

Use of Heliox in Children

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For over 70 years, helium-oxygen mixture (heliox) has been promoted as adjunctive therapy to overcome airflow-obstructive disorders and lesions. In the past 2 decades heliox has gained widespread support in many pediatric emergency departments and intensive care units, in treatment of infants and children with both upper and lower airway obstruction. Because heliox is less dense than air or oxygen, it provides more laminar flow in obstructed airways, and it is purported to reduce work of breathing, respiratory distress, and postextubation stridor. Clinical evidence of the effectiveness of heliox in pediatric patients with airflow obstruction is relatively sparse and appears in the literature primarily as case presentations, case series, and small, uncontrolled studies. This article reviews the rationale and methods for heliox treatment of children with asthma, airway obstruction, bronchiolitis, and croup. Key words: helium, heliox, airway obstruction, asthma, bronchiolitis, croup, pediatrics. [Respir Care 2006;51(6):619–631. © 2006 Daedalus Enterprises]

Introduction

In 1934, Barach first described the use of helium as a therapy for upper-airway obstruction and asthma exacer-

bation.¹ Despite numerous advances in medicine, pharmacology, and technology over the subsequent 70 years, the optimal use and efficacy of helium-oxygen mixture (heliox) for managing airflow-obstructive disorders remains sporadically documented, largely anecdotal, and not clearly supported by the evidence. The low density and other physical properties of heliox would seem to make it ideal

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for reducing work of breathing in obstructed airways of pediatric patients.

Helium is an odorless, tasteless, nonexplosive, noncombustible, inert gas that has few pharmacologic properties of its own. For medicinal use, helium is administered as a gaseous mixture with oxygen. Helium is substituted for nitrogen and is generally delivered in concentrations $> 50\%$.

Airflow patterns in the pulmonary system are products of the physical conditions in the airway (eg, diameter, anatomic shape, branching, and smoothness of airway lining) and the composition of the inhaled gas. Lung periphery airflow is primarily laminar because of the large cross-sectional surface area that the gas flows through in the periphery. Conversely, airflow in the larger upper airways is turbulent, with relatively high flow and relatively small cross-sectional surface area.

Children with the smallest airways are hypothetically the most likely to benefit from heliox's physical properties. This article reviews the rationale for and methods used for heliox treatment of children with asthma, airway obstruction, bronchiolitis, and croup.

Asthma

Asthma is a complex, multi-factorial disease characterized by airway inflammation, airway hyperresponsiveness, and airflow obstruction that may or may not be at least partially reversible.² Asthma is one of the most common chronic diseases of childhood, today affecting an estimated 7 million children in the United States, with increasing prevalence in children < 5 years of age and increasing emergency-department visits and hospitalizations. Asthma exacerbations are usually associated with increased airflow obstruction, which is often reversible, either spontaneously or with treatment. During asthma exacerbations, not all children initially respond to bronchodilators and systemic corticosteroids. It is the restricted gas flow through the constricted airways that hypothetically positions heliox as an adjunctive treatment for pediatric asthma. The 2002 update of the asthma diagnosis and management guidelines issued by the National Asthma Education and Prevention Program (NAEPP)³ highlights the potential benefits of heliox for asthma exacerbation, especially as an alternative to intubation. The use of heliox in the management of pediatric asthma exacerbation is relatively common in today's clinical environment; however, strong evidence of its efficacy or the most efficient method of delivery has not been well documented in large randomized controlled trials. I will review 4 randomized trials of heliox with spontaneously breathing children, and one trial of heliox with asthmatic children who required intubation and mechanical ventilation.

Kudukis et al conducted a double-blind randomized controlled study of the efficacy of heliox in 18 children (ages 6 months to 16 years) with status asthmaticus.⁴ Efficacy of early administration of 80% helium/20% oxygen (80:20 heliox) through a nonrebreather face mask was defined as a reduction in pulsus paradoxus, reduction in dyspnea score, or an improvement in peak expiratory flow. All the children were continuously administered β agonists and received intravenous methylprednisolone. Status asthmaticus was defined as continuous wheezing with observable respiratory distress and a pulsus paradoxus > 15 mm Hg after 30 min of receiving asthma treatment. Data were collected by 2 independent observers. Supplemental oxygen was supplied via nasal cannula contained within the nonrebreather mask, to maintain oxygen saturation $> 88\%$. Data were collected at baseline and every 15 min during and after the blinded administration of the study gas (heliox) and the control gas (oxygen). Ten children received heliox; eight received oxygen. Within 15 min of the start of administration, heliox was associated with significantly lower pulsus paradoxus (10.6 ± 2.8 mm Hg vs 21.2 ± 9.8 mm Hg, $p < 0.005$) and dyspnea index (1.9 ± 1.7 vs 5.5 ± 1.6 , $p < 0.005$) than was oxygen. There was significantly less pulsus paradoxus among all 10 patients who received heliox (mean pulsus paradoxus 23.3 ± 6.8 mm Hg vs 10.6 ± 2.8 mm Hg, $p < 0.001$), and pulsus paradoxus increased when heliox was discontinued (mean pulsus paradoxus 18.5 ± 7.3 mm Hg, $p > 0.15$). Eleven children (7 in the heliox group, 4 in the control group) had peak expiratory flow measured with a density-corrected flow meter. Heliox was associated with a significant increase in peak flow ($69.4 \pm 12.8\%$ above baseline, $p < 0.05$) and a significant decrease in dyspnea index (from 5.7 ± 1.3 to 1.9 ± 1.7 , $p < 0.001$). The dyspnea index increased (4.0 ± 1.6) after heliox discontinuation. The authors concluded that early intervention and use of heliox in children with status asthmaticus relieves dyspnea and decreases the work of breathing.

In a double-blind randomized controlled trial, Carter et al investigated the impact of heliox on pulmonary function, dyspnea, and clinical symptom score in 11 children hospitalized with status asthmaticus.⁵ All children received nebulized albuterol (5 mg every 1–4 h) and intravenous corticosteroids before study entry, and were randomized to either 70:30 heliox or 30% oxygen for 15 min, and, after spirometry, were crossed over to the opposite treatment arm for 15 min. There was no difference between the groups in clinical or dyspnea symptom scores, forced expiratory volume in the first second (FEV_1), or forced vital capacity (FVC). Heliox was associated with a small but statistically significant improvement in peak flow ($p < 0.04$) and the percent-of-predicted mean flow in the middle half of the FVC (FEF_{25-75}) ($p < 0.006$). Heliox provided the least benefit in patients who had the greatest

Table 1. Pulmonary Index Scoring System

	Pulmonary Index Score			
	0	1	2	3
Respiratory rate of patients < 6 y old (breaths/min)	< 30	31–45	46–60	> 60
Respiratory rate of patients ≥ 6–20 y old (breaths/min)	< 20	21–35	36–50	> 50
Wheezing	None	End-expiratory	Throughout entire expiration	No air entry, or wheezing throughout inspiration and expiration, audible without stethoscope
Accessory respiratory-muscle use	None	Mild	Moderate	Severe
Inspiratory-expiratory ratio	2:1	1:1	1:2	1:3
S _{pO₂} (%)	99–100	96–98	93–95	< 93

S_{pO₂} = blood oxygen saturation, measured via pulse oximetry

degree of airflow obstruction. The authors suggested that lack of response to heliox may have been partly attributable to the inability of young patients to use the spirometer and the extended treatment with conventional therapy, for a minimum of 6 hours, prior to heliox. The authors concluded that heliox use in the management of pediatric status asthmaticus did not benefit this group of children during its short-term use in this study. However, one could argue that administering heliox may serve as a “bridge” between emergency department arrival and onset of conventional therapy effectiveness.

In a single-blind randomized controlled trial conducted with a convenience sample of children, Kim and colleagues investigated the effectiveness of a 70:30-heliox-driven versus 100%-oxygen-driven continuous aerosol therapy in the treatment of asthmatic children (ages 2 to 18 years) with moderate-to-severe exacerbations and pulmonary index of ≥ 8.⁶

The pulmonary index (Table 1) is a validated emergency assessment tool for asthma. Pulmonary index scores range from 0 to 15. A score of ≥ 8 indicates a moderate-to-severe asthma exacerbation. On arrival in the emergency department, potential enrollees were initially treated with 5 mg of inhaled albuterol via face mask, from a large-volume oxygen-driven nebulizer at a flow of 10 L/min and a dose of oral prednisone or prednisolone, while the patient was being assessed by an investigator for entry criteria.

After 20 min of initial nebulized treatment, patients who met eligibility criteria were randomly assigned to receive continuously nebulized albuterol (15 mg/h) with either heliox (*n* = 15) or oxygen (*n* = 15) for 60 min, followed by 500 μg of ipratropium bromide over 5 min. After 60-min assessment by the unblinded recruiting investigator, patients whose pulmonary index was ≥ 3 received a second hour of continuous albuterol (15 mg/h) and a second dose of ipratropium bromide. After 120 min, patients were as-

sessed again, and those with a pulmonary index score of ≥ 3 received a third hour of continuous albuterol.

Pulmonary index scores were determined by an unblinded pediatric emergency-medicine attending physician (who did not participate in the study), from blinded video recordings over 240 min (at 30-min intervals for the first 3 hours) or until emergency-department discharge (if < 240 min). Heliox was initiated with 70:30 heliox and reduced to 50:50 heliox as possible while maintaining blood oxygen saturation ≥ 93%. Patients who required ≥ 50% oxygen were considered heliox-treatment failures, taken off the heliox, and treated with 100% oxygen.

Thirty-five children (of 75 screened) met eligibility criteria, and five were excluded (four due to no parental consent, and one for failure to tolerate the mask). There were no differences between the groups with regard to age, gender, race, duration of symptoms, recent use of asthma medications, initial pulmonary index score, or oxygen saturation (measured via pulse oximetry [S_{pO₂}]). The heliox group had a significantly greater reduction in pulmonary index than did the oxygen group (mean change 6.67 vs 3.33, *p* < 0.001). The mean pulmonary index improvement with heliox was greater at 125 min (*p* < 0.05) and was sustained at 150, 180, and 240 min (*p* < 0.01). Discharge rate in < 12 hours was higher in the heliox group (73% vs 33%, *p* < 0.05). Kim and colleagues concluded that, among children presenting to the emergency department with moderate-to-severe asthma exacerbation, continuously nebulized albuterol delivered with heliox was associated with greater clinical improvement than when delivered with oxygen.

In a blinded randomized controlled trial by Rivera et al, a comparison of initial response to albuterol nebulized with heliox (versus control) was undertaken in children presenting to a pediatric emergency department for moderately severe asthma.⁷ Children 1–6 years old who presented with a history of asthma (defined as ≥ 3 prior episodes of reversible bronchospasm) and a modified dys-

pnea index score ≥ 4 were randomized to receive continuous albuterol therapy (0.45 mg/kg, maximum 15 mg/h) delivered with heliox via nonrebreather face mask ($n = 20$) or with 30% oxygen (control, $n = 21$). Intervention began after three 2.5-mg doses of aerosolized albuterol and 2 mg/kg intravenous methylprednisolone (maximum 60 mg). There was no significant difference between the groups with regard to dyspnea index score evaluated at 10 min ($p = 0.169$) or 20 min ($p = 0.062$) after randomization. There was no statistically significant difference in admission rate (oxygen 81%, heliox 60%, $p = 0.181$), and no patients required endotracheal intubation in either group. The authors concluded that heliox offered no direct clinical benefit over standard therapy in the initial treatment of moderately severe asthma in the emergency department.

Abd-Allah and colleagues conducted a retrospective review of heliox in 28 children with acute severe asthma who required mechanical ventilation. Helium concentration ranged from 32% to 74% (mean $57 \pm 4\%$).⁸ Patients served as their own controls. Prior to heliox administration, patients were stabilized on volume ventilation within 24 hours of intubation or admission, and were provided bronchodilator therapy, corticosteroids, and antibiotics when indicated. Oxygen administration was titrated to maintain $S_{pO_2} \geq 90\%$. Arterial blood gases were measured and hypercapnia was permitted while maintaining $pH \geq 7.25$.

Heliox therapy was initiated at 5–7 L/min. Periodic arterial blood gas measurements were made to ensure continued appropriate ventilation. Heliox therapy was continued until either extubation or resolution of severe asthma; the latter was identified as substantial improvement in clinical lung examination and decreased need for bronchodilator therapy. During this trial, 75 patients with severe asthma who required mechanical ventilation received heliox, and 28 patients (37%) met inclusion criteria for the study.

Mean age and weight were 8.8 years and 32.3 kg, respectively. Baseline settings prior to heliox administration included: mean respiratory rate 12 ± 1 (range 7–24) breaths/min, tidal volume 16.6 ± 1.6 mL/kg, and peak inspiratory pressure 40.5 ± 4.2 cm H_2O . With the initiation of heliox therapy, significant decreases occurred in mean peak inspiratory pressure (from 40.5 ± 4.2 cm H_2O to 35.3 ± 3.0 cm H_2O , $p < 0.05$) and mean P_{aCO_2} (from 58.2 ± 8.5 mm Hg to 50.5 ± 7.4 mm Hg, $p < 0.05$), and there was a significant increase in mean pH (from 7.26 ± 0.05 to 7.32 ± 0.06 , $p < 0.05$). Though no patients required reintubation, 5 patients continued to receive heliox therapy via face mask for a short period following extubation. The maximum heliox benefit was seen in patients with moderate-to-severe symptoms. This single-center trial suggests that heliox can improve gas flow and CO_2 elimination while reducing peak inspiratory pressure in the early phase

of an asthma exacerbation that requires mechanical ventilation.

Clinical Application

The reports on the use of heliox in children with asthma have provided conflicting results. Conventional treatment is sufficient for the majority of asthma exacerbations. As heliox is a relatively expensive gas (compared to oxygen or compressed air), first-line use of heliox is not warranted for most patients.

Heliox appears to benefit patients with the most severe exacerbations and airflow obstruction. Early use of heliox may decrease work of breathing and dyspnea, improve gas exchange, and even prevent intubation in some patients. Heliox has a relatively safe treatment profile, and clinical benefits should be rapid.

In summary, it is difficult to draw conclusions from these studies, which had different study designs, assessment criteria, severity of illness, treatment settings, times of intervention, and outcome measures. Questions regarding the treatment of acute asthma with heliox remain unanswered. Additional studies are needed to determine the role of heliox in acute asthma exacerbation.

Upper-Airway Obstruction

Upper-airway obstruction is the most common indication for which heliox is used. Children have smaller airways than adults and are more commonly affected by diseases that cause upper-airway obstruction. Upper-airway obstruction is most commonly associated with postextubation stridor, subglottic injury or trauma, space-occupying lesions, and infections. A common strategy for treating these conditions that increase airway resistance is insertion of an artificial airway. Laryngeal edema, inflammation, mucosal ischemia, subglottic swelling, and/or stenosis related to local trauma from tracheal intubation can increase airway resistance and work of breathing, and potentially cause respiratory failure. Regardless of the etiology of the upper-airway obstruction, heliox may improve gas flow, improve oxygenation, decrease work of breathing, and resolve clinical signs and symptoms, thus obviating intubation.

In a 3-year retrospective study of patients with upper-airway obstruction from a multitude of etiologies, Grosz and colleagues evaluated heliox in 42 children (ages 1–14 years) admitted and treated (44 occurrences) for substantial upper-airway obstruction.⁹ A positive response to heliox was defined as a documented reduction in the work of breathing in the patients' medical record. Using this largely anecdotal criteria, 32 (73%) of the children had a decrease in work of breathing with heliox. All the prematurely-born children had a positive response, whereas the majority

(67%) of children who had congenital anomalies or syndromes were nonresponders. Grosz et al concluded that heliox was effective and useful as an adjunct therapy for upper-airway obstruction.

In a convenience-sample study by Connolly and McGuirt, 14 consecutive patients with severe subglottic edema or injury and severe airway distress, and who met criteria for intubation, were treated with heliox as their initial therapy.¹⁰ Ten children (71%) who received heliox did not need intubation. Four of the children required intubation (75% with a prior history of subglottic stenosis) and mechanical ventilation. The authors concluded that heliox was a relatively safe and effective alternative therapy for children with severe subglottic edema or injury prior to initiating intubation and mechanical ventilation.

In a double-blind randomized controlled crossover trial, Kemper and colleagues evaluated the effectiveness of heliox in reducing postextubation stridor in 13 children (15 total extubations) with burns and trauma.¹¹ Children (< 15 years of age) electively extubated with postextubation stridor and an oxygen requirement of $F_{IO_2} < 0.35$ were enrolled in this study. A blinded physician assessed study participants for respiratory distress after 15 min of study-gas administration before crossing over to the other study gas. Respiratory distress was assessed on a 0–3 scale for changes in respiratory rate, stridor, air movement, retractions, and S_{pO_2} . Seven of the 15 patients required subsequent treatment with racemic epinephrine or reintubation. Respiratory distress scores were significantly better (2.8 vs 3.7, $p < 0.005$) with heliox. Anecdotally, in 8 out of 9 trials the physicians preferred heliox. Kemper and colleagues concluded that heliox decreases stridor score in children with postextubation stridor and that it is a preferred treatment.

In a convenience-sample study, Rodeberg and colleagues sought to determine whether heliox would reduce postextubation stridor in children with burns.¹² Eight children with postextubation stridor and retractions and who were refractory to racemic epinephrine were given a trial of heliox prior to reintubation. Helium concentrations between 50% and 70% were administered for 28 ± 5 hours. Two of the children required reintubation, but six of them had a decrease in respiratory distress score (6.8 ± 0.7 vs 2.0 ± 0.7) with heliox and did not require reintubation. The authors concluded that heliox relieved postextubation stridor, reduced respiratory distress, and prevented reintubation in the majority of these children with burns.

Clinical Application

In summary, heliox therapy for upper-airway obstruction relieves stridor, reduces respiratory distress, and decreases the work of breathing. Although the evidence is

largely from uncontrolled trials, heliox may decrease the need for intubation and/or reintubation.

Croup (Laryngotracheobronchitis)

Acute viral laryngotracheitis is the most common form of croup syndrome. Croup syndromes typically create inflammation of subglottic tissue and, to a lesser extent, the tracheal mucosa, resulting in swelling and narrowing of the upper airway. This severe obstruction may require intubation. Corticosteroids^{13–15} often require several hours to relieve obstruction and are not efficacious in all patients.

In some of the earliest reports of heliox in the management of croup, Duncan described a case series of 7 patients with acute airway obstruction: two by croup and the others by mass effect or postextubation edema.¹⁶ Children treated with heliox had a significant decrease in croup score (mean croup score 7.9 decreased to 3.9) and an overall improvement in gas exchange. In another case series report of 14 patients (ages 3–21 months) admitted to the hospital with the diagnosis of croup, the authors reported reduced respiratory distress almost immediately upon initiation heliox. None of those children required intubation.¹⁷

In a randomized double-blind placebo-controlled trial with 15 pediatric patients with mild croup who presented to an emergency department, Terregino et al administered either humidified 30% oxygen or humidified 70:30 heliox.¹⁸ The children who received heliox had a nonsignificantly greater improvement in croup score than did the oxygen group. Terregino et al concluded that patient assessment with a croup-scoring system and blood gas analysis suggests heliox as a safe, well-tolerated, and useful alternative to tracheostomy or tracheal intubation in children with croup.

Weber et al compared the additive effect of 70:30 heliox with racemic epinephrine on a modified croup score in 29 children with moderate-to-severe croup in the emergency department or pediatric intensive care unit (PICU).¹⁹ In this randomized double-blind trial, all the children received initial treatment with humidified oxygen and 0.6 mg/kg of intramuscular dexamethasone. Children with a moderate-to-severe croup score (≥ 5 , based on skin color, air entry, retractions, level of consciousness, and degree of stridor) were assigned to either heliox or racemic epinephrine. There were no differences between the groups in mean croup score, oxygen saturation, respiratory rate, or heart rate, at baseline or at the treatment end period. Croup score decreased in both the heliox and racemic epinephrine groups. Weber and colleagues concluded that racemic epinephrine and heliox have equal treatment efficacy in children with croup.

Clinical Application

These studies suggest that while heliox improves respiratory distress, as evidenced by improvement in croup scores, heliox is not superior to other conventional therapies. Proponents of heliox may argue that the combination of heliox and conventional therapies allows a substantial reduction in work of breathing, respiratory distress, and the likelihood of intubation while waiting for the corticosteroids to take effect.

Bronchiolitis

Bronchiolitis is one of the most common infectious diseases in infants, causing an estimated 91,000 hospitalizations annually in the United States, typically between November and April.²⁰ The primary pathogens responsible for bronchiolitis are respiratory syncytial virus, parainfluenza virus, and *Haemophilus influenzae*. In bronchiolitis the inflammation causes edema, excessive mucus production, and airway obstruction. Evidence suggests that β_2 agonists and corticosteroids are of little therapeutic value in the treatment of bronchiolitis. It is less controversial to use the more supportive therapeutic approach of ensuring adequate hydration and providing supplemental oxygen when indicated. Since bronchiolitis is associated with airway obstruction, which increases turbulence in the airways, heliox may be of benefit.

In a randomized double-blind controlled crossover study, Hollman and colleagues sought to determine the efficacy of heliox versus oxygen-enriched air administered at 20-min intervals to 13 infants with respiratory syncytial virus bronchiolitis.²¹ Five additional nonrandomized patients (considered severely ill) received heliox as initial therapy to prevent intubation. Clinical Asthma Score, respiratory rate, heart rate, and S_{pO_2} were measured prior to randomization and after each 20-min treatment period (heliox or oxygen-enriched air). Nonrandomized patients were studied 20-min into heliox delivery. During heliox administration the Clinical Asthma Score decreased in all 18 patients (mean 1.23, $p < 0.01$), as well as in the 13 randomized patients (mean 0.46, $p < 0.05$). Improvements in Clinical Asthma Score were most pronounced ($p = 0.009$) in children with the greatest respiratory compromise (Clinical Asthma Score < 6). Hollman and colleagues concluded that heliox provided greater clinical improvement in overall respiratory status in children with acute respiratory syncytial virus.

In a multicenter randomized double-blind placebo-controlled trial, Liet and colleagues sought to determine if heliox administered via a plastic inflatable head hood could reduce the need for positive-pressure mechanical ventilation in infants (< 9 months old and weight < 10 kg) admitted in 4 PICUs, with first episode of severe bronchi-

olitis and respiratory failure.²² Inclusion criteria were (1) signs of respiratory failure ($S_{pO_2} < 92\%$ on room air or $P_{aO_2} < 40$ mm Hg), and (2) at least two of the following: tachypnea, chest retractions, wheezing, or hyperinflation on chest radiograph. Exclusion criteria were air leaks, cystic fibrosis, uncorrected cyanotic congenital heart disease, cardiac failure, neuromuscular disease, bronchopulmonary dysplasia, in PICU for > 8 hours, or prior initiation of mechanical ventilation.

Infants were randomized to receive either 78:22 heliox or 78:22 nitrogen-oxygen mixture administered via the plastic inflatable head hood, and the fraction of inspired oxygen (F_{IO_2}) was reduced to the lowest level that provided adequate oxygenation ($S_{pO_2} \geq 92\%$). Study gas could not be weaned until 24 hours of therapy had elapsed, and the gas (heliox or nitrogen-oxygen mixture) could be discontinued when the oxygen requirement dropped to $F_{IO_2} < 25\%$. Severity of respiratory distress was assessed hourly, using the Respiratory Distress Assessment Instrument.²³⁻²⁵

Only 39 infants of the 157 screened met all eligibility criteria and were randomized to study gas. No crossover to the other treatment was allowed. There were no significant group differences in baseline data at PICU admission or at time of entry into the study. Heliox (mean fraction of inspired helium $62 \pm 5\%$) was used without any adverse effects in all patients for 24 hours. Inhaled bronchodilator therapy was administered to 30 infants (17 in the control group, 13 in the helium group, $p =$ not significant). There was no significant difference between the groups in the primary outcomes of positive-pressure ventilation (control 19%, helium 22%), endotracheal intubation (control 14%, helium 22%), or time to intubation (control 26 ± 15 h, helium 36 ± 24 h), and no clinically important differences in secondary outcome measures, including clinical scores, oxygen requirement, P_{aCO_2} , duration of study-gas administration, or PICU stay. The authors concluded that heliox provided no significant clinical benefit in this trial.

In a prospective interventional comparative study with infants consecutively admitted to the PICU, Martín-Torres et al evaluated 70:30 heliox in 38 nonintubated infants (ages 1 month to 2 years) with moderate-to-severe respiratory syncytial virus bronchiolitis.²⁶ The first 19 infants admitted received nebulized epinephrine (control). The second 19 infants admitted received nebulized epinephrine and heliox therapy through a nonrebreather face mask. At baseline, the groups were similar in demographics and illness severity. Infants were evaluated with a modification of the Wood's clinical asthma scoring system (which assesses oxygen saturation, quality of inspiratory breath sounds, expiratory wheezing, accessory muscle use, and level of consciousness). Clinical score, heart rate, respiratory rate, and oxygen saturation improved in both groups. At both 1 hour and at the end of the observation period, the infants who received heliox had a more rapid

improvement in clinical score and better clinical improvement, based on respiratory and heart rates. PICU stay was significantly shorter in the heliox group than in the control group. Martínón-Torres et al concluded that heliox enhanced clinical respiratory status in infants with moderate-to-severe bronchiolitis.

In a nonrandomized unblinded repeated-measures case series involving 10 infants (ages 1–9 months) with bronchiolitis, Gross and colleagues²⁷ assessed the response of infants who were mechanically ventilated with synchronized intermittent mandatory ventilation and administered the following study gases in 15-min intervals: 50% nitrogen/50% oxygen, 50:50 heliox, 60:40 heliox, 70:30 heliox, and then returned to 50% nitrogen/50% oxygen. During study-gas administration, the protocol stipulated that no ventilator parameters could be adjusted during the 75 min of the study. The investigators obtained the following baseline variables at study onset and at 15-min intervals, or just before changing the gas mixture: temperature, heart rate, mean arterial blood pressure, measured oxygen saturation, arterial blood gases, P_{aO_2}/F_{IO_2} , and alveolar-arterial oxygen difference ($P_{(A-a)O_2}$).

Heliox was well tolerated by all the patients, and none of the patients had any adverse effects. Heliox did not improve gas exchange during mechanical ventilation for bronchiolitis at any of the concentrations evaluated. There were no significant differences in mean P_{aCO_2} , P_{aO_2}/F_{IO_2} , or $P_{(A-a)O_2}$ with any of the 4 gas mixtures ($p = 0.93, 0.98, 0.96$, respectively). Gross and colleagues hypothesized that they failed to see a significant improvement in ventilation and oxygenation because of one or more of the following: small sample size ($n = 10$), the patients having only mild-to-moderate lung disease, the mode of ventilation (synchronized intermittent mandatory ventilation), and an ineffective concentration of helium. The authors concluded that the heliox mixtures they studied did not significantly decrease P_{aCO_2} or increase P_{aO_2}/F_{IO_2} or $P_{(A-a)O_2}$, compared to traditional oxygen-air mixtures. The authors noted in a second publication that higher helium concentrations (60:40 and 70:30) reduced the amount of intrapulmonary shunt, as measured by the $P_{(A-a)O_2}$.²⁸

Clinical Application

Though the evidence is somewhat scarce and controversial, heliox may decrease work of breathing and improve gas exchange in infants with bronchiolitis. The beneficial effect of heliox was largely witnessed in nonintubated infants who were assessed as having moderate-to-severe respiratory distress. Administration via hood did not appear to be effective. Although the effect has not been statistically significant in the few trials to date, heliox may reduce the need for intubation and mechanical ventilation for acute bronchiolitis, and shorten overall stay.

Table 2. Four Subgroups, Based on Airflow Obstruction Severity and Gas Inhaled

Gas	Severity of Obstruction	
	Mild	Severe
Heliox	$FEV_1/FVC > 0.75$	$FEV_1/FVC_1 < 0.75$
	$FEF_{75}/FVC > 0.25$	$FEF_{75}/FVC < 0.25$
Oxygen	$FEV_1/FVC > 0.75$	$FEV_1/FVC < 0.75$
	$FEF_{75}/FVC > 0.25$	$FEF_{75}/FVC < 0.25$

Heliox = helium-oxygen mixture
 FEV_1/FVC = ratio of forced expiratory volume in the first second to forced vital capacity
 FEF_{75}/FVC = ratio of forced expiratory flow at 75% of the FVC to the total FVC

Aerosol Delivery With Heliox

Inhaled medications (eg, α and β_2 agonists, corticosteroids) are a vital component of treatment regimens for patients suffering from airflow obstruction. Effective aerosol therapy requires deposition of the medication to or beyond the site of the obstruction. Heliox has been advocated for delivery of aerosol through obstructed airways. Most of the research and investigation of heliox's ability to improve aerosol delivery in obstructed airways has been conducted in research laboratories or clinically with adult asthmatics. Under the best of conditions, aerosol delivery from a continuous-flow nebulizer powered by a compressed gas source (ie, air or oxygen) deposits < 10% of the medication in the target lung region; the other 90% is wasted to the atmosphere, deposited in the oropharynx, or left as residue in the nebulizer cup.^{29,30} The deposition efficiency is even lower in infants and small children.

Heliox improves particle deposition and retention in adult asthmatics,³¹ but, to date, only one study of heliox aerosol deposition in children has been reported.³² Piva and colleagues compared the distribution and deposition of a nebulized, radiolabeled aerosol inhaled with oxygen or heliox. This randomized double-blind controlled study included 20 children, ages 5–15 years, who had chronic lower-airway obstruction and continuous respiratory symptoms, despite daily administration of bronchodilators and/or other respiratory drugs.³²

Four subgroups were identified according to airflow obstruction (mild or severe) and study gas (heliox or oxygen) (Table 2). Before starting the study, the same technician instructed each child regarding optimal drug-delivery breathing pattern (deep and slow breathing) and the importance of a snug and tightly fitted mask (to avoid room-air contamination or waste of study gas). The technician allowed 5 min for the patient to acclimate to the equipment and practice the provided instructions. Participants were then randomized to receive either 80:20 heliox or oxygen to nebulize the radiolabeled aerosol (diethylenetriamine-

pentaacetate labeled with technetium-99m) for 15 min during the scintigraphy study.

When comparing children with mild and severe peripheral airway obstruction in each group, there was a significant difference in the ratio of FEV₁ to FVC and the ratio of FEF₇₅ to FVC (heliox $p = 0.007$ and 0.002 , respectively, and oxygen $p = 0.008$ and 0.003 , respectively). Scintigraphy scans from children with severe peripheral airway obstruction in the heliox group showed significantly higher cumulative lung irradiation ($p = 0.045$) and significantly higher slope of the curve ($p = 0.017$) than did the other 3 subgroups. The mean diameter of the particles produced by heliox ($2.13 \pm 0.62 \mu\text{m}$) when used as the nebulizer driving gas was significantly larger ($p < 0.004$) than the mean diameter of the particles produced by oxygen ($0.88 \pm 0.99 \mu\text{m}$). The authors concluded that heliox improved deposition of the radiolabeled particles in children with severe lower-airway obstruction, but not in children with less severe obstruction.

Several groups have identified the effect of heliox on particles and output rate from jet nebulizers, alone and during mechanical ventilation.^{32–35} In general, jet nebulizers driven by heliox at the same suggested flow as with oxygen produce significant smaller aerosol particles and have lower output rate and lower inhaled mass.³³ When heliox flow is increased by 50–100% greater than the flow used with oxygen, particle size and output increase to the range of the jet nebulizer operated with air.^{33,35}

In models that simulated mechanical ventilation, heliox increased aerosol delivery by as much as 50% in both infant³⁴ and adult³⁵ conditions. Habib and colleagues³⁴ compared albuterol delivered to a model of pediatric mechanical ventilation with 70:30 heliox and 70% oxygen. A simulated pediatric patient was mechanically ventilated with a volume-cycled infant/pediatric ventilator and a minimal-dead-space nonhumidified pediatric circuit through a 4.0-mm inner diameter, 19-cm long endotracheal tube (ETT) and a lung simulator. The metered-dose-inhaler (MDI) canister and Aerochamber spacer was inserted between the circuit and an elbow adapter connected to the ETT, which was positioned at 90 degrees on a template to simulate in vivo placement. The distal end of the ETT was connected to an airway resistor to simulate pulmonary resistance (50 cm H₂O/L/s) of lower-airway obstruction in children.

A hydrophobic filter was placed between the resistor and lung simulator to collect the albuterol delivered. This filter's membrane prevents passage of liquid and airborne particles (> 99.99% efficiency with particles > 0.3 μm) while maintaining a relatively low-resistance flow. The lung simulator was ventilated with settings for a 15-kg child with obstructive airway disease, with a constant flow of 70% oxygen at 25 L/min. For the test with 70:30 heliox, the settings were identical except that the flow was den-

sity-adjusted to 16 L/min, because the ventilator's flow meter is not calibrated for heliox. The 70:30 heliox and regulator was connected to the oxygen port on the ventilator. During administration of heliox, the blender on the ventilator was set for F_{IO₂} of 1.0. Lung-simulator compliance was set at 10 mL/cm H₂O.

Four pressure-volume/flow-volume loops were recorded so that dynamic compliance could be calculated using a standard formula for both heliox and oxygen. Data for static compliance and expiratory resistance were compiled from 8 sequential measurements with an automated occlusion technique. After baseline measurements, the pneumotachograph was removed from the circuit and albuterol was administered. To ensure consistency during albuterol administration, tidal volume was measured. An approximate albuterol dose of 2,000 μg was administered (20 puffs \times 100 μg /puff) without interrupting mechanical ventilation. Two ventilator breaths were delivered prior to each MDI activation. The spacer, filter, and ETT were replaced after each test. Albuterol delivery was measured by rinsing the circuit filter twice with 25 mL of high-performance-liquid-chromatography-grade water, and was verified in triplicate. The percentage delivery was calculated by dividing the amount of albuterol by 2,000 μg administered and multiplying by 100. Differences in albuterol delivery and pulmonary mechanics and volumes were compared. The mean amount and percentage of albuterol delivered were significantly ($p < 0.05$) greater with 70% heliox ($395 \pm 29 \mu\text{g}$ and $20 \pm 3.2\%$, respectively) than with oxygen ($241 \pm 29 \mu\text{g}$ and $12 \pm 1.7\%$, respectively) during this ventilator simulation. Habib and colleagues concluded that albuterol delivery via pressurized MDI in a model of pediatric mechanical ventilation can be improved by heliox; however, further in vitro and clinical studies are necessary to determine the role of heliox in inhaled-drug administration.

Goode et al³⁵ sought to determine the effect of various heliox mixtures on albuterol delivery from MDIs and jet nebulizers in an in vitro model of mechanical ventilation. Three different experiments were conducted: (1) influence of gas density on aerosol delivery with an MDI, (2) influence of heliox on nebulizer efficiency, and (3) optimizing aerosol delivery with a nebulizer during mechanical ventilation.

Experiment 1 indicated that albuterol delivery from an MDI with spacer was greater with higher concentrations of heliox (80:20 heliox $46.7 \pm 3.3\%$, 70:30 heliox $43.9 \pm 1.0\%$, 60:40 heliox $39.0 \pm 0.9\%$, and 50:50 heliox $39.9 \pm 1.3\%$, $p \leq 0.04$). Albuterol delivery with each heliox mixture was significantly greater than with air ($30.2 \pm 1.3\%$ greater, $p \leq 0.001$) or oxygen ($29.1 \pm 1.3\%$ greater, $p \leq 0.001$). Albuterol delivery was inversely related to gas density in the ventilator circuit ($r = -0.98$, $p \leq 0.005$). Active humidification of the ventilator circuit decreased

aerosol deposition under all conditions, but the delivery of albuterol in a humidified ventilator circuit was significantly greater with 80:20 heliox than with air ($p \leq 0.02$).

In experiment 2, albuterol delivery from jet nebulizers operated with the same flow rate (6 L/min) was related to gas density ($r = 0.944$, $p \leq 0.001$). Oxygen provided the highest drug delivery. As heliox flow was increased (10 L/min vs 5 L/min, $p \leq 0.001$), albuterol delivery was greater than that with oxygen at the same flow rates ($p \leq 0.01$). Increasing the nebulizer flow from 10 L/min to 15 L/min significantly increased nebulizer efficiency with 70:30 heliox ($p \leq 0.01$). Albuterol delivery distal to the nebulizer T-piece was significantly greater when the nebulizer was operated with 15 L/min of 70:30 heliox than with oxygen at 10 L/min ($p \leq 0.001$).

In the third set of experiments, albuterol delivery to the tracheobronchial model was highest when the jet nebulizer was operated with oxygen and the ventilator circuit contained 70:30 heliox. Goode and colleagues concluded that aerosol delivery from both MDIs and nebulizers was enhanced with helium in the ventilator circuit. Aerosol delivery was incrementally increased with higher concentrations of helium in the ventilator circuit. In contrast, nebulizer efficiency was markedly reduced when operated with helium, unless the flow was increased (eg, 80:20 heliox needed a flow 2.5 times higher). Maximum efficiency was achieved with an oxygen-driven nebulizer that emitted aerosol into a ventilator circuit containing heliox.

Clinical Application

In conclusion, heliox appears to enhance delivery of inhaled bronchodilators to the lower airways in patients with (and in models of) severe airway obstruction. To provide similar particle size and output, pneumatic nebulizers require higher flow when operated with heliox. Delivering the aerosol with heliox appears to increase aerosol deposition in obstructed airways. The efficiency of aerosol delivery with heliox relates to heliox’s lower density

Heliox Delivery Systems

Other than the specialty-mix gas cylinders of heliox, the implementation and initiation of heliox therapy do not require any additional equipment beyond the standard equipment in most respiratory care departments. Commercial-grade heliox is available in H-size cylinders, which contain approximately 1,200 L of gas, at approximately 2,200 psi. If the patient requires supplemental oxygen, this limits the helium concentration that can be administered. Standard heliox cylinders contain 80:20 heliox, though heliox also is also available in 70:30 and 60:40 mixtures. Though the evidence is somewhat anecdotal, a patient with an F_{IO_2} requirement above 0.40 is less likely to benefit

Table 3. Heliox Correction Factors for Oxygen Flow Meters

Helium-Oxygen Ratio	Correction Factor
80:20	1.8 times the liter flow
70:30	1.6 times the liter flow
60:40	1.4 times the liter flow

heliox = helium-oxygen mixture

from the limited amount of helium in a 60:40 heliox, because the lower the helium concentration, the higher the gas density and the more turbulent the flow through the airways.³⁶

One of the biggest issues with heliox is that clinicians have had to “jury-rig” heliox setups to treat various patient populations, by assembling and/or modifying various respiratory equipment components designed for the general function of gas-delivery but not designed for gases of much less density than air or oxygen. The lower density of heliox causes inaccurately high readings from flow meters calibrated for air and/or oxygen. When “off-the-shelf” oxygen flow meters are used to deliver heliox, the liter-flow correction factor is based on the density of the heliox being administered (Table 3). In vitro evaluation in our laboratory suggests that flow meters that have not been density-corrected have a unique set of correction factors that may not be consistent among various flow meters.³⁷

The ability to deliver heliox both to spontaneously breathing and to mechanically ventilated pediatric patients can be problematic. Heliox administration via noninvasive ventilation has been investigated in the adult literature,^{38–40} but its role in the pediatric population remains unclear, since the evidence is largely anecdotal, from single-patient case studies, or was conducted with potentially inferior systems. The delivery of heliox during mechanical ventilation has its challenges.^{41–44} The specifics of the delivery and administration of heliox, through both noninvasive and invasive ventilation, is discussed further in other papers from this symposium.^{45–46}

For spontaneously breathing patients, heliox is most efficacious and best delivered with a closed system, meaning a system that is not susceptible to problematic leaks or air-entrainment. Administration through a snugly fitting, nonbreathing face mask reduces the chance that the heliox will be diluted with room air. A typical clinical setup for heliox administration to a spontaneously breathing patient consists of a face mask and reservoir bag or a non-rebreather system. A Y-piece attachment can be placed between the mask and the reservoir bag to add a nebulizer for concurrent β -agonist administration. This type of delivery system needs to be continuously supplied with a flow of 12–15 L/min to maintain reservoir-bag inflation, and will require 2–5 H-size cylinders per day. Other tra-

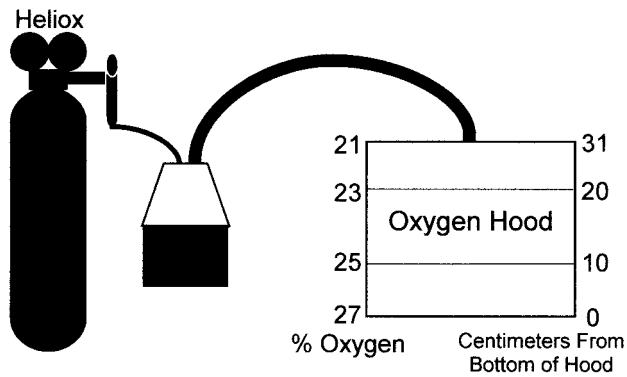


Fig. 1. By sampling the gas at various levels in the hood, Stillwell et al discovered that helium-oxygen mixture separates in the hood and the helium concentrates in the top. (Adapted from Reference 47.)

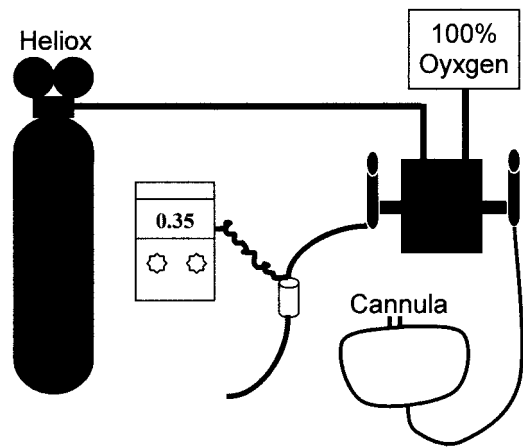


Fig. 2. Williams et al blended an 80% helium/20% oxygen mixture with 100% oxygen from a wall source and delivered the gas via nasal cannula. (Adapted from Reference 49.)

ditional methods of oxygen delivery to pediatric patients, such as nasal cannulas, oxygen hood, oxygen tents, and simple or Venturi-type masks, are not routinely recommended for heliox delivery because of their propensity to entrain unknown quantities of room air.

Stillwell and colleagues investigated the effectiveness of various traditional oxygen-delivery systems for administering heliox.⁴⁷ The study measured the density dependence at 50% vital capacity in 5 adult volunteers spontaneously breathing heliox through 3 different oxygen-delivery systems: a nonrebreather mask, a simple mask, and a nasal cannula. Statistically better ($p < 0.05$) heliox delivery was achieved with the nonrebreathing mask and the simple mask than with the nasal cannula. Specifically, the density dependence at 50% vital capacity was 1.32 ± 0.89 with the nonrebreathing mask, 1.21 ± 0.87 with the simple mask, and 1.00 ± 0.13 with the nasal cannula.

In a later study with asthmatics who presented in acute distress to the emergency department, Kress et al⁴⁸ modified a heliox delivery system to prevent room-air entrainment. The investigators nebulized albuterol with 80:20 heliox to 45 adults who met American Thoracic Society criteria for asthma and had severe persistent symptoms (baseline $FEV_1 < 50\%$ of predicted). They concluded that, compared with using oxygen as the nebulizer driving gas, using 80:20 heliox to nebulize the albuterol significantly improved spirometry values.

This set of studies shows that limiting room-air contamination of the heliox enhances the chance of obtaining a clinical effect.

In a laboratory bench test, Stillwell and colleagues examined heliox delivery via oxygen hood.⁴⁷ They found that the helium concentrates in the top of the hood well above the patient's mouth and nares (Fig. 1). They concluded that the nonrebreather and simple masks were potentially satisfactory heliox delivery systems, that heliox delivery via oxygen hood may be suboptimal, and that

nasal cannula is the least effective of the traditional gas-delivery systems.

A recent case series reported by Williams et al provided a conflicting opinion on the efficacy of the nasal cannula.⁴⁹ They sought to determine the benefits of heliox via nasal cannula for pediatric upper and lower respiratory disorders in the emergency department. Five spontaneously breathing infants received a mixture of 80:20 heliox blended with 100% oxygen from a wall source, delivered via nasal cannula to infants with respiratory distress at flows of 2–3 L/min (Fig. 2). For infants who required supplemental oxygen, F_{IO_2} could be increased by adjusting the blender dial. To decrease helium consumption caused by the inherent leak of the blender, the investigators sealed the bleed-off valve on the blender. Treatment efficacy was retrospectively extracted from nursing, respiratory therapist, and physician entries in the medical record, specifically focusing on changes in respiratory rate, work of breathing, and oxygenation and/or ventilation variables. In this retrospective review, the authors noted that all 5 infants tolerated the nasal cannula well, and in 2 infants the nasal cannula was used after attempts to use a face-mask system were not tolerated. The patients had rapid improvement in respiratory variables that were documented in the charts. All 5 infants had an overall decrease in work of breathing, four had decrease in respiratory rate, two had decrease in transcutaneously measured carbon dioxide levels and decreased stridor, and one had improved oxygenation after heliox administration. One patient had recurrence of respiratory distress shortly after discontinuation of heliox, but the distress was rapidly reversed with the reinstatement of heliox. Williams and colleagues concluded that, in infants with respiratory distress who do not tolerate a face mask, nasal cannula is a viable and efficacious alternative for heliox delivery. However, the study's small sample

size, anecdotal assessment measures, and concurrent therapies make this conclusion difficult to generalize.

Clinical Application

Heliox should be delivered with a closed system that prevents or at least minimizes the entrainment of room air, assuring that the fraction of inhaled helium is $> 50\%$. Standardization of heliox equipment or equipment that is “density-corrected” is often difficult to accomplish.

Summary

While the implementation and initiation of heliox therapy can be accomplished using devices typically available in most respiratory care departments, it is obvious from the studies reviewed above that the efficient and effective delivery of heliox therapy is perhaps as much an art as a science. Despite its medical use for over 70 years, the equipment available, heliox monitoring capabilities, and standardization of the equipment differs not only from institution to institution, but often within an institution. This complicates clinical care and makes it difficult to analyze the data and outcomes in the literature. As an example, when in 2003 Rodrigo et al performed a meta-analysis for a Cochrane review on the use of heliox in asthmatics, they were able to use only 6 trials (5 adult, 1 pediatric, 2 added since the previous review in 2002) for the evidence-based review, which included 369 patients.⁵⁰ But problems with heliox-delivery technology may soon be mitigated. In 2005, GE Healthcare (Madison, Wisconsin) received Food and Drug Administration approval to manufacture and market the Aptair as a stand-alone heliox delivery system to administer heliox to a broad range of patients, from pediatric to adult (Fig. 3). This system delivers heliox while providing spontaneous noninvasive pressure support with an electronic demand valve and an active exhalation valve via a face mask. The system’s coaxial breathing circuit includes a vibrating-mesh nebulizer (Aeroneb Pro, Nektar Therapeutics, Mountain View, California) positioned at the outlet of the delivery device to provide in-line aerosol delivery. The Aptair system delivers gas only during the inspiratory phase, which should decrease heliox consumption and thereby decrease clinician time spent changing heliox cylinders and assembling equipment. The Aptair and future devices like it may lead to more standardization of heliox delivery and promote more clinical trials

In summary, it seems reasonable for the clinician to consider heliox a relatively safe “therapeutic bridge” for diseases that cause airflow obstruction and increase airway turbulence, which may allow more time for better planning of definitive respiratory support, the onset of action of medications, or the natural resolution of a disease process.



Fig. 2. The Aptair heliox system delivers heliox from an H-size cylinder, and provides spontaneous, monitored, noninvasive pressure support, with alarm settings, via face mask.

The benefits of heliox are rapid after initiation and quickly disappear after discontinuation, so the clinician will quickly know if heliox is beneficial for an individual patient or if it should be abandoned for other therapies.

The evidence appears neither to strongly support nor to definitively refute the use of heliox in children with obstructed airflow. Patients with the most severe obstruction or the smallest anatomical airways may stand to benefit the most from heliox. A variety of evidence across many of the diseases addressed in this review indicate that heliox can decrease work of breathing, respiratory distress, dyspnea score, and obstruction score, while potentially improving gas exchange and aerosol deposition. Further randomized clinical trials are needed with pediatric patients to determine the utility and benefits of heliox therapy.

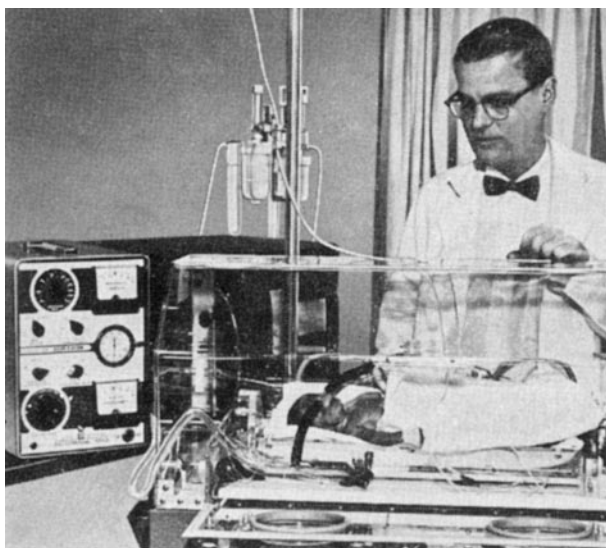
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