Primary research
Helium–oxygen mixture does not improve gas exchange in mechanically ventilated children with bronchiolitis

Matthew F Gross, Robert M Spear and Bradley M Peterson

Children's Hospital and Health Center, San Diego, California, USA

Crit Care 2000, **4**:188–192

© Current Science Ltd

Statement of findings

Varying concentrations of helium–oxygen (heliox) mixtures were evaluated in mechanically ventilated children with bronchiolitis. We hypothesized that, with an increase in the helium:oxygen ratio, and therefore a decrease in gas density, ventilation and oxygenation would improve in children with bronchiolitis. Ten patients, aged 1–9 months, were mechanically ventilated in synchronized intermittent mandatory ventilation (SIMV) mode with the following gas mixtures delivered at 15-min intervals: 50%/50% nitrogen/oxygen, 50%/50% heliox, 60%/40% heliox, 70%/30% heliox, and return to 50%/50% nitrogen/oxygen. The use of different heliox mixtures compared with 50%/50% nitrogen/oxygen in mechanically ventilated children with bronchiolitis did not result in a significant or noticeable decrease in ventilation or oxygenation.

Keywords: bronchiolitis, helium, mechanical ventilation, pediatrics, respiratory failure

Synopsis

Introduction: Heliox has been found to reduce both the arterial carbon dioxide tension ($PaCO_2$) and work of breathing in children and adults with status asthmaticus. We hypothesized that, in mechanically ventilated children with bronchiolitis, increasing the ratio of helium:oxygen concentrations would improve both ventilation and oxygenation.

Objective: To examine the effect of varying concentrations of heliox mixtures on ventilation and oxygenation in mechanically ventilated children with bronchiolitis.

Patients and methods: This was a case series, with a nonrandomized, unblinded, repeated-measures design, which was conducted in a pediatric intensive care unit in a children's hospital. Ten patients, aged 1–9 months, were mechanically ventilated in SIMV mode with the following gas mixtures delivered at 15-min intervals: 50%/50% nitrogen/ oxygen, 50%/50% heliox, 60%/40% heliox, 70%/30% heliox, and return to 50%/50% nitrogen/oxygen. Two-factor, repeated-measures analysis of variance was used to determine whether the different gas mixtures affected the mean $PaCO_2$, the ratio of arterial oxygen tension (PaO_2) to fractional inspired oxygen (FiO_2), or the ratio of PaO_2 to alveolar oxygen tension (PAO_2).

Results: No statistical or noticeable difference was found between the mean $PaCO_2$, PaO_2/FiO_2, or PaO_2/PAO_2 values while the patients were receiving the four different gas mixtures ($P = 0.93$, 0.98, and 0.96, respectively).

Conclusion: The use of different heliox mixtures compared with 50%/50% nitrogen/oxygen in mechanically ventilated children with bronchiolitis did not result in a significant or noticeable decrease in ventilation or oxygenation.

FiO_2 = fractional inspired oxygen; heliox = helium–oxygen; $PaCO_2$ = arterial carbon dioxide tension; $PACO_2$ = alveolar carbon dioxide tension; PaO_2 = arterial oxygen tension; SIMV = synchronized intermittent mandatory ventilation.

Full article

Introduction

Bronchiolitis is a disease that is epidemic during winter months worldwide. The pathogen that is most commonly found to be responsible for this illness is the respiratory syncytial virus. Each year, up to 2% of all infants in a community require hospitalization for bronchiolitis due to feeding difficulty, respiratory distress, apnea, or the need for supplemental respiratory support. Bronchiolitis in premature infants, infants less than 3 months of age, children with chronic lung disease, children with cardiac disease, and children with severe disease often mandates endotracheal intubation and mechanical ventilation.

Helium gas reduces the work of breathing in obstructive pulmonary disease and is an effective adjunct in the management of status asthmaticus [1–4]. Heliox has been found [1–4] to reduce both the $PaCO_2$ and work of breathing in children and adults with status asthmaticus. One recent study [5] found an improvement in clinical asthma scores in nonintubated children with bronchiolitis. However, no controlled studies have been published that examined the use of heliox in conjunction with positive-pressure ventilation in children with bronchiolitis. We hypothesized that, in mechanically ventilated children with bronchiolitis, increasing the ratio of helium:oxygen concentrations would improve both ventilation and oxygenation. To evaluate this hypothesis, we prospectively assessed the effect of different concentrations of heliox on $PaCO_2$, PaO_2/FiO_2, and PaO_2/PAO_2 in mechanically ventilated children with bronchiolitis.

Patients and methods

Study population

We studied 10 pediatric patients with the diagnosis of viral bronchiolitis and respiratory failure mandating endotracheal intubation and mechanical ventilation who were admitted to the Critical Care Unit at Children's Hospital and Health Center, San Diego, California, USA. Bronchiolitis was defined by either a positive viral pathogen study or a clinical diagnosis with negative tracheal bacterial culture at the time of endotracheal intubation. Enrolment was from November 1996 to April 1998. The study protocol was approved by the Institutional Review Board for the Children's Hospital, San Diego, California, USA. Informed written consent was obtained from the patient's parent(s) before study enrolment. Enrolment criteria included the following: corrected gestational age greater than 38 weeks and less than 2 years at time of entry into the study; patient intubated more than 3 h and less than 48 h at onset of the study; no administration of brochodilators within 4 h of the initiation of the study; hemodynamic stability requiring no blood products or vasoactive medications before or during the study period; and no underlying congenital heart disease, chronic pulmonary disease, terminal illness, immune disease, or neuromuscular disease.

Study design

This study was a case series, and was of a nonrandomized, unblinded, repeated-measures design. All patients were mechanically ventilated using a Servo 900C ventilator (Siemens-Elema, Stockholm, Sweden) in SIMV mode with a tidal volume of 7–12 ml/kg, positive end-expiratory pressure of 5 cmH_2O, inspiratory time of 0.8–1.0 s (mean inspiratory:expiratory ratio of 1:2.2), and ventilator rate of 15–30 breaths/min (Table 1). None of these ventilator parameters were adjusted during the 75 min of the study. Before the initiation of the study, 50%/50% nitrogen/oxygen was delivered. All patients were sedated with a fentanyl infusion and were paralyzed with vecuronium during the trial. Demographic data collection, review of chest radiographs, and respiratory examination were performed by the primary clinical investigator before onset of the trial. Physiologic data collection was performed using the cardiorespiratory monitor (Marquette Transcope 12C, GE Medical Systems, Milwaukee, WI, USA) in conjunction with an arterial catheter for continuous blood pressure and intermittent blood gas analysis.

No patient had tracheal suctioning within 20 min before or during the study. The only change made to the respiratory circuit during the study was to the gas mixture, as defined below. The different heliox concentrations provided by the ventilator were obtained by adjusting the relative flow rates of 100% oxygen to 100% helium gas supplied to the ventilator until the desired ratio was obtained, which was determined by measuring the oxygen fraction (55/90 oxygen analyzer, Hudson RCI, Ventronics Division, Temecula, CA, USA) in the inspiratory limb of the ventilator circuit. The ventilator was calibrated to deliver a constant tidal volume to each patient on the different gas mixtures. Protocol required that the trial be terminated in the event of any pulmonary toilet, other ventilator adjustment, interruption of the respiratory circuit, or acute deterioration in patient status requiring other interventions.

Temperature, heart rate, mean arterial blood pressure, measured oxygen saturation, arterial blood gas, and calculated PaO_2/FiO_2 and PaO_2/PAO_2 ratios were obtained at study onset and at 15-min intervals, just before changing the gas mixture. For each patient, data sets were collected 15 min apart while the patient was receiving the following sequence of gas mixtures: 50%/50% nitrogen/oxygen, 50%/50% nitrogen/oxygen, 50%/50% heliox, 60%/40% heliox, 70%/30% heliox, and 50%/50% nitrogen/oxygen.

Statistical analysis

Data are presented as mean ± standard deviation for normal distributions. Statistical analysis was performed using two-factor, repeated-measures, univariate analysis of variance to determine whether the different gas mixtures

Table 1

Changes in ventilation and oxygenation with changes in gas mixture in 10 infants with bronchiolitis on mechanical ventilation

Variable	Patient									
	1	2	3	4	5	6	7	8	9	10
Age (months)	9	1	1	6	4	7	2	1	4	2
RSV positive	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Ventilator rate (breaths/min)	20	22	18	15	28	18	15	30	20	25
IT (s)	1.0	0.8	0.8	0.8	1.0	1.0	1.0	1.0	1.0	0.8
I:E	1:2	1:2	1:3	1:4	1:1	1:2	1:3	1:1	1:2	1:2
$PaCO_2$ (mmHg)										
50/50 Nitrogen/oxygen	45	53	44	40	47	53	65	28	35	40
50/50 Heliox	43	53	41	38	46	52	62	28	39	36
60/40 Heliox	34	51	44	39	48	45	65	26	37	38
70/30 Heliox	35	53	44	37	45	41	69	26	34	36
PaO_2/FiO_2										
50/50 Nitrogen/oxygen	183	251	246	193	174	351	395	485	167	225
50/50 Heliox	190	284	182	200	232	366	364	450	188	212
60/40 Heliox	245	220	325	200	203	370	330	445	183	230
70/30 Heliox	237	290	303	233	190	313	240	360	213	207
$PaO_2/P{\scriptsize A}O_2$										
50/50 Nitrogen/oxygen	0.30	0.42	0.39	0.31	0.28	0.26	0.35	0.58	0.68	0.74
50/50 Heliox	0.30	0.47	0.29	0.31	0.37	0.30	0.33	0.60	0.62	0.69
60/40 Heliox	0.39	0.38	0.54	0.33	0.34	0.29	0.37	0.62	0.60	0.69
70/30 Heliox	0.40	0.54	0.54	0.40	0.34	0.36	0.35	0.54	0.50	0.57

I:E, ratio of ventilator inspiratory to expiratory times; IT, ventilator inspiratory time; RSV, respiratory syncytial virus.

resulted in significant change in the mean $PaCO_2$, PaO_2/FiO_2, or $PaO_2/P{\scriptsize A}O_2$ values. $P<0.05$ was considered statistically suignificant.

Results

Ten patients, seven male and three female, with a mean age of 4 ± 3 months (range 1–9 months), were enroled into the study. Six patients were positive for respiratory syncytial virus on viral pathogen study. On average, the patients had upper respiratory symptoms for 2 days and increased work of breathing for 1 day before intubation. All patients required mechanical ventilation for respiratory failure as indicated by refractory tachypnea with fatigue or apnea.

Data presented for 50%/50% nitrogen/oxygen in Tables 1 and 2 are the averages of the initial two baseline 50%/50% nitrogen/oxygen data sets (obtained 15 min apart) and the final data set (obtained at 75 min from the onset of the study period) on return to 50%/50% nitrogen/oxygen. All patients' hemodynamic, respiratory status, and blood gas determinations were stable at the onset and on return to baseline 50%/50% nitrogen/oxygen at the end of the study period. There was no statistical or clinically significant difference between any of these three data sets on 50%/50% nitrogen/oxygen for an individual patient. Therefore, any change in ventilation or oxygenation seen with the different heliox gas mixtures should be the result of the change in gas mixture.

Changes in ventilation and oxygenation with changes in gas mixture for the 10 patients studied are presented in Table 1, with statistical analysis presented in Table 2. No statistical differences were found between the mean $PaCO_2$, PaO_2/FiO_2, or $PaO_2/P{\scriptsize A}O_2$ values while receiving the four different gas mixtures ($P=0.93$, 0.98, 0.96, respectively).

Table 2

Statistical analysis of the changes in ventilation and oxygenation with changes in gas mixture in 10 infants with bronchiolitis who were on mechanical ventilation

Gas mixture	$PaCO_2$ (mmHg)	PaO_2/FiO_2	PaO_2/P_AO_2
50%/50% Nitrogen/oxygen	45 ± 10	267 ± 108	0.43 ± 0.17
50%/50% Heliox	44 ± 10	267 ± 95	0.43 ± 0.15
60%/40% Heliox	43 ± 11	275 ± 87	0.45 ± 0.14
70%/30% Heliox	42 ± 12	259 ± 55	0.45 ± 0.09

Values are expressed as mean ± standard deviation. Two-factor, repeated-measures analysis of variance found no statistically significant difference between the mean values for $PaCO_2$, PaO_2/FiO_2, and PaO_2/P_AO_2 for the different gas mixtures ($P = 0.93$, $P = 0.98$, and $P = 0.96$, respectively).

All patients who were enroled completed the study, with no complications or departures from the protocol. Only three out of the 10 patients were continued on heliox after the study period at the discretion of the primary care team.

Discussion

In normal conducting airways convective forces dominate, whereas in small airways diffusive forces dominate. A sharp gradient exists in the intermediate airways where these different forces meet, accounting for the majority of alveolar and inspired gas mixing [3]. This gradient is diminished when either the airways are narrowed or obstructed, or both, as in asthma or bronchiolitis.

Reynolds number ($Re = \rho Ud/\mu$, where ρ is the gas density, U is the velocity, d is the diameter of the tube, and μ is the viscosity of the gas) predicts whether flow through a straight, unbranched tube will be laminar or turbulent. When the Reynolds number in a straight, unbranched tube is greater than 1500–2000 units, turbulent flow occurs. In a branching tube or around an obstructed region, turbulent flow occurs at a lower Reynolds number. Laminar gas flow through a straight, unbranched tube is described by the Hagen–Poiseuille equation ($\Delta P = RV = 8L\mu/\pi r^4$, where ΔP is the change in pressure, R is the resistance, V is the gas flow rate, L is the length of the tube, and r is the radius). When flow of a given gas mixture exceeds a critical velocity, the flow becomes turbulent and the flow equation changes to $\Delta P = V^2 \rho fL/4\pi^2 r^5$ (where f is frictional factor). Note that laminar flow is directly dependent on the gas viscosity μ, whereas turbulent flow is directly dependent on the gas density ρ.

Helium is an inert gas that is insoluble in human tissues and has no bronchodilatory or anti-inflammatory properties. Long-term inhalation of heliox mixtures at a pressure of 1 atmosphere has no discernible deleterious effects [6]. Heliox at 70%/30% has about the same viscosity as 70%/30% nitrogen/oxygen but only one fifth the density, and thus, when turbulent flow predominates, an increase in flow will occur with heliox [7]. Helium further lowers airway resistance by reducing the Reynolds number approximately fourfold, so that some areas of turbulent flow are converted to laminar flow [8,9]. Thus, for a given driving pressure, an overall increase in both inspiratory and expiratory turbulent and laminar flow should be seen with helium compared with nitrogen [3]. In addition, with the same FiO_2, helium allows for increased diffusion of carbon dioxide, via its lower density compared with that of nitrogen [10]. Thus, the substitution of helium for nitrogen enhances both convective and diffusive forces, effectively recruiting low ventilation/perfusion units [3]. In addition, helium may enhance gas transport through collateral ventilation [11].

The effect of airway narrowing caused by bronchiolitis is much more pronounced with a smaller initial airway. This is because airway resistance increases exponentially in relation to a decreasing airway radius, a phenomenon that is more pronounced in situations where turbulent flow exists ($R \sim 1/r^5$; where R is the resistance and r is the radius) compared with laminar flow ($R \sim 1/r^4$). The patient with bronchiolitis compensates for the marked increase in airway resistance by increasing both the force of respiration and the respiratory rate to maintain minute ventilation and gas exchange. This can result in muscle fatigue and ultimately respiratory failure.

Elleau et al [12] found that infants with respiratory distress syndrome of prematurity ventilated with heliox required a lower FiO_2, and had a shorter duration of mechanical ventilation, lower incidence of bronchopulmonary dysplasia, and fewer deaths. Hollman et al [5] found in nonintubated children with bronchiolitis that the beneficial effects of heliox were most pronounced in those children with the greatest degree of respiratory compromise. Also, multiple studies of patients with status asthmaticus and carbon dioxide retention have demonstrated that heliox may be beneficial in reducing $PaCO_2$ and decreasing the degree of respiratory distress, thus avoiding mechanical ventilation [2–4].

In the present study, a statistically significant reduction in $PaCO_2$ was not observed with any heliox mixture compared with baseline 50%/50% nitrogen/oxygen ($P = 0.93$).

Only patients 1 and 6 showed a moderate decrease in the level of $PaCO_2$ (Table 1). Clinically significant carbon dioxide retention was not problematic in any of the patients studied, and the level of $PaCO_2$ was easily controlled before the onset of the study by increasing the ventilator rate or tidal volume. Possibly, had we ventilated the patients in a pressure control mode that allowed for changes in tidal volumes, a reduction in $PaCO_2$ with heliox administration might have occurred.

Because of its lower density, helium decreases resistance to gas flow in turbulent conditions. With all other factors kept constant, the turbulent gas flow equation for a straight unbranched tube would predict 70%/30% heliox to have 2.2 times more flow than 50%/50% nitrogen/oxygen. No noticeable or statistical change in oxygenation, as indicated by an increase in PaO_2/FiO_2 and PaO_2/PAO_2 ratios, was found. However, there was a modest improvement in both the PaO_2/FiO_2 and PaO_2/PAO_2 ratios for patients 1, 2, 3, and 4 (Table 1).

It is possible that we failed to show a significant improvement in ventilation and oxygenation as a result of one or more of the following: the small sample size ($n=10$); the patients had only mild to moderate lung disease; the mode of ventilation (ie SIMV); and an ineffective concentration of helium.

In conclusion, the use of different heliox mixtures compared with 50%/50% nitrogen/oxygen in mechanically ventilated children with bronchiolitis did not result in a statistically significant decrease in $PaCO_2$ or increase in PaO_2/FiO_2 or PaO_2/PAO_2 ratios. Heliox was well tolerated by all patients, and no adverse effects were noted. Further studies are needed to determine whether helium can improve ventilation and oxygenation, and allow for lower ventilating pressures in patients with more severe lung disease or with higher concentrations of helium.

Acknowledgement

References

1. Kudukis TM, Manthous CA, Schmidt GA, Hall JB, Wylam ME: **Inhaled helium-oxygen revisited: effect of inhaled helium-oxygen during the treatment of status asthmaticus in children.** *J Pediatr* 1997, **130**:217–224.
2. Austan F, Camden NJ: **Heliox inhalation in status asthmaticus and respiratory acidemia: a brief report.** *Heart Lung* 1996, **25**:155–157.
3. Gluck EH, Onorato DJ, Castriotta R: **Helium-oxygen mixtures in intubated patients with status asthmaticus and respiratory acidosis.** *Chest* 1990; **98**:693–698.
4. Kass JE, Castriotta RJ: **Heliox therapy in acute severe asthma.** *Chest* 1995, **107**:757–760.
5. Hollman G, Shen G, Zeng L, *et al*: **Helium-oxygen improves clinical asthma scores in children with acute bronchiolitis.** *Crit Care Med* 1998, **26**:1731–1736.
6. Strauss RS: **Diving medicine.** *Am Rev Respir Dis* 1979, **119**:1001–1023.
7. Polaner DM: **The use of heliox and the laryngeal mask airway in a child with an anterior mediastinal mass.** *Anesth Analg* 1996, **82**: 208–210.
8. Radford EP: **Resistance to breathing.** In: *Handbook of Physiology, vol I, section 3, Respiration.* Fenn WO, Rahn H (editors). Washington: The American Physiological Society; 1964:452–453.
9. McIlroy MB, Mead J, Radford EP, *et al*: **The measurement of lung tissue viscus resistance using gases of equal kinematic viscosity.** *J Appl Physiol* 1955, **9**:485–490.
10. Moore WJ (editor). **The kinetic theory.** In: *Physical Chemistry: the Kinetic Theory.* Englewood Cliff, NJ: Prentice-Hall Inc, 1962:227–228.
11. Terry PB, Traystman RJ, Newball HH, Batra G, Menkes HA: **Collateral ventilation in man.** *N Engl J Med* 1978, **298**:10–15.
12. Elleau C, Galperine RI, Guenard H, Demarquez JL: **Helium-oxygen mixture in respiratory distress syndrome: a double-blind study.** *J Pediatr* 1993, **122**:132–136.

Authors' affiliation: Department of Pediatric Critical Care, Children's Hospital and Health Center, San Diego, California, USA

Correspondence: Brad Peterson, MD, Children's Hospital and Health Center, 3030 Children's Way, Suite 115, San Diego, CA 92123, USA. Tel: +1 619 576 5863; e-mail: elizasuain@chsd.org