Heliox administration in the pediatric intensive care unit: An evidence-based review

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Objective: **To provide a comprehensive, evidence-based review of helium–oxygen gas mixtures (heliox) in the management of pediatric respiratory diseases.**

Data Source: **A thorough, computerized bibliographic search of the preclinical and clinical literature regarding the properties of helium and its application in pediatric respiratory disease states.**

Data Synthesis: **After an overview of the potential benefits and technical aspects of helium–oxygen gas mixtures, the role of heliox is addressed for asthma, aerosolized medication delivery, upper airway obstruction, postextubation stridor, croup, bronchiolitis, and high-frequency ventilation. The available data are objectively classified based on the value of the therapy or intervention as determined by the study design from which the data are obtained.**

Conclusions: **Heliox administration is most effective during conditions involving density-dependent increases in airway resistance, especially when used early in an acute disease process. Any beneficial effect of heliox should become evident in a relatively short period of time. The medical literature supports the use of heliox to relieve respiratory distress, decrease the work of breathing, and improve gas exchange. No adverse effects of heliox have been reported. However, heliox must be administered with vigilance and continuous monitoring to avoid technical complications. (Pediatr Crit Care Med 2005; 6:204–211)**

Key Words: helium; mechanical ventilation; acute lung injury; gas exchange; pediatrics; carbon dioxide; heliox; respiration; asthma; airway obstruction; bronchiolitis; croup; extubation; acute lung injury; respiratory distress; respiratory failure

Helium as a medical therapy was first described in 1934 by Barach (1) for the treatment of asthma and upper airway obstruction. Subsequently, helium–oxygen mixtures (heliox) have been demonstrated to improve gas exchange in patients with asthma, bronchiolitis, upper airway obstruction, cystic fibrosis, chronic obstructive pulmonary disease, and, most recently, acute lung injury (2–12). With the increased use of helium for the treatment of respiratory conditions, it is imperative for the clinician to understand the mechanisms of action and scenarios in which heliox therapy is and is not warranted. By reviewing the literature over the last 70 yrs, it is our hope that this evidence-based medicine review will shed light on the clinical applications of helium.

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To objectively assess the value of each of the studies, a classification system is used based on the study type and the rigors of the study design. This approach, as detailed in Table 1, is modeled after the classification system used in the construction of the *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents* (13). In each section, data are presented in the order of the study classification with the most reliable studies listed first. It should be noted that all heliox studies in the literature are limited by small sample sizes.

HELIOX: AN OVERVIEW

Helium is a colorless, odorless gas, which was first discovered during a solar eclipse in 1868. Helium is an inert gas with no direct pharmacologic or biologic effects. It has no intrinsic bronchodilatory or anti-inflammatory properties. The variable that makes helium so attractive for medical use lies in the differences between the density of helium vs. other gases. The density of helium is one-seventh that of air (Table 2). Helium has the lowest density of any gas except hydrogen and, unlike hydrogen, is nonflammable. Equally important, carbon dioxide diffuses through helium four to five times faster than through air (5, 12, 14, 15).

Figure 1 demonstrates the differences in relative density between heliox and oxygen-enriched air at various concentrations of oxygen. There is an insignificant difference in relative gas density at various oxygen concentrations with nitrogen as the balance gas. However, with helium as the balance gas, there is a wide variability in relative density between various oxygen concentrations. By its lower density, heliox improves gas flow through high-resistance airways.

Gas flow can vary from laminar at one end of the spectrum to turbulent at the other. Laminar flow rate (Q) is determined by the Hagen-Poiseuille equation:

$$Q = \Delta P \pi r^4 / 8 \eta l \qquad [1]$$

where ΔP is the pressure drop, r is the radius, η is the gas viscosity, and l is the length. Because the viscosity of the gases are similar (Table 2) and laminar flow velocity is independent of density, heliox has no effect on areas of laminar flow.

As flow velocity decreases and/or airway resistance increases, there is a critical level in which the flow pattern changes from turbulent to laminar. This transitional zone is defined by Reynolds number (Re):

$$Re = 2Vr\rho/\eta \qquad [2]$$

Table 1. Classification system

- *Class I evidence* represents randomized, controlled trials–the "gold standard" of clinical trials. However, some may be poorly designed, lack sufficient patient numbers, or suffer from other methodologic inadequacies.
- *Class II evidence* represents nonrandomized clinical studies in which the data were collected prospectively and retrospective studies, which were based on clearly reliable data. Types of studies so classified include observational studies, cohort studies, prevalence studies, and case-control studies.
- *Class III evidence* represents most retrospective studies. Evidence used in this class indicates clinical series, databases, registries, case reviews, case reports, and expert opinion.

Table 2. Densities

Gas	Viscosity (η) (micropoises)	Density (ρ) (g/L)	Co_2 Diffusion Coefficient (cm^2/sec)	Thermal Conductivity (μcal · cm · sec · °K)
Nitrogen	167.4	1.251	0.165	58
Oxygen	192.6	1.429	0.139	58.5
Air	170.8	1.293	0.138	58
Helium	188.7	0.179	—	352
Heliox (80:20)	—	0.43	0.56	—

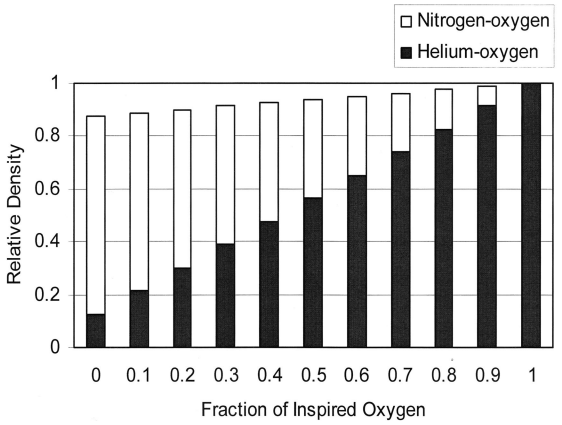

Figure 1. The differences in relative density between heliox and oxygen-enriched air at various concentrations of oxygen.

where ρ is the gas density and V is gas velocity. A Reynolds number <2,000 predicts laminar flow and >4,000 predicts turbulent flow. Thus, helium with its lower density will decrease Reynolds number in those airways operating in the transitional zone of flow patterns and will change turbulent flow into a more laminar flow type with improved diffusion characteristics.

When evaluating extremely turbulent flow patterns, flow rate becomes dependent on gas density according to the Bernoulli equation:

$$Q = (2\Delta P/\rho)^{1/2} \quad [3]$$

Therefore, with a lower gas density, helium will provide a higher flow rate even if it remains turbulent (16). Thus, with its lower density, helium as a "carrier gas" results in a lower resistance to gas flow allowing for increased bulk flow, increased oxygen flow, and decreased work of breathing (17, 18).

HELIOX AND MECHANICAL VENTILATOR FUNCTION

The administration of heliox during mechanical ventilation must occur with vigilance and continuous monitoring because helium can interfere with the accuracy of pneumotachometers and ventilator function (19–23). For example, most modern microprocessor ventilators use a differential flow pneumotachometer to measure the pressure differential across a resistor or a heated wire sensor to measure temperature changes. These measurements are not affected by different concentrations of oxygen-enriched air because density does not significantly vary. However, gas density and thermal conductivity significantly differ at varying oxygen concentrations with heliox. Thus, helium, with its lower gas density and increased heat-carrying capability, results in imprecise pressure and temperature changes, and, subsequently, false tidal volume measurements. Therefore, in-line respiratory mechanic monitors and/or ventilators with heliox calibration capabilities are needed to accurately determine delivered tidal volume with heliox (20–22). Alternatively, mathematic correction factors are required.

Tanks of 100% helium are available and require a blender to dilute the helium to provide a source of oxygen to the patient. An interruption in oxygen delivery could possibly result in the accidental administration of a hypoxic gas mixture, including the possibility of delivering 100% helium (21). Premixed heliox tanks with at least a 20% oxygen concentration avoids this potentially fatal complication. Continuous in-line monitoring of inspired oxygen concentration to ensure adequate oxygen delivery to the airways is warranted.

It is essential to humidify and warm the delivered heliox gas to prevent significant heat loss, especially in the pediatric patient. The thermal conductivity of helium is approximately four to six times that of nitrogen (Table 2). It is also essential to ensure that there is no accidental contamination of the heliox mixture with air or oxygen. As discussed, any accidental introduction of other gases will lower the helium concentration in the total gas mixture, thus increasing the density of the delivered gas.

Any pressure exerted on the lungs through an endotracheal tube inevitably results in some degree of lung injury (24–30). Because the major determinants of ventilator-induced lung injury are airway pressure and lung distension, heliox as the balance gas may allow for similar gas exchange at lower airway pressures. If this is correct, then, theoretically, heliox administration may decrease the risk of iatrogenic lung injury.

ASTHMA

Asthma is a chronic disease with significant morbidity and mortality. In the 2002 update from the National Asthma Education and Prevention Program (NAEPP) (31, 32), the potential benefits of heliox in the treatment of asthma exacerbations was stated, especially as an al-

ternative to intubation. Theoretically, heliox is an ideal treatment strategy for status asthmaticus because the primary pathophysiology is restricted gas flow through narrowed airways.

In a double-blind, randomized, controlled trial performed in 18 children with status asthmaticus (14), early use of 80:20 heliox for 15 mins improved pulsus paradoxus (PP), peak expiratory flow, and dyspnea score as compared with control patients breathing oxygen-enriched air. The PP and dyspnea score worsened once heliox was discontinued. Heliox prevented intubation for three patients who were felt by clinicians (not involved in the study and blind to the study gas) to be in significant respiratory distress to necessitate this intervention. The authors cited no adverse effects to heliox administration. Thus, this class I study suggests early heliox use relieves dyspnea and improves the work of breathing.

The next class I study is an unblinded, prospective, randomized, controlled trial in adults with acute severe asthma who presented to the emergency department (ED) (3). Twenty-three patients were randomized to receive either 70:30 heliox or oxygen-enriched air (F_{IO_2} 0.30) within 1 hr of initiating conventional treatment. Within 20 mins, patients in the heliox group had a significant decrease in dyspnea score and respiratory rate. The heliox patients also demonstrated significantly increased percent predicted peak expiratory flow (PEF) (58.4%) vs. the control group (10.1%), providing additional class I data to suggest a positive role for early heliox therapy.

In a double-blind, prospective, randomized, controlled trial, Carter et al. (33) presented 11 children hospitalized with status asthmaticus. These patients received inhaled albuterol and intravenous corticosteroids before study entry. Patients randomly received either 70:30 heliox or oxygen-enriched air (F_{IO_2} 0.30) for 15 mins and were then switched to the alternate gas mixture after spirometric values were obtained. This class I study demonstrated a small but statistically significant improvement in PEF rate ($p = .04$) and mean mid-expiratory flow rate (FEF_{25-75}) of the predicted value ($p = .006$) with heliox. Heliox did not improve forced vital capacity, forced expiratory volume in 1 sec (FEV_1), clinical signs of asthma, or dyspnea. These authors acknowledge several factors, which may account for the lack of significant improvement with heliox. As a dedicated pediatric study, age-related factors in the disease process or compliance with spirometry measurements may have been confounding variables. Additionally, this was an inpatient study as compared with previous ED studies involving early heliox administration. These patients were also treated with conventional therapy for a minimum of 6 hrs before heliox administration and possibly already experienced significant benefit from conventional therapy (i.e., corticosteroids).

Recognizing the limitations to the Carter study, one can speculate that although late heliox use did not benefit these inpatients, there may be a beneficial role for heliox early in the ED course or in those patients requiring mechanical ventilation. Thus, this study suggests administering heliox as a "therapeutic bridge" for the 4- to 12-hr interval between arrival to the ED and onset of corticosteroid effect (2, 3, 5, 14, 34, 35).

In another prospective, randomized, placebo-controlled study in adults who presented to the ED with moderate to severe asthma, Dorfman et al. (36) compared 80:20 heliox (n = 20) and air (n = 19) for 1 hr. Both sets of patients had an average duration of symptoms of at least 40 hrs before study entry and had received continuously nebulized bronchodilators. Both groups had respiratory rates in the 20s and room air saturations ≥95% at study entry. No significant differences were noted in the posttreatment percent peak expiratory flow rate (PEFR) between the two groups. Patients were studied relatively late in the disease process, which may have eliminated any potential heliox benefit.

Manthous et al. (35) presented an unblind, nonrandomized, prospective study evaluating the effects of heliox on PP and PEF in 27 adult ED patients. The first 16 patients received a 15-min trial of 80:20 heliox for which data were collected before, during, and after gas administration. Data for the remaining 11 patients were obtained at similar time intervals during air breathing. All patients received inhaled albuterol and intravenous corticosteroids within 1 hr of study entry. Although PP decreased in both groups (reflecting the effects of standard therapy), the change in PP with heliox was significantly greater than with air breathing ($p < .05$). No effect on gas exchange with heliox was noted by arterial blood gas measurements obtained before and during administration of the gas for the seven patients who consented to the procedure. Patients receiving heliox reported less dyspnea. In addition, heliox patients had a more significant improvement in PEF than the air-breathing group ($p < .001$). This class II study demonstrated heliox improved expiratory flow, decreased hyperinflation, and reduced the work of breathing.

In 1999, Schaeffer et al. (4) presented a retrospective class II study comparing 11 adults with status asthmaticus who received heliox during the first 2 hrs of mechanical ventilation vs. 11 case-matched control patients ventilated without heliox. With no changes in ventilator settings, a significant drop in alveolar to arterial (A-a) gradient ($p < .0003$) occurred with heliox. The reduction in A-a gradient allowed clinicians to wean the F_{IO_2} from 0.81 ± 0.25 to 0.37 ± 0.27 and, thus, increase the helium concentration in the gas mixture, further enhancing its beneficial role in lowering gas density, improving gas flow characteristics, and reducing the risk of oxygen toxicity.

A recent article describes the effects of heliox in children with acute severe asthma during mechanical ventilation (19). This retrospective review of 28 patients used helium concentrations from 32% to 74%. With similar ventilator settings, peak inspiratory pressure (PIP) significantly decreased (40.5 ± 4.2 vs 35.3 ± 3.0 cm H_2O; $p < .05$) with heliox. The effect of heliox on PIP seemed most prominent at higher pressures (PIP >40 cm H_2O). The authors suggest that heliox decreases the obstruction to gas flow and, thus, augments laminar flow with a resultant decrease in PIP. The authors also reported significant improvements in CO_2 elimination and pH with heliox. This class III pediatric study suggests that in the early acute phase of asthma, heliox can improve gas flow and CO_2 elimination while reducing PIP and the potential risk of barotrauma and air leak.

Barach (37) was the first to describe the role of heliox for severely ill asthmatic patients who were refractory to conventional therapies. These patients demonstrated improved respiratory effort within minutes of heliox initiation. Improvements in intrapleural pressure were associated with decreased cardiovascular side effects and decreased pulmonary edema formation. In this class III study, patients with mild symptoms experienced variable degrees of relief, whereas the maximal benefit was seen in patients with moderate to severe symptoms.

In 1990, Gluck et al. (5) presented a case series of seven adult patients with status asthmaticus who required intubation. These patients developed a persistent respiratory acidosis associated with high PIPs ranging from 75 to 100 cm H_2O. With 60:40 heliox, the respiratory acidosis dramatically resolved, a mean reduction in $Paco_2$ of 35.7 mm Hg within 20 mins ($p < .001$) and a rise in pH (0.30 $\pm$ 0.06 units, $p < .001$). In six patients, PIP significantly decreased by an average of 32.9 cm H_2O within minutes of heliox administration. Thus, similar to Schaeffer's class II study, this class III study suggests heliox benefits patients with status asthmaticus requiring mechanical ventilation and may allow for a stepwise reduction in the fraction of inspired oxygen.

Clinical Application. In summary, it is difficult to form definitive conclusions based on these studies involving various study designs, patient groups, degrees of illness, treatment settings, time of intervention, and outcome measures. Additional studies involving a larger number of patients and more definitive study designs and outcome measures are needed to clearly define any potential beneficial role of heliox for acute asthma exacerbations.

The addition of heliox to the treatment regimen for acute asthma is not warranted for all patients. Because most patients do well with conventional therapies, there may not be an added benefit with heliox. However, in select patients with severe exacerbations, early heliox therapy may decrease airflow obstruction and facilitate gas exchange, especially as conventional therapies are implemented but before these therapies achieve full effect. Using heliox as a temporizing measure may prevent intubation for some patients. Evidence suggests heliox is more effective for the sicker patient (2, 3, 14, 35, 38, 39). The beneficial effects of heliox seem most efficacious when used early in the disease course (<24 hrs).

It is important to stress that there are no reported adverse effects of heliox. Thus, a trial of this gas mixture seems reasonable in patients with significant respiratory distress. Patients with a severe ventilation-to-perfusion mismatch may require an elevated Fio_2, but, as was revealed in the Schaeffer study (4), even those patients with high oxygen requirements (Fio_2 0.80 or greater) demonstrated improved gas exchange with the ability to wean the Fio_2. The clinician should see beneficial effects almost instantaneously, and if the patient is not improved within a few minutes, heliox should be abandoned and other therapies considered. Heliox is a relatively inexpensive and safe treatment option with a better side effect profile than many "conventional therapies" (eg, aminophylline). Perhaps with additional study, heliox can be included within the realm of standard therapy for asthma exacerbations.

Aerosol Delivery

Inhaled β-agonists are the mainstay for patients with acute asthmatic exacerbations. Maximal benefit is achieved when an adequate amount of medication reaches the lower airways. Unfortunately, <10% of nebulized drug reaches the lungs because most is deposited in the posterior oropharynx (40, 41). Although the increased use of nebulizers (42, 43) and meter dose-inhaler spacer devices (44, 45) have improved medical delivery as compared with traditional metered-dose inhalers alone, potential for significant improvement persists.

Several studies have investigated helium's role in improving nebulized medication delivery through constricted airways to more peripheral lung regions. The associated improved gas flow characteristics of heliox, theoretically, should facilitate delivery of β-agonists further down the tracheobronchiolar tree.

In an early pilot class II study (46), no difference was detected in spirometry measurements between heliox and oxygen when used to nebulize albuterol. These authors believed there was accidental entrainment of room air in their delivery system resulting in the dilution of the delivered helium. After modifying the delivery system to prevent this complication, the same group later published a class I study performed in asthmatics presenting in acute distress to the ED. In this study (47), the investigators identified 45 adults who met ATS criteria for asthma and had severe persistent symptoms as defined by a baseline FEV_1 <50% predicted. Using a noninvasive, semiclosed delivery system, these authors concluded that 80:20 heliox to nebulize albuterol significantly improved spirometry measurements when compared with oxygen as the driving gas. As this class I study shows, limiting contamination of the lower-density heliox gas with air is paramount to providing an improved clinical effect.

In a prospective, randomized study of 205 nonintubated adults with mild to moderate asthma exacerbations presenting to the ED, Henderson et al. (48) determined no benefit in FEV_1 or PEFR using heliox vs. oxygen during intermittent nebulization of a β-agonist. Patients were randomized to receive three 5-mg doses of albuterol 15 mins apart with either oxygen or 70:30 heliox. Clinical parameters were obtained before medication administration. There was no validation of a patient's asthma history, and inclusion for the study was based on patient self-reporting. This study used effort-dependent parameters as a measure of efficacy instead of more objective criteria. The delivery system was not described, and the actual helium-to-oxygen ratio was not measured with an external oxygen analyzer. Although this study met class I classification, concerns in the study design, patient selection criteria, heliox administration methods, and data collection exist, which make application of these results difficult.

In one of the earlier studies (49), ^{111}I-labeled Teflon particles similar in size to nebulized medications were administered to ten asthmatics in air or heliox. After 24 hrs, there was a greater deposition of particles to the alveolar level with heliox as the delivery gas. This class II study suggests the administration of inhaled bronchodilators with heliox may be of therapeutic value by enhanced peripheral deposition of the agent, thus improving clinical effect and outcome.

Hess and colleagues (50) conducted a laboratory study investigating the potential differences on nebulizer function between heliox and air. They investigated intermittent and continuous delivery of albuterol. The amount of albuterol deposited on a cotton plug placed at the mouthpiece was spectrophotometrically determined during a simulated spontaneous breathing model. They defined a particle size of 1–5 μm to represent the respirable range (49). Decreased delivery of albuterol occurred for intermittent and continuous delivery systems when heliox was used at a similar flow rate as air. The administration of heliox at a higher flow rate (8–11 L/min with intermittent delivery and 2–3 L/min during continuous delivery) resulted in significantly increased delivery of the total mass of albuterol and the 1- to 5-μm sized particles. The authors concluded the use of heliox to power a nebulizer affects both the size of the delivered particles and the total

amount delivered. They recommend increasing flow rates when using heliox as a driving gas for nebulizer therapy. In a subsequent study (6), Goode et al. determined that heliox in a ventilatory circuit could increase aerosol delivery by as much as 50% for metered-dose inhalers and nebulizers in a mechanical ventilation model. They also stressed the importance of appropriate flow rates. Both of these class II studies demonstrate a higher deposition of albuterol when using heliox at an appropriate flow rate.

Clinical Application. In conclusion, heliox improved delivery of inhaled bronchodilators to the lower airway and improved gas movement as measured by spirometry. It is essential to limit the accidental entrainment of air or oxygen, which may inadvertently result in a lower helium concentration and, thus, limit any clinical benefit. Higher flow rates may be necessary to produce a beneficial effect with heliox.

Upper Airway Obstruction

In the early medicinal application of heliox, Barach (1, 37) suggested a beneficial effect could be obtained with heliox for pediatric patients with upper airway diseases and edema. An obstruction in the upper airway results in an increased resistance to gas flow, turbulence and, therefore, less efficient gas exchange. Upper airway obstruction results from several disease processes: postextubation stridor (PES), trauma, space-occupying lesions, infections, and others. As the density of inspired gas is reduced, there is an exponential increase in flow through areas of constriction for the same pressure gradient (51). Regardless of etiology, heliox may improve gas flow, improve oxygenation, and decrease the work of breathing.

Laryngeal edema related to local trauma from tracheal intubation can result in increased airway resistance, increased work of breathing, and potentially respiratory failure. Humidified air/oxygen and racemic epinephrine remain standard treatment adjuncts. Dexamethasone is commonly administered; however, its ability to reduce postextubation complications remains controversial and requires several hours for full effect (52). Not infrequently, the degree of respiratory distress necessitates reintubation, which can further increase local trauma and swelling.

In a double-blind, randomized, controlled crossover trial of 13 children with PES (53), heliox was evaluated. Patients served as their own control and were randomly administered either heliox or oxygen-enriched air for 15 mins before crossing over to the alternate gas. The degree of respiratory distress was assessed on a 0–3 scale (respiratory rate, stridor, air movement, retractions, and oxygen saturations) by physicians blinded to gas type. In this class I study, respiratory scores for heliox were significantly improved ($p < .005$).

A prospective study of 18 adult patients in the immediate postextubation period compared heliox and oxygen-enriched air to evaluate respiratory effort (54). After extubation, three trials were performed consecutively: oxygen-enriched air, heliox, and oxygen-enriched air. Transdiaphragmatic pressure (using esophageal and gastric balloons), gas exchange, and a subjective comfort scale were the primary end points. Transdiaphragmatic pressure and, thus, work of breathing, significantly decreased ($p < .05$) with heliox. On the readministration of oxygen-enriched air, the work of breathing returned to baseline. On a dyspnea scale, patients reported a significant improvement in comfort while breathing heliox ($p < .001$). No significant differences in gas exchange were seen. The results of this class II trial demonstrate heliox may decrease inspiratory effort and improve comfort in the immediate postextubation period.

The use of heliox for PES has also been described in several case reports. On extubation, a 9-yr-old boy (7) and a 23-yr-old woman (51) experienced tachypnea, stridor, hypercarbia, and increased respiratory effort despite treatment with racemic epinephrine and corticosteroids. After the introduction of heliox, both patients demonstrated improved respiratory effort and gas exchange. In these class III studies, heliox relieved the increased airway resistance and work of breathing associated with postextubation stridor, which may have prevented reintubation.

In a class III review (51), intubation was prevented in seven of ten patients with upper airway obstruction by heliox administration. In three patients with airway narrowing secondary to a tumor, heliox temporarily stabilized the respiratory status. This intervention afforded the clinicians time to further assess the obstruction and prepare for a safer definitive intervention. Similar applications of heliox for "buying time" have been described in children (7, 55) and adults with tumor masses causing obstruction lower in the respiratory tree (56–58).

Clinical Application. In summary, heliox therapy for upper airway obstruction relieves respiratory distress, decreases the work of breathing, and improves gas exchange. Heliox may alleviate the need for reintubation in the postextubation period.

Croup (Laryngotracheobronchitis)

The most common form of the croup syndrome is acute viral laryngotracheitis. Croup causes an inflammation affecting the subglottic tissues and sometimes the tracheal mucosa. Until the airway inflammation resolves, severe upper airway obstruction may develop and occasionally may require intubation. Although corticosteroids have been demonstrated to relieve the associated airway obstruction, this therapy requires several hours for full effect and is not efficacious in all patients (59–61).

A 70:30 mixture of heliox was compared with racemic epinephrine in a prospective, randomized, double-blind trial of 29 children with moderate to severe croup receiving treatment with humidified oxygen and corticosteroids (62). Clinical effect was evaluated through a modified croup score (skin color, air entry, retractions, level of consciousness, and degree of stridor). This class I study demonstrated that heliox administration resulted in similar improvements in croup score as compared with racemic epinephrine.

In a class I prospective, randomized, double-blind, controlled trial of 15 pediatric patients with mild croup presenting to the ED (63), the group treated with a 70:30 heliox gas mixture trended toward a greater improvement in croup score than the oxygen-enriched air treatment group, although this difference did not meet statistical significance.

In a class III study, Duncan (64) described seven patients with croup and critical airway narrowing in whom heliox resulted in a decrease in croup score and improved gas exchange. No patient required intubation.

Clinical Application. The results from these class I and III studies suggest that heliox improves work of breathing as evidenced by croup score but to no greater degree than seen with conventional ther-

apies. Although one may argue that heliox should be the preferred agent because it has a lower side effect profile than corticosteroids or racemic epinephrine, it is important to keep in mind that heliox, as is suggested by the asthma literature, may act as a "therapeutic bridge," whereas corticosteroids and epinephrine have a direct therapeutic effect. Perhaps in those patients in whom the administration of steroids (65) or racemic epinephrine is contraindicated, heliox may be an effective alternative. Additionally, heliox may help to prevent intubation in those patients with impending respiratory failure.

Bronchiolitis

Approximately 91,000 infants are hospitalized with respiratory syncytial virus (RSV) infections annually in the United States (66). Routine supportive therapy for RSV-induced bronchiolitis includes oxygen and intravenous hydration. Bronchodilators and corticosteroids are generally not effective; however, this issue remains controversial. Sixteen percent of hospitalized patients require support in a pediatric intensive care unit (PICU) setting, and approximately 50% of these patients require intubation (8). From 1996 through 1998, 229 bronchiolitis-associated infant deaths occurred in the United States (67). Because bronchiolitis is associated with airway obstruction and turbulent gas flow, theoretically, heliox has a beneficial role.

In a randomized, double-blind, controlled crossover study heliox was compared with oxygen-enriched air in 13 infants with RSV bronchiolitis (8). Five additional patients were considered severely ill and nonrandomly received heliox to prevent intubation. For heliox and oxygen-enriched air, the F_{IO_2} was adjusted to maintain Sp_{O_2} >92%. The F_{IO_2} was maintained constant throughout the study period. Clinical Asthma Score decreased in the 13 randomized patients ($p < .05$) and in the 18 patients overall ($p < .01$) during the 20 mins of heliox delivery. Beneficial effects were most pronounced in children with the greatest degree of respiratory compromise. This class I study demonstrated a significant improvement in the work of breathing with heliox, and the authors suggest heliox may prevent intubation.

In a prospective class II study specifically studying patients admitted to the PICU, Martinon-Torres et al. (9) evaluated 70:30 heliox in 38 nonintubated infants with moderate-to-severe RSV bronchiolitis. This study used a modification of the Wood's clinical asthma scoring system based on oxygen saturation, quality of inspiratory breath sounds, expiratory wheezing, accessory muscle use, and level of consciousness. Patients receiving heliox had a more rapid improvement in clinical score and a greater magnitude of clinical improvement based on respiratory and heart rates. Heliox did not affect gas exchange. Importantly, the length of PICU stay was significantly shorter for the heliox group.

In a nonrandomized, unblinded case series involving ten patients (69), heliox did not improve gas exchange during mechanical ventilation for bronchiolitis. However, higher helium concentrations (60/40 and 70/30 heliox compared with 50/50 heliox) reduced the amount of intrapulmonary shunting as measured by the alveolar–arterial oxygen gradient (70). The authors of these class III studies suggest further studies are required to determine whether helium can allow for lower ventilating pressures in patients with more severe lung disease when using higher concentrations of helium.

Clinical Application. As is suggested by these studies, there may be a beneficial role for heliox to improve the work of breathing and gas exchange for infants with bronchiolitis. The beneficial effect of heliox was greater in patients with a larger degree of respiratory distress, may prevent the need for intubation and mechanical ventilation, and may shorten the length of PICU stay.

High-Frequency Ventilation

Not infrequently, the degree of acute lung injury requires a significant escalation in support, including the conversion from conventional to "nonconventional" ventilation such as high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV). Despite the utilization of these ventilator strategies, significant morbidity and mortality remain (71). Studies have evaluated the combination of these nonconventional modes of ventilation with adjunct agents such as inhaled nitric oxide (iNO) (72–76), surfactant (77, 78), and partial liquid ventilation with perflubron (79). Over the last several years, the combination of heliox with nonconventional modes of ventilation has been investigated.

In a prospective crossover laboratory study (11), heliox vs. oxygen-enriched air was evaluated during HFOV in a model of acute lung injury. This class II study demonstrated improved oxygenation and CO_2 elimination with heliox. These investigators found a 16% decrease in Pa_{CO_2} with heliox and a modest improvement in oxygenation. However, on further investigation, it was noted this improvement was related to larger tidal volume delivery by the oscillator with heliox. Once tidal volume was maintained constant, there was no significant improvement in gas exchange (80).

Winters et al. (12) reported improved CO_2 elimination in a series of five children with acute respiratory distress syndrome (ARDS) when heliox was administered during HFOV. In this class III paper, the authors noted a 24% decrease in Pa_{CO_2} within 45 mins of initiating heliox and an ultimate decrease of 43%. Heliox did not improve oxygenation. It must be speculated that this improvement in gas exchange was also related to increased tidal volume delivery.

One of the limiting factors in using heliox with HFOV is the high bias flow requirements of oscillatory ventilation and the resultant rapid consumption of heliox. Recently, this concern was addressed in a study in normal rabbits with the use of a low bias flow technique in normocapnic and hypercapnic conditions (81). By modifying the ventilator circuit, exhaled gas travels through a canister in which CO_2 is removed, thus allowing for the rebreathing of a relatively helium-rich gas. These investigators demonstrated that higher helium concentrations in the inspired gas resulted in larger improvements in CO_2 elimination. Further studies involving this interesting rebreathing technique are required before a recommendation for clinical application can be made.

Clinical Application. Based on these results, routine heliox use during nonconventional ventilation cannot be recommended. Given the high morbidity and mortality in patients requiring this escalation in respiratory support, a trial of heliox may be attempted in select patients. Because heliox administration with these nonconventional modes of ventilation is less reliable than when used during conventional mechanical ventilation, the need for continuous monitoring of oxygen and gas exchange is again stressed.

CONCLUSION

The improved flow properties and higher CO_2 diffusion coefficient of heliox make it an interesting adjunct in the treatment of acute respiratory failure. It is imperative to keep in mind that heliox has no direct treatment effects and is only a temporizing measure until more definitive therapies become effective or the disease process naturally resolves. Heliox may also allow time for the clinician to prepare for high-risk interventions such as intubation in certain patient populations (i.e., upper airway compression from tumors or trauma). Throughout this review, studies have both supported and contested a beneficial role for the clinical administration of heliox. However, most studies agree that heliox administration is extremely safe. No adverse effects of heliox have been reported. Heliox seems most effective during conditions involving density-dependent increases in airway resistance, especially when used early in an acute disease process.

In summary, it seems reasonable to consider heliox as a relatively safe "therapeutic bridge" for disease processes involving respiratory distress related to turbulent gas flow. This bridge may allow time for the planning of more definitive respiratory support, the onset of therapeutic medications, or the natural resolution of a disease process. The effects of heliox are relatively instantaneous. Thus, the clinician will quickly know if heliox therapy will be beneficial for an individual patient or if heliox should be abandoned for other therapies.

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