a clinically severe exacerbation of asthma, as defined by a peak flow of < 200 L/min after treatment with 5 mg of nebulized albuterol. The diagnosis of asthma was made from the patient’s history or from the medical record, consistent with the American Thoracic Society criteria.10 The exclusion criteria included a smoking history defined as > 10 pack-years total or any smoking in the prior year, a known history of chronic bronchitis or emphysema, chronic PCO₂ retention (PCO₂ > 45 mm Hg with pH > 7.35), coronary artery disease, congestive heart failure, cardiac arrhythmias, or current endotracheal intubation.

All patients were initially treated with IV methylprednisolone, 125 mg, and two 2.5-mg nebulized albuterol treatments. If they did not clinically improve and their PEF remained < 200 L/min, they were then randomized to receive a 70% helium/30% oxygen (heliox) gas mixture via a nonrebreathing mask or 30% oxygen via a Venturi mask. The patients received their test gas approximately 1 h after initiation of treatment. It was determined that it was not possible to maintain blinding in the study, because different masks were needed to control for the inspired percentage of oxygen and patients’ voices change with heliox. Immediately before receiving the randomized test gas, an arterial blood gas was drawn and a peak flow measurement, dyspnea score, respiratory rate (RR), heart rate, and systolic and diastolic BP were obtained. These parameters, except for the arterial blood gas, were repeated at 20, 120, 240, 360, and 480 min after starting the test gas. After baseline, the PEF was measured using the gas that was randomized to the treatment program. At 8 h the study was terminated. The parameters were repeated in the heliox group immediately after the heliox was discontinued in order to assess whether there was a clinical effect of heliox after 8 h. Nebulized albuterol, 2.5 mg, was given every 2 h for the 8-h duration, but none was given in the 30 min before or in the first 20 min after the test gas was started. The patients were monitored with continuous pulse oximetry. If a failure occurred to maintain a saturation of ≥ 90% on 30% inspired oxygen fraction (FiO₂), they were withdrawn from the study.

PEF was measured with an Assess Peak Flow Meter (Health Scan Products Inc; Cedar Grove, NJ). The patient was instructed in the proper use of the peak flowmeter by a respiratory therapist, and the value was measured as the highest of three maneuvers. After taking a deep breath of the test gas, the PEF maneuver was performed with a forced expiration into the peak flowmeter. PEF was reported as percent predicted PEF (%PEF).11 The dyspnea assessment was performed from a visual analog dyspnea scale from 0 to 10 (10 being the maximal shortness of breath).12 Because the pretest gas FiO₂ varied, oxygenation was reported as the ratio of PaO₂ to alveolar oxygen tension (respiratory exchange ratio is assumed to be 0.8), which has been shown to remain stable with changing FiO₂.11

Statistical Analysis

When assessing the difference between groups, the values were expressed as mean ± SEM. A multivariate analysis of variance with repeated measures was used to assess the differences between and within groups vs time. Two-tailed Student’s t tests were used to analyze variables between groups. A 25% increase in PEF at 20 min was determined to be a clinically significant improvement.14 A Fisher’s Exact Test was used to analyze the difference between the groups in 25% improvement in PEF at 20 min. We based our sample size on the prediction that 80% of the heliox group and 20% of the oxygen group would have a clinically significant improvement in PEF. For α = 0.05 and β = 0.2, 11 subjects would be needed in each group.

Results

There were no significant differences between the groups for gender, age, smoking history, years of asthma, duration of asthma exacerbation, or arterial blood gas findings (Table 1). Before the study, 20 patients were maintained on an inhaled β-agonist, 6 patients on theophylline, 3 patients on oral corticosteroids, and 5 patients on inhaled corticosteroids, and there were no significant differences between the groups for these prestudy medications (p > 0.1). Nineteen of the 23 subjects (83%) were known asthmatics from previous hospital records.

At baseline before the institution of the test gas, the only significant difference between the heliox and oxygen groups was that the heliox group had a higher RR (Table 2). Notably, there was not a significant difference between the groups for PEF and %PEF. Additionally, there were no significant differences between the groups for accessory muscle use or for systolic and diastolic BP (p > 0.1). Only one patient, who was in the oxygen group, required endotracheal intubation and mechanical ventilation. Two patients in each group improved enough clinically to be discharged from the emergency department before 480 min (two patients in the heliox group and one patient in the oxygen group were discharged by 240 min, and one patient in the oxygen group was discharged by 360 min). The data from these five patients were not included in the 8-h analysis.

<table>
<thead>
<tr>
<th>Table 1—Entry Data*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry Data</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Years of asthma</td>
</tr>
<tr>
<td>Smoking history</td>
</tr>
<tr>
<td>Hours of exacerbation</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>PCO₂, mm Hg</td>
</tr>
<tr>
<td>PaO₂/FiO₂, mm Hg</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SEM unless otherwise indicated. p > 0.1 for all comparisons of heliox with oxygen. PaO₂ = alveolar oxygen tension.
Both the heliox and the oxygen group showed a significant \((p < 0.001\) and \(p < 0.05\), respectively) improvement in %PEF during the 8 h of the study (Fig 1). There was not a significant difference between the groups at each time (\(p > 0.1\)) for %PEF; however, during the entire study, there was a significant difference between the groups (\(p < 0.001\)). In the first 20 min in the heliox group there was a 58.4% increase in %PEF (\(p < 0.01\)), whereas in the oxygen group, there was a 10.1% increase in %PEF (\(p > 0.1\)). In the heliox group, 9 of 11 patients (82%) had a \(>25\%\) increase in %PEF at 20 min, whereas only 2 of 12 patients (17%) in the oxygen group did so (\(p < 0.01\)).

After the first 20-min period in the heliox group, there was not another significant improvement in %PEF until 480 min (\(p < 0.01\)). For the oxygen group, the first significant improvement in %PEF occurred at 360 min (\(p < 0.05\)). For the heliox group at the end of the study, there was not a significant difference in PEF on and off heliox (270.6 to 264.2 L/min; %PEF, 50.4% to 49.2%; \(p > 0.1\)).

There were no interactions of test gas and dyspnea score, RR, heart rate, and systolic and diastolic BP vs time between the groups (\(p > 0.1\)). However, during the first 20 min, the heliox group showed a significant decrease in dyspnea score and RR (Table 2).

### Table 2—Comparison of Variables in Heliox vs Oxygen Groups*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Time 0</th>
<th>20 min</th>
<th>480 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF, L/min</td>
<td>Heliox</td>
<td>120.9 ± 12.0</td>
<td>194.1 ± 20.6</td>
<td>270.6 ± 31.3</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>140.0 ± 12.0</td>
<td>154.2 ± 18.2</td>
<td>235.0 ± 23.2</td>
</tr>
<tr>
<td>%PEF</td>
<td>Heliox</td>
<td>26.2 ± 8.2</td>
<td>41.5 ± 9.9</td>
<td>57.4 ± 14.5</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>30.6 ± 9.4</td>
<td>33.7 ± 14.5</td>
<td>50.4 ± 16.0</td>
</tr>
<tr>
<td>Dyspnea score</td>
<td>Heliox</td>
<td>6.18 ± 0.76</td>
<td>3.81 ± 0.56</td>
<td>1.56 ± 0.31</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>4.94 ± 0.85</td>
<td>3.13 ± 0.72</td>
<td>1.22 ± 0.37</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>Heliox</td>
<td>30.1 ± 1.71</td>
<td>22.8 ± 3.91</td>
<td>20.6 ± 1.51</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>24.3 ± 1.3</td>
<td>21.5 ± 4.0</td>
<td>22.0 ± 1.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>Heliox</td>
<td>115.4 ± 6.0</td>
<td>101.1 ± 5.2</td>
<td>104.9 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>104.6 ± 7.2</td>
<td>101.5 ± 7.6</td>
<td>104.0 ± 7.4</td>
</tr>
</tbody>
</table>

*Values are mean ± SEM.
†\(p < 0.05\) between groups.
‡\(p < 0.05\) compared with time 0.
§\(p < 0.001\) compared with time 0.
¶\(p < 0.01\) compared with time 20 min.
∥\(p < 0.05\) compared with time 20 min.

This is the first study to demonstrate in a prospective, randomized, controlled fashion that heliox causes both a rapid improvement in peak flow and a decrease in dyspnea in adult patients with acute severe asthma that is maintained for at least 8 h. Similar objective improvements have been demonstrated in children.15,16 All of the heliox patients had a \(>20\%\) increase in %PEF at 20 min, whereas only two patients of the oxygen group did. Helium, because of its lower density than nitrogen or oxygen and its reduction of the Reynolds number, should alter flow from turbulent to laminar in the large airways, thereby effectively lowering airway resistance. This objective improvement in airflow obstruction, along with the decrease in dyspnea, probably represents a decreased work of breathing secondary to diminished airway resistance. After the rapid improvement in %PEF at 20 min in the heliox group, there were no further significant improvements in %PEF until 8 h; in the heliox group, there

![PFP, % Predicted](image)

**Figure 1.** %PEF in L/min for the heliox and oxygen groups vs time in minutes.

**Discussion**

This is the first study to demonstrate in a prospective, randomized, controlled fashion that heliox causes both a rapid improvement in peak flow and a decrease in dyspnea in adult patients with acute severe asthma that is maintained for at least 8 h. Similar objective improvements have been demonstrated in children.15,16 All of the heliox patients had a \(>20\%\) increase in %PEF at 20 min, whereas only two patients of the oxygen group did. Helium, because of its lower density than nitrogen or oxygen and its reduction of the Reynolds number, should alter flow from turbulent to laminar in the large airways, thereby effectively lowering airway resistance. This objective improvement in airflow obstruction, along with the decrease in dyspnea, probably represents a decreased work of breathing secondary to diminished airway resistance. After the rapid improvement in %PEF at 20 min in the heliox group, there were no further significant improvements in %PEF until 8 h; in the heliox group, there...
was a significant improvement in %PEF at 20 min, it
took the oxygen group 6 h to achieve a significant
improvement. By the termination of the study, the
oxygen group had improved such that there were no
longer any significant differences between the
groups, which suggests that the immediate and
ongoing benefits of heliox may no longer be neces-
sary. Improvements at 6 to 8 h after the start of
therapy are most likely secondary to the delayed
impact of corticosteroid therapy.9

Inasmuch as physicians’ assessments of airflow
obstruction are commonly inaccurate,17 and patients’
subjective reports are also unreliable indicators of
airflow obstruction,18,19 it has been recommended
that airflow obstruction in patients with acute severe
asthma should be objectively measured.20 Although
spirometry is the standard measurement of airflow
obstruction, in patients with acute severe asthma,
PEF may be easier to perform than spirometry.8
Although PEF is effort dependent, it has been
shown to correlate with spirometric FEV1.21

Although the baseline variables suggest that the
heliox group may have had more severe exacerbations
of their asthma than did the oxygen group, only
the RR was significantly different. This raises the
possibility that the lack of significant improvement
seen early in the oxygen group is related to lessened
baseline severity. However, there were no significant
differences at baseline between the groups for the
objective measures of airflow obstruction by %PEF,
oxygenation, or ventilation.

Heliox causes an underestimation of peak flow
when measured by the peak flowmeter. Manthous et
al5 found that it was underestimated by a factor of
1.32. Because the main measurements were within
the groups, calibrating the peak flowmeters would
not change the very significant improvement in the
heliox group and would only increase the differences
between the groups.

The literature suggests that acute vocal cord dys-
function may mimic an acute asthmatic exacerbation
and that more than half of patients with vocal cord
dysfunction also have asthma.22 Although the density
properties of heliox may be beneficial in upper
airway obstruction, there were no clinical data to
suggest vocal cord dysfunction in our series.

It has been suggested that heliox might improve
the rate of response to aerosol treatments, because
heliox improves the lung retention of aerosolized
particles.23 In the heliox group, there was no further
improvement in PEF until 8 h, despite continued
treatment with a heliox-driven nebulized β-agonist.
The rapid marked initial improvement in PEF in the
heliox group and the lack of subsequent significant
improvement in PEF until 8 h raises the possibility
that during this period, nebulized β-agonist may not
add any incremental benefit in acute severe asthma
over heliox alone. In addition, the therapeutic ratio
may be much higher with heliox, because there are
well-reported side effects of β-agonists,24 whereas
there are no reported side effects with heliox. Fur-
ther studies are needed to address this issue.

In conclusion, heliox rapidly improves airflow ob-
struction and dyspnea in patients with acute severe
asthma and may be useful as a therapeutic bridge
until the corticosteroid effect occurs. A larger study
specifically designed to evaluate the prevention of
intubation, the need for ICU monitoring, or the need
for hospital admission is needed to more clearly
define the role of heliox in the treatment of acute
severe asthma in the emergency department and
possibly the prehospital setting.

ACKNOWLEDGMENT: The authors thank Gerald Arnold,
PhD, for his statistical consultation and Melvin Pratter, MD,
for his review of the manuscript.

REFERENCES
1 Barach AL. The use of helium in the treatment of asthma and
obstructive lesions of the larynx and trachea. Ann Intern Med
1935; 9:739–765
2 Shine ST, Gluck EH. The use of helium-oxygen mixtures in the
support of patients with status asthmaticus and respiratory
3 Gluck EH, Onorato DJ, Castriotta R. Helium-oxygen mix-
tures in intubated patients with status asthmaticus and respira-
4 Kass JE, Castriotta RJ. Heliox therapy in acute severe asthma.
pulmonary paradoxus and peak expiratory flow in nonintubated
patients with severe asthma. Am J Respir Crit Care Med
1995; 151:310–314
treatment of airflow obstruction: a critical review of the
literature. Respir Care 1997; 42:1034–1042
7 Madison JM, Irvin BS. Heliox for asthma. Chest 1995;
107:597–598
8 Corbridge TC, Hall JB. The assessment and management of
adults with status asthmaticus. Am J Respir Crit Care Med
1995; 151:1296–1316
9 Fanta CF, Rossing TH, McFadden EB. Glucocorticoids in
10 American Thoracic Society. Chronic bronchitis, asthma, and
225
11 Leiner GC, Abramowitz S, Small MJ. Expiratory peak flow
rate: standard values for normal subjects; use as a clinical test
12 Borg G. Psychophysical bases of perceived exertion. Med Sci
Sports Exerc 1982; 14:377–381
13 Hess D, Maxwell C. Which is the best index of oxygenation:
P(A-a)O2, PaO2/FIO2, or PaO2/FIO2? Respir Care 1985; 30:
961–963
14 Pennock BE, Cottrell JJ, Rogers RM. Pulmonary function
testing: what is normal? Arch Intern Med 1983; 143:2123–
2127
15 Carter ER, Webb CR, Moffit DR. Evaluation of heliox in