

Helium/oxygen-driven albuterol nebulization in the management of children with status asthmaticus: A randomized, placebo-controlled trial*

Michael T. Bigham, MD; Brian R. Jacobs, MD; Marie A. Monaco, BSN, CCRN; Richard J. Brill, MD; Dan Wells, RRT; Edward M. Conway, RRT; Scott Pettinichi, RRT; Derek S. Wheeler, MD

LEARNING OBJECTIVES

After participating in this educational activity, the participant should be better able to:

1. Analyze the physiology of the effects of heliox in pediatric critical care.
2. Demonstrate the potential mechanisms of action of heliox in the treatment of pediatric asthma.
3. Measure the impact of heliox-powered albuterol nebulization on outcomes in children with status asthmaticus.

Unless otherwise noted below, each faculty or staff's spouse/life partner (if any) has nothing to disclose.

Dr. Wheeler has disclosed that he received grants/research fees from Praxair, Inc. to conduct this study. The remaining authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

The authors have disclosed that the U.S. Food and Drug Administration has not approved Heliox for the treatment of status asthmaticus in critically ill children discussed in this article. Please consult the product's labeling information for approved indications and usage.

All faculty and staff in a position to control the content of this CME activity have disclosed that they have no financial relationship with, or financial interests in, any commercial companies pertaining to this educational activity.

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Objectives: We investigated the effect of heliox-powered albuterol therapy on hospital length of stay and clinical status in children with moderate to severe status asthmaticus.

Design: Prospective, randomized, placebo-controlled trial.

Setting: Twenty-five-bed pediatric intensive care unit at an academic children's medical center.

Patients: Forty-two children (2–21 yrs of age) with moderate to severe status asthmaticus.

Interventions: Patients were randomized to receive either heliox-powered nebulized albuterol or air/oxygen-powered nebulized albuterol (placebo) until they were transitioned to albuterol delivered by a metered dose inhaler.

Measurements and Main Results: Clinical asthma scores were

recorded on enrollment and every 4 hrs thereafter. Patients in the heliox group (n = 22) and the control group (n = 20) had similar ages (mean \pm SEM: 88 \pm 9.9 vs. 98 \pm 11.1 months, respectively; $p = .51$), time to study enrollment (618 \pm 70.4 vs. 597 \pm 84.1 mins, respectively; $p = .72$), and clinical asthma scores at study entry (5.9 \pm 0.2 vs. 5.7 \pm 0.3, respectively; $p = .72$). There were no significant differences between groups in time to eligibility to hospital discharge (66.2 \pm 8.7 vs. 63.4 \pm 8.6 hrs, respectively; $p = .61$), time to clinical asthma score <3 (22 \pm 2.8 vs. 21.2 \pm 5.3 hrs, respectively; $p = .27$), or time to eligibility for intensive care unit discharge (34.4 \pm 6.8 vs. 33.3 \pm 8.2 hrs, respectively; $p = .64$). There were no significant differences in adverse events between groups.

*See also p. 428.

Clinical Assistant Professor of Pediatrics (MTB), Division of Critical Care Medicine, Akron Children's Hospital, Akron, OH; Medical Director (MTB), Pediatric Transport, Akron Children's Hospital, Akron, OH; Professor (BRJ), Pediatrics, Children's National Medical Center, Washington, DC; Vice President and Chief Medical Information Officer (BRJ), Children's National Medical Center, Washington, DC; Research Nurse III (MAM), Cincinnati Children's Medical Center, Cincinnati, OH; Chief Medical Officer (RJB), Nationwide Children's Hospital, Cincinnati, OH; Clinical Manager (DW), Pediatric Intensive Care Unit, Cincinnati Children's Hospital, Cincinnati, OH; Clinical RT Manager (EMC), Cincinnati Children's Hospital, Cincinnati, OH; Senior Clinical Director (SP), Division of Respiratory Care, Cincinnati Children's Hospital, Cincinnati, OH; and Clinical Director (DSW), Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

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For information regarding this article, E-mail: Derek.wheeler@cchmc.org

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Conclusions: Despite the previously demonstrated effects of heliox on improved aerosol particle delivery into the distal airways, heliox-powered nebulized albuterol therapy for children admitted to the hospital with moderate to severe status asthmaticus does not shorten hospital length of stay or hasten rates of

clinical improvement when compared with air/oxygen-powered nebulized albuterol. (*Pediatr Crit Care Med* 2010; 11:356–361)

KEY WORDS: heliox; helium/oxygen; asthma; status asthmaticus; pediatric; hospitalized; length of stay

INTRODUCTION

The physician will be able to better select the manner to deliver albuterol in children with moderate to severe status asthmaticus.

Asthma is one of the most common reasons children require hospitalization in the United States (1), accounting for two million emergency department (ED) visits, 500,000 hospitalizations, and nearly \$6 billion in total healthcare expenditures on an annual basis (2–6). Status asthmaticus is an acute condition of progressively worsening bronchospasm and respiratory dysfunction resulting from asthma, which is unresponsive to conventional therapy (oxygen, nebulized β_2 -adrenergic agonists, and corticosteroids). Although recent trends suggest that the incidence of childhood asthma may have reached a plateau, asthma morbidity and mortality continue to rise (1, 5, 7–11). As a result, there is continued interest in the identification and development of treatment strategies to improve the outcome of children hospitalized with status asthmaticus.

Barach (12) first described the clinical use of helium–oxygen mixtures (heliox) as a potential therapy for asthma in 1935. Heliox is less dense than air and improves expiratory flow and decreases resistive work of breathing by converting density-dependent turbulent air flow within the airways to laminar flow (13). Heliox also improves the delivery of aerosolized β_2 -adrenergic agonists to the distal airways, offering additional advantages over conventional albuterol nebulization (14). Since Barach’s initial report, several small series have suggested that heliox decreases the work of breathing and im-

proves respiratory mechanics in both children and adults with status asthmaticus. A recent Cochrane Database review by Rodrigo et al (15) concluded that the existing evidence does not currently support the therapeutic use of heliox-driven albuterol in all patients presenting to the ED with status asthmaticus. Notably, this review included only three pediatric trials enrolling a total of 82 patients (16–18). The study by Carter et al (16) assessed the response to heliox alone (not albuterol) and was limited to only 15 mins of heliox therapy. The study by Kim et al (17) randomly assigned children presenting to the ED with moderate-to-severe asthma exacerbations to continuously nebulized albuterol delivered with either heliox (70% helium:30% oxygen) or oxygen alone and demonstrated statistically significant improvement in the pulmonary index score at 240 mins in the heliox group (17). In contrast, Rivera et al (18) failed to show any benefit to heliox-driven albuterol in 41 children presenting to the ED with asthma.

To our knowledge, there have been no prospective, randomized trials comparing heliox-driven nebulized albuterol with standard care in pediatric inpatients with status asthmaticus. The authors of the Cochrane Database review (15) noted that patients with a moderate-to-severe asthma exacerbation were perhaps more likely to benefit from albuterol delivered with heliox. Accordingly, we hypothesized that heliox-driven albuterol nebulizer therapy would result in a decreased length of stay and more rapid improvement in a standardized asthma severity score in hospitalized children with status asthmaticus.

METHODS

Study Participants. Our study was approved by the Cincinnati Children’s Hospital Institutional Review Board and registered on ClinicalTrials.gov (NCT00410150) with approval from the US Food and Drug Administration (FDA-IND 74067). Patients were enrolled following informed consent/assent. Entry criteria for study participants included: age 2 to 21 yrs, history of asthma, modified Becker Clinical Asthma Score (CAS) ≥ 3 (Table 1) (19, 20), and admission to the pediatric intensive care unit (PICU) or asthma ward. We specifically excluded children age < 2 yrs to avoid enrolling children admitted to the hospital with wheezing secondary to viral bronchiolitis. Alternative diagnoses associated with wheezing were excluded by history, physical examination, and chest radiograph. Additional exclusion criteria included the need for invasive or noninvasive mechanical ventilation, impending respiratory failure (respiratory acidosis with $Paco_2 > 60$ torr, altered mental status, excessive work of breathing), and need for supplemental oxygen with an $FIO_2 \geq 0.4$. We recorded the duration of ED stay (time from initiation of ED triage to departure from ED for admission), time to ED corticosteroids (the time from initiation of ED triage to administration of the medication dose), and time from ED to study enrollment (time from initiation of ED triage to initial delivery of the first study dose medication) for each study subject. An independent Data Safety Monitoring Board performed interval reviews for study safety after enrollment of the first 20 subjects.

Study Protocol. Children were screened for enrollment on admission and assigned a baseline CAS. If eligible, written informed consent/assent was obtained, and study participants were randomized using a sealed envelope technique in blocks of five using a random-number generator. Participants randomized to the heliox group received albuterol (either intermittent or continuous) delivered using a 70% helium/30% oxygen mixture through a nonbreathing face mask. Control group participants received albuterol delivered using air–oxygen mixtures $FIO_2 \leq 0.40$ through a nonbreathing face mask. To assure a standard albuterol delivery rate of 15 mg/hr, oxygen flows of 10 L/min and heliox flows of 16 L/min were used.

Each individual scorer was trained in the use of the CAS before the start of the study. The CAS, heart rate, respiratory rate, inspired oxygen concentration, and oxygen saturation as measured by pulse oximetry were recorded at 4-hr intervals by a scorer blinded to treat-

Table 1. Modified Becker Clinical Asthma Score

Variables	0	1	2	3
Respiratory rate, respirations per minute	<30	30–40	41–50	>50
Wheezing	None	Terminal expiration	Entire expiration	Inspiration and expiration
Inspiratory/expiratory ratio	1:1.5	1:2	1:3	>1:3
Accessory muscle use	None	One site	Two sites	Three sites or neck strap muscles

ment group. Additionally, potential adverse events were recorded at 4-hr intervals. The blinded care team dictated albuterol therapy and made decisions regarding weaning/discontinuation of therapy, escalation of care, and PICU/hospital discharge. Treatment was continued until participants met discharge criteria from the hospital or on discontinuation of albuterol nebulizer therapy. In addition, participants were removed from the study if they developed incipient respiratory failure, the need for either invasive or noninvasive mechanical ventilatory support, or $F_{iO_2} > 0.40$ to maintain oxygen saturations $> 90\%$.

The primary outcome variable for the study was the length of hospital stay (time from study enrollment to hospital discharge readiness). Hospital discharge readiness was defined as the time when the participant: 1) maintained room-air oxygen saturations $> 90\%$; and 2) transitioned from intermittent nebulizer treatments to two consecutive metered-dose inhaler treatments spaced ≥ 4 hrs apart. Secondary outcome variables included the differences between the two groups in: 1) length of time required to reach a CAS ≤ 3 ; 2) adverse event rate; and 3) PICU length of stay (time from study enrollment to PICU transfer readiness). PICU transfer readiness was defined as the time when the participant successfully transitioned from continuous albuterol nebulizer therapy to hourly handheld intermittent nebulizer therapy.

Study Gas Setup. The setup of study gas was the same for all participants. To maintain blinded administration of study gas, a 70/30 heliox tank with a regulator and flowmeter was placed in all participants' room. An air-oxygen blender (Bird Corporation, Palm Springs, CA) calibrated to $\pm 2\%$ was connected to both a 100% oxygen source from the wall outlet and the factory calibrated 70/30 heliox cylinder (Praxair, Danbury, CT). Two oxygen flow meters (Precision Medical, Northampton, PA) were attached to the air-oxygen blender such that one flow meter supplied gas to power the nebulizer containing the albuterol, whereas the other flow meter supplied gas to a reservoir bag attached to the patient's face mask to provide a constant reservoir of gas to entrain into the face mask. The setup was designed so that whenever the air-oxygen blender was set at 21%, all of the gas delivered to the participant was drawn from the 70/30 heliox cylinder, thus delivering 30% oxygen and 70% helium to the participant. If the participant required $> 30\%$ oxygen to maintain oxygen saturations $> 90\%$, the air-oxygen blender was adjusted accordingly. Participants who required $> 40\%$ oxygen to maintain oxygen saturations $> 90\%$ were removed from the study. Before the study, the described delivery system was validated through analysis of delivered oxygen concentration with an inline oxygen analyzer. Aerosol therapy was delivered through a small-volume jet nebulizer (Salter Labs 8900 Series Small Volume Jet Nebulizer; Salter Labs, Arvin, CA).

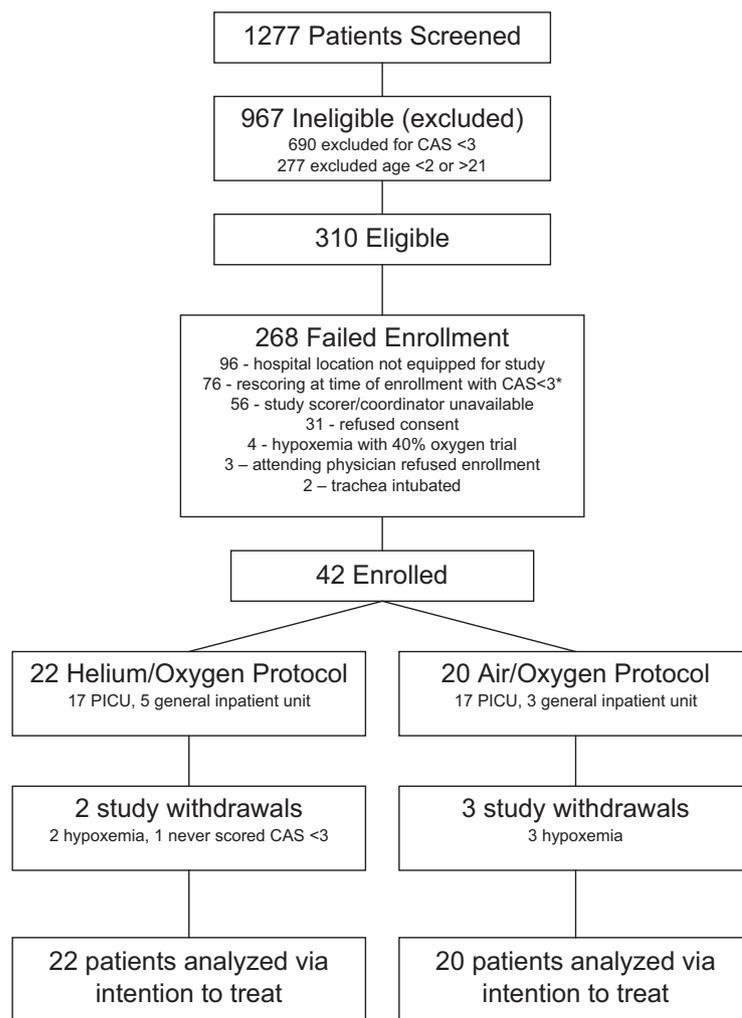


Figure 1. Flowchart of patient enrollment. CAS, Clinical Asthma Score; PICU, pediatric intensive care unit.

Table 2. Baseline patient demographics^a

	Heliox Group Mean \pm SEM	Control Group Mean \pm SEM	<i>p</i>
Age, months (median)	88 \pm 9.9	97.9 \pm 11.2	.51
White race	9	8	.80
Nonwhite race	13	12	.73
Male sex	13 (59%)	14 (70%)	.679
Weight, kg	26.4 \pm 2.3	36.2 \pm 5.7	.58
Duration of ED stay, mins ^b	255.7 \pm 12.7	320.4 \pm 33.1	.36
Time to ED corticosteroids, mins ^c	57.2 \pm 6.8	41.3 \pm 7.6	.24
Initial ED oxygen saturation, %	91.8 \pm 0.7	91.3 \pm 1.1	.73
Time from ED to study enrollment, mins ^d	617.6 \pm 70.4	597 \pm 84.1	.72
CAS at study enrollment	5.9 \pm 0.2	5.7 \pm 0.3	.73

ED, emergency department; CAS, Clinical Asthma Score; PICU, pediatric intensive care unit.

^aHeliox group, *n* = 22 and control group, *n* = 20); ^btime defined as initiation of ED triage to departure for inpatient unit or PICU; ^ctime from initiation of ED triage to administration of medication; ^dtime from initiation of ED triage to initiation of study therapy (control or placebo albuterol delivery).

Statistical Analysis. Based on an average hospital length of stay for children with status asthmaticus at our institution of 4.5 ± 1.6 days, an *a priori* power analysis determined that a sample size of 348 participants (174 participants in each group) would be required

to demonstrate a 0.5-day reduction in hospital length of stay in the heliox group with a power of 80% and two-tailed significance level of 0.05. The interim Data Safety Monitoring Board analysis of the first 20 patients showed no safety concerns and recommended that the

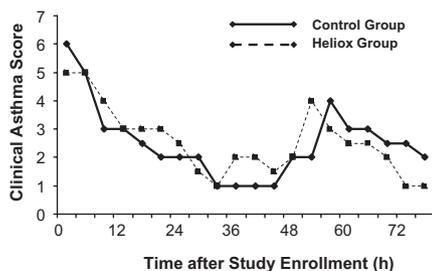


Figure 2. Median clinical asthma scores during study enrollment period (heliox group, n = 22 and control group, n = 20).

study be continued without modifications. Because of persistently slow enrollment rates, the study was prematurely terminated after 42 study subjects completed the study.

Abstracted data were tabulated in a Microsoft Excel 2003 spreadsheet (Microsoft, Redmond, WA) and analyzed using SigmaStat for Windows (Systat Software, Inc., San Jose, CA). Categorical data, including sex, race, presence or absence of adverse event symptoms, and need for mechanical ventilation, were compared between the two groups using Fisher's exact or chi-square testing. Baseline and final continuous variables such as age, asthma scores, Pediatric Risk of Mortality scores, respiratory rate, heart rate, time to meeting PICU and hospital discharge criteria, and PICU and hospital length of stay were analyzed using the Student's *t* test for parametric variables and with the Mann-Whitney *U* test for nonparametric variables. Differences in variables that changed over time such as the change in asthma scores between groups were analyzed using repeated-measures analysis of variance. A *p* value $\leq .05$ was considered significant. Values are expressed as mean \pm SEM.

Table 3. Key study end points for heliox (n = 22) versus control (n = 20) study groups

	Heliox Group Mean \pm SEM	Control Group Mean \pm SEM	<i>p</i>
Time to hospital discharge eligibility, hrs	66.2 \pm 8.7	63.4 \pm 8.6	.614
Time to CAS <3, hrs	22 \pm 2.7	21.2 \pm 5.3	.273
CAS at 24 hrs	2.9 \pm 0.3	2.4 \pm 0.6	.172
CAS at study end	1.6 \pm 0.4	1.6 \pm 0.4	.876

CAS, Clinical Asthma Score.

Table 4. PICU subgroup analysis of key study end points for heliox (n = 17) versus control (n = 17) study groups

	Heliox Group Mean \pm SEM	Control Group Mean \pm SEM	<i>p</i>
Time to hospital discharge eligibility, hrs	74.0 \pm 9.0	65.8 \pm 9.1	.242
Time to PICU discharge eligibility, hrs	34.4 \pm 6.2	33.3 \pm 7.6	.642
Time to CAS <3, hrs	24.4 \pm 2.8	23.7 \pm 5.7	.336
Duration of continuous gas administration, hrs	25.6 \pm 4.6	24.33 \pm 5.8	.514

PICU, pediatric intensive care unit; CAS, Clinical Asthma Score.

RESULTS

During the study period (May 2006 to December 2007), 1277 children were screened for participation in the study. The majority of patients were excluded for a CAS <3 at the time of screening (n = 690) or at rescoring immediately before study enrollment (n = 76). Consent/assent was obtained from 42 eligible children (Fig. 1). There were no significant baseline clinical or demographic differences between the two study groups (Table 2). Importantly, there were no significant differences in baseline CAS in the heliox group vs. the control group: (5.9 \pm 0.2 vs. 5.7 \pm 0.3; *p* = .73), time to corticosteroid administration (heliox group 57.2 \pm 6.8 vs. control group 41.3 \pm 7.6 mins; *p* = .24), or time to study enrollment (heliox group 618 \pm 70.4 vs. control group 597 \pm 80.1 mins; *p* = .72). Importantly, there were no significant differences in the number of albuterol treatments received before randomization (median, three albuterol treatments in each group) or in the percentage of subjects treated with magnesium sulfate (heliox group vs. control group: 16 of 22 [72%] vs. 14 of 20 [70%]; *p* = .88), terbutaline (heliox group vs. control group: two of 22 [9%] vs. two of 20 [10%]; *p* = .99), ipratropium bromide (heliox group vs. control group: 17 of 22 [77%] vs. 11 of 20 [55%]; *p* = .23), or subcutaneous epinephrine (heliox group vs. control group: three of 22 [14%] vs. one of 20 [5%]; *p* = .61) in the ED before study randomization and enrollment.

Table 5. Adverse events in the heliox (n = 22) and control (n = 20) groups

Adverse Event	Heliox Group	Control Group	<i>p</i>
Cardiovascular			
Tachycardia ^a	21	20	1
Hypotension ^b	5	3	.7
Chest pain	0	2	.22
Respiratory			
Hypoxemia ^c	4	3	1
Tachypnea ^d	21	20	1
Worsening asthma/BiPAP	1	2	.61
Gastrointestinal			
Emesis	4	6	.48
Nausea	4	2	.67
Abdominal pain	0	1	.48
Neurologic			
Headache	1	1	1
Agitation	2	1	1
Constitutional			
Fever ^e	0	2	.22
Hematologic			
Anemia ^f	3	1	.61
Leukocytosis ^g	6	4	1
Metabolic			
Hypokalemia ^h	5	9	.23
Hypophosphatemia ⁱ	4	6	.48
Hyperphosphatemia ^j	4	1	.35
Hypocalcemia ^k	2	2	1
Hypercalcemia ^l	1	1	1
Hyponatremia ^m	5	2	.41
Hypernatremia ⁿ	0	1	.48
Hyperchloremia ^o	4	5	.71
Hyperglycemia ^p	12	13	.71
Acidosis ^q	12	12	.96

BiPAP, bilevel positive airway pressure.

^aTachycardia (heart rate >2 sds above age-based normals); ^bhypotension (blood pressure <2 sds below age-based normals mean arterial pressure); ^chypoxemia (oxygen saturation by pulse oximetry <90%); ^dtachypnea (respiratory rate >2 sds above age-base normals); ^efever (temperature >38.5°C); ^fanemia (hemoglobin <80 g/L); ^gleukocytosis (white blood cell count >15 \times 10⁹ k/uL); ^hhypokalemia (potassium <3.0 mmol/L); ⁱhypophosphatemia (phosphorous <0.969 mmol/L); ^jhyperphosphatemia (ionized calcium <0.9 mmol/L); ^khypocalcemia (ionized calcium <0.9 mmol/L); ^lhypercalcemia (ionized calcium >1.3 mmol/L); ^mhyponatremia (sodium <135 mmol/L); ⁿhypernatremia (sodium >145 mmol/L); ^ohyperchloremia (chloride >106 mmol/L); ^phyperglycemia (glucose >11.1 mmol/L); ^qacidosis (serum bicarbonate <20 mmol/L or pH <7.3 nmol/L).

Aside from the study gas, treatment was not protocolized and was left to the discretion of the healthcare team. Importantly, there were no differences in the percentage of subjects treated with magnesium (heliox group vs. control group: nine of 22 [40%] vs. five of 20 [25%]; *p* = .44), terbutaline (heliox group vs. control group: six of 22 [27%] vs. three of 20 [15%]; *p* = .46), or ipratropium bromide

(heliox group vs. control group: one of 22 [5%] vs. zero of 20 [0%]; $p = .99$) during the study. All of the patients were treated with corticosteroids.

There were no significant differences in CAS between the two study groups at any time point after randomization (Fig. 2). The primary outcome variable, hospital length of stay, was not different between the two study groups (heliox group 66.2 ± 8.7 vs. control group 63.4 ± 8.6 hrs; $p = .61$; Table 3). Additionally, there was no difference between groups in the secondary outcome variable of time to CAS <3 (heliox group 22 ± 2.8 vs. control group 21.2 ± 5.3 hrs; $p = .27$). The secondary outcome variables of 24-hr CAS and CAS at study end were not different between groups.

We analyzed children admitted to the PICU separately. There were no differences in time to CAS <3 in the heliox group vs. the control group (24.4 ± 2.8 vs. 23.7 ± 5 hrs; $p = 0.34$) or PICU length of stay (34.4 ± 6.8 vs. 33.3 ± 8.2 hrs; $p = .64$) (Table 4). The vast majority of patients admitted to the PICU were on continuous nebulized albuterol, permitting analysis of the duration of continuous study gas administration, which was not different between the two study groups (heliox group 25.6 ± 4.6 vs. control group 24.3 ± 5.8 hrs; $p = .51$).

There were no differences in the rates of adverse events between groups (Table 5). There were no cases of dysrhythmia in either group. Five patients exited the study as a result of persistent hypoxemia (two patients in the heliox group and three patients in the control group, $p =$ nonsignificant). However, none of our patients developed incipient respiratory failure or a need for mechanical ventilatory support.

DISCUSSION

Although initial reports suggest potential benefits to heliox in asthmatics, the results of our single-center trial indicate that treatment with heliox-driven nebulized albuterol does not reduce hospital length of stay or hasten time to clinical improvement in hospitalized children with moderate to severe status asthmaticus. Furthermore, in the subset of patients admitted to the PICU requiring continuous nebulized albuterol, there is no benefit from treatment with heliox-powered nebulized albuterol compared with conventional oxygen-powered nebulized albuterol. Based on a previous Co-

chrane review (15), our study focused on this sicker population of hospitalized asthmatic children. We prospectively identified patients meeting our study enrollment criteria (CAS <3) either in the ED or on admission to the inpatient unit or PICU. Over the 19-month study period, we screened >1200 children for possible study enrollment. The majority of patients excluded from the study were ineligible as a result of a low clinical asthma score (<3). Importantly, we speculate that this group may represent patients with moderate to severe status asthmaticus that responded to early, conventional treatment in the ED with a subsequent improvement in CAS <3 . We acknowledge that this excludes a large number of patients who may respond early to heliox therapy as reported by Kim et al (17). Children with status asthmaticus who are admitted to the PICU have a greater degree of peripheral airway obstruction compared with those children who are managed on the hospital ward (15, 21, 22). Thus, we analyzed the PICU subset of patients and identified no differences in duration of PICU length of stay or duration of continuous gas administration (duration of continuous nebulized albuterol).

Although the results of the current study contradict the study by Kim et al (17), our results are consistent with previously published, equivocal studies performed in the ED setting, which minimize the benefit of heliox (15, 18). Some limitations inherent in our study may have contributed to our results. First and foremost, although the current study is the largest pediatric trial involving heliox-powered albuterol in the treatment of asthma published to date, we did not reach our original enrollment target and therefore cannot exclude a type II error. The low enrollment severely underpowered our study and represents a major limitation to our study. Second, although all study subjects were assessed for CAS by an independent investigator not directly involved with patient care, the rest of the healthcare team was not unequivocally blinded to study group assignment and therefore could have been biased in therapeutic decision-making as well as transfer and discharge assessments. Third, study subjects were not randomized until after hospital admission. Previous ED studies randomized children presenting to the ED with moderate to severe asthma exacerbations to continuously nebulized albuterol delivered with either heliox (70% helium:30% oxygen)

or oxygen alone. Kim et al (17) showed that the use of heliox-driven albuterol resulted in a shorter length of stay in the ED. The aforementioned study may have demonstrated an effect related to heliox early in the disease process, before corticosteroids exert their maximal anti-inflammatory effect (17). Conversely, the current study enrolled patients after they had received conventional ED care, including corticosteroid therapy, with the average study enrollment occurring approximately 10 hrs after arrival in the ED and >9 hrs after administration of corticosteroids (Table 2). We speculate that later in the course of asthma (i.e., the time points examined in this study), the benefit of β -agonist delivery lessens as a result of the effect of corticosteroids on airway inflammation. Finally, we used a small-volume jet nebulizer in this study. Corcoran and Gamard (23) previously showed that the use of a large-volume nebulizer in older children and adolescents in whom the minute ventilation requirements exceed the output of small-volume nebulizers may improve the distal delivery of β -agonists and improve the efficacy of heliox.

We were able to examine in detail the risk profile associated with heliox-powered albuterol. Despite the tachyarrhythmia risks associated with improved β -agonist delivery to the lung parenchyma (24–26), none of the patients in this study experienced tachyarrhythmias. Albuterol is known to drive potassium into the intracellular compartment resulting in hypokalemia. There were no differences between groups in adverse effects, suggesting that heliox is safe for use in this population. Importantly, hypoxemia resulting in withdrawal from the trial occurred in only five subjects, and there were no differences in hypoxemia between the two study groups. Therefore, although the current study was unable to demonstrate an improvement in outcome, it would appear that the use of helium–oxygen mixtures to drive albuterol nebulization is as safe as conventional oxygen-powered nebulized albuterol in this patient population.

The current trial characterizes a population of children with moderate to severe asthma admitted to a large pediatric tertiary care center. Notably, the majority of the patients admitted to the hospital with status asthmaticus who were screened during the study had CAS <3 at the time of screening. This suggests that most children respond early and effec-

tively to standard, conventional ED and initial inpatient therapy. The majority of patients who were enrolled in this study received aggressive management in the ED with continuous nebulized albuterol, ipratropium, intravenous corticosteroids, and often intravenous magnesium sulfate. In addition, we believe that the current study illustrates some of the unique challenges posed by clinical trials in this population. We screened >1200 patients for participation, although we enrolled only 42 subjects in our trial. We believe that a multidisciplinary approach combining research efforts among ED physicians, pediatric intensivists, and pediatric hospitalists is both warranted and justified. Future clinical trials in the management of status asthmaticus should seek to enroll patients in the ED setting using both admission to the hospital and hospital length of stay as primary outcomes.

In conclusion, we have shown that heliox-powered nebulized albuterol therapy does not reduce the duration of hospitalization nor hasten the time to clinical improvement for children admitted to the hospital with moderate to severe status asthmaticus. Our *post hoc* analysis demonstrates no measurable benefits to heliox-powered nebulized albuterol in the subset of patients requiring continuous albuterol and admission to the PICU. Based on these data, heliox-powered albuterol cannot be recommended for regular use in the treatment of hospitalized children with moderate to severe status asthmaticus.

CONCLUSION

The physician will gain the knowledge that the use of heliox-powered nebulized albuterol therapy did not hasten rate of clinical improvement or shorten hospital stay, supporting the use of air/oxygen-powered nebulized albuterol.

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REFERENCES

- Akinbami L: The state of childhood asthma, United States, 1980–2005. *Adv Data* 2006; 381:1–24
- Smith DH, Malone DC, Lawson KA, et al: A national estimate of the economic costs of asthma. *Am J Resp Crit Care Med* 1997; 156: 787–793
- Lozano P, Sullivan SD, Smith DH, et al: The economic burden of asthma in US children: Estimates from the National Medical Expenditure Survey. *J Allergy Clin Immunol* 1999; 104:957–963
- Goodman DC, Stukel TA, Chang C: Trends in pediatric asthma hospitalization rates: Regional and socioeconomic differences. *Pediatrics* 1998; 101:208–213
- Mannino DM, Homa DM, Akinbami LJ, et al: Surveillance for asthma: United States, 1980–1999. *Mor Mortal Wkly Rep CDC Surveill Summ* 2002; 51:1–13
- Mannino DM, Homa DM, Pertowski CA, et al: Surveillance for asthma: United States, 1960–1995. *Morb Mortal Wkly Rep CDC Surveill Summ* 1998; 47:1–27
- Sly RM: Decrease in asthma mortality in the United States. *Ann Allergy Asthma Immunol* 2000; 85:121–127
- Wennergren G, Strannegard IL: Asthma hospitalizations continue to decrease in schoolchildren but hospitalization rates for wheezing remain high in young children. *Acta Paediatr* 2002; 91:1239–1245
- Akinbami LJ, Schoendorf KC: Trends in childhood asthma: Prevalence, health care utilization, and mortality. *Pediatrics* 2002; 110:315–322
- Weinberger M: Seventeen years of asthma guidelines: Why hasn't the outcome improved for children? *J Pediatr* 2009; 154:786–788
- Akinbami LJ, Moorman JE, Garbe PL, et al: Status of childhood asthma in the United States, 1980–2007. *Pediatrics* 2009; 123: S131–S145
- Barach AL: The therapeutic use of helium. *JAMA* 1935; 107:1273–1280
- Chan-Yeung M, Aboud R, Tsao MS, et al: Effect of helium on maximal expiratory flow in patients with asthma before and during induced bronchoconstriction. *Am Rev Respir Dis* 1976; 113:433–443
- Kim IK, Saville AL, Sikes KL, et al: Heliox-driven albuterol nebulization for asthma exacerbations: An overview. *Respir Care* 2006; 51:613–618
- Rodrigo G, Pollack C, Rodrigo C, et al: Heliox for nonintubated acute asthma patients. *Cochrane Database Syst Rev* 2006; CD002884
- Carter ER, Webb CR, Moffitt DR: Evaluation of heliox in children hospitalized with acute severe asthma. A randomized crossover trial. *Chest* 1996; 109:1256–1261
- Kim IK, Phrampus E, Venkataraman S, et al: Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: A randomized, controlled trial. *Pediatrics* 2005; 116:1127–33
- Rivera ML, Kim TY, Stewart GM, et al: Albuterol nebulized in heliox in the initial ED treatment of pediatric asthma: A blinded, randomized controlled trial. *Am J Emerg Med* 2006; 24:38–42
- Becker AB, Nelson NA, Simons FER: The pulmonary index: Assessment of a clinical score for asthma. *Am J Dis Child* 1984; 138:574–576
- DiGiulio GA, Kerckmar CM, Krug SE, et al: Hospital treatment of asthma: Lack of benefit from theophylline given in addition to nebulized albuterol and intravenously administered corticosteroid. *J Pediatr* 1993; 122:464–469
- Papo MC, Frank J, Thompson AE: A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. *Crit Care Med* 1993; 21:1479–1486
- Craig VL, Bigos D, Brilli RJ: Efficacy and safety of continuous albuterol nebulization in children with severe status asthmaticus. *Pediatr Emerg Care* 1996; 12:1–5
- Corcoran TE, Gamard S: Development of aerosol drug delivery with helium oxygen gas mixtures. *J Aerosol Med* 2004; 17:299–309
- Chang LH, Honiden S, Haightcock JA, et al: Utilization of bronchodilators in ventilated patients without obstructive airways disease. *Respir Care* 2007; 52:154–158
- Cook P, Scarfone RJ, Cook RT: Adenosine in the termination of albuterol-induced supraventricular tachycardia. *Ann Emerg Med* 1994; 24:316–319
- Duane M, Chandran L, Morelli PJ: Recurrent supraventricular tachycardia as a complication of nebulized albuterol treatment. *Clin Pediatr (Phila)* 2000; 39:673–677