Should Heliox Be Used for Mechanically Ventilated Patients?

William E Hurford MD and Ira M Cheifetz MD FAARC

Helium is an inert gas with a very low density (0.18 g/L), which allows it to pass through narrowed passages with less turbulence than nitrogen or oxygen. For many years, helium-oxygen mixture (heliox) has been used for patients with severe airway obstruction. However, the data supporting the clinical application of heliox are few and clearly nondefinitive. This article reviews the medical literature on whether heliox should be used for mechanically ventilated patients. No definitive randomized studies have attempted to answer this question. Studies both support and contest the benefit of heliox during mechanical ventilation. Most studies agree that heliox is extremely safe; no adverse effects have been reported. However, heliox must be administered with vigilance and continuous monitoring to avoid technical complications. As is the case with all therapies that have not been definitively studied, the risk/benefit ratio for an individual patient must be assessed by the clinical care team. *Key words: heliox, oxygen, helium, mechanical ventilation, asthma, ventilation, chronic obstructive pulmonary disease, bronchodilator, airway obstruction, resistance*. [Respir Care 2007;52(5):582–591.

William E Hurford MD is affiliated with the Department of Anesthesiology, University of Cincinnati College of Medicine, Cincinnati, Ohio. Ira M Cheifetz MD FAARC is affiliated with the Division of Pediatric Critical Care Medicine, Duke Children's Hospital, Duke University, Durham, North Carolina.

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Correspondence: William E Hurford MD, Department of Anesthesiology, University of Cincinnati Medical Center, PO Box 670531, 231 Albert Sabin Way, Cincinnati OH 45267-0531. E-mail: william.hurford@uc.edu.

Introduction

Helium is an inert noble gas with a very low atomic weight (4 g/mol) and density (0.18 g/L). These properties allow helium to pass through narrow openings (such as a constricted airway) with less turbulence than air or oxygen. Carbon dioxide also diffuses more rapidly through a helium-oxygen mixture (heliox) than through a nitrogen-oxygen mixture. Since helium is nontoxic and biologically inert, it can safely be mixed with oxygen. Generally, heliox is available in mixtures of 80% oxygen and 20% helium (80:20 heliox) or 70:30 heliox; however, heliox can be blended with other gases.[1]

Heliox was initially used as a breathing mixture for deep-sea divers, because the absence of nitrogen in heliox reduced the formation of the nitrogen bubbles responsible for decompression sickness. The use of heliox to improve symptoms of airway obstruction was first noted in the 1930s.[2]

The density of a heliox mixture depends on the proportion of the 2 gases (80:20 and 70:30 heliox have densities of 0.43 g/L and 0.55 g/L, respectively). In comparison, oxygen and air have densities of 1.4 g/L and 1.3 g/L, respectively. The rate of turbulent gas flow is proportional to the density of the gas, so in turbulent flow a less-dense gas has a higher flow at a given driving pressure. The likelihood that flow within a gas will have a laminar or turbulent pattern depends on the density and viscosity of the gas, which is expressed by the gas mixture's Reynolds number:

$$\mathrm{Re} = (\rho \upsilon r)/\eta$$

where Re is the Reynolds number, ρ is the density, υ is the velocity, r is the cross-sectional radius, and η is the viscosity. A lower Reynolds number is associated with laminar flow. Turbulent flow is more likely with a higher Reynolds number. The Reynolds number for heliox is 3 times lower than that of air, which favors laminar flow.[1,3]

Heliox has been suggested for use in a variety of mechanically ventilated patients. Advantages that have been cited include improving the delivery of aerosolized medications and improving the ease of breathing during both noninvasive and invasive ventilation, primarily by reducing resistance to gas flow through narrowed airways. The strength of evidence supporting these assertions, however, is somewhat limited. Heliox therapy also has some inherent workability issues and technical disadvantages.

Pro: Heliox Should Be Used With Mechanically Ventilated Patients

It must be acknowledged at the outset of this section that there are no large, randomized clinical studies supporting the use of heliox for mechanically ventilated patients. However, it is also important to acknowledge that no study has reported an adverse event related to heliox, as long as it is administered correctly. With the known risks of mechanically ventilating a patient with severe airway obstruction (eg, status asthmaticus or severe chronic obstructive pulmonary disease [COPD]), a trial of heliox seems reasonable, especially when standard management strategies are failing.[4]

Aerosol Delivery

Currently available nebulizers are designed to be powered by nitrogen-oxygen mixtures. Thus, nebulizer performance can be affected by decreasing the density of the gas mixture by adding helium. Hess et al reported that powering a nebulizer with heliox decreased the fraction of the total dose and the respirable mass of drug, compared to powering the nebulizer with air.[5] However, this effect was negated by increasing the heliox flow. This finding emphasizes the point that technical considerations must always be taken into account when administering heliox.

In a pediatric model of mechanical ventilation, 70:30 heliox gave better deposition of albuterol from a metered-dose inhaler (MDI) than did oxygen-enriched air (fraction of inspired oxygen [F_{IO_2}] 0.30).[6] The authors speculated that the improved albuterol deposition is related to decreased turbulence and concluded that their findings suggest a potential role for heliox in the care for mechanically ventilated patients. In a follow-up study, Goode et al had similar findings: with 80:20 heliox the lung deposition was 46.7 $\pm$ 3.3% of the nominal dose, whereas with nitrogen-oxygen mixture it was 30.2 $\pm$ 1.3% ($p < 0.001$) with MDI aerosols delivered to a model of mechanical ventilation.[7] They also found significantly improved delivery of nebulized albuterol with heliox. These studies support the view that heliox may improve aerosol delivery in mechanically ventilated patients with severe airway obstruction.

Mechanical Ventilation of the Asthmatic Patient

Studies by Menitove and Goldring[8] and Darioli and Perrett[9] demonstrated that mortality in the setting of mechanical ventilation for status asthmaticus can be reduced with techniques to reduce dynamic hyperinflation. Thus, one might infer that heliox, which physiologically improves gas flow in asthmatic patients, might improve outcomes. This discussion can be based only on theoretical grounds and on smaller, nondefinitive studies, because an appropriately powered investigation has yet to be performed.

Gluck et al was one of the first groups to study heliox in intubated patients with status asthmaticus.[10] With heliox, each of 7 patients had a rapid decrease in airway pressure, improved carbon dioxide clearance, and resolution of ac-

idosis. No adverse effects were noted, and Gluck et al concluded that heliox "should be considered for use in mechanically ventilated asthmatics with respiratory acidosis who fail conventional therapy." Kass and Castriotta had similar findings, but their study was also small: 12 status asthmaticus patients, of whom only 5 were mechanically ventilated.[11]

Schaeffer et al found that there is no magical concentration of helium that must be delivered to generate a therapeutic effect.[12] The F_{IO_2} in a heterogeneous group of ventilated asthmatics was decreased with heliox, from 0.8 ± 0.2 to 0.4 ± 0.2 over a 2-hour period. These patients, on average, received only 20% helium at the initiation of this therapy. However, that relatively low helium concentration improved gas delivery and allowed gradual reduction in F_{IO_2} and gradual increase in helium concentration. Again, no adverse effects were reported.

In a relatively small study ($n = 28$) of mechanically ventilated pediatric patients with status asthmaticus, Abd-Allah et al demonstrated reduced peak inspiratory pressure, increased pH, and reduced P_{aCO_2}.[13] The heliox concentration ranged from 32% to 74% (mean $57 \pm 4\%$), and patients served as their own controls. Although clearly not a definitive study, this report indicates that heliox administration is safe and improves physiologic variables associated with status asthmaticus. However, the study was not sufficiently powered to determine any differences in outcome variables such as survival or duration of ventilation.

In a systematic review of the medical literature, Rodrigo et al attempted to answer the question of whether heliox is indicated in the treatment of acute asthma.[14] This meta-analysis included 7 trials and 392 patients in the emergency department setting. They concluded that the existing evidence does not support heliox for moderate-to-severe asthma but acknowledged that their conclusions were based on small studies and that their results should be interpreted with caution. Subsequently, Rodrigo et al completed a Cochrane review of heliox for nonintubated asthmatics.[15] This analysis reviewed 10 trials that involved 544 patients. Rodrigo et al stated that new evidence suggests improvements in pulmonary function in patients with more severe obstruction. Although they concluded that at this time heliox "does not have a role to play in the initial treatment of patients with severe asthma," this conclusion should be interpreted with caution. The Rodrigo et al review clearly does not contradict the use of heliox for severe asthma; it simply says that we need more data. As these reviews were based on nonintubated asthmatics, it should be apparent that even fewer data are available for intubated asthmatics.

Mechanical Ventilation of the Patient With COPD

In a retrospective review, Gerbeaux et al reported heliox administration in 81 patients with severe COPD exacerbation in an emergency department setting.[16] Those patients treated with heliox ($n = 39$) had a lower intubation rate (8% vs 50%, $p < 0.01$), mortality (3% vs 24%, $p < 0.01$), and duration of intensive care unit (ICU) stay among the survivors (8 d vs 18 d, $p < 0.01$).

Tassaux et al reported a prospective interventional study in which they administered heliox to 23 mechanically ventilated COPD patients.[17] Heliox reduced the trapped lung volume by 54%, the positive end-expiratory pressure (PEEP) by 45%, the peak airway pressure by 17%, and the mean airway pressure by 13% (Fig. 1), and with each of those variables the improvements quickly dissipated with the discontinuation of the heliox.

In a prospective randomized multicenter study of heliox during noninvasive pressure-support ventilation, Jolliet et al studied the application of heliox in 123 patients with decompensated COPD.[18] Heliox was associated with a shorter hospital stay (13 ± 6 d vs 19 ± 12 d, $p < 0.002$) and lower hospital costs ($\$18{,}211 \pm \$9{,}469$ vs $\$23{,}874 \pm \$15{,}123$, $p < 0.001$). Although this study did not find a lower incidence of intubation with heliox, the intubated patients had important benefits from heliox, including shorter ICU stay (11 ± 7 d vs 13 ± 7 d, $p < 0.001$) and lower hospital cost ($\$28{,}535 \pm \$14{,}085$ vs $\$36{,}466 \pm \$17{,}551$, $p < 0.002$). Jolliet et al concluded that heliox "can be safely administered and could prove to be a cost-effective strategy."

In a companion study by Jolliet et al,[19] heliox again improved intrinsic PEEP (from 7.7 ± 4.0 cm H_2O to 4.2 ± 4.0 cm H_2O, $p < 0.001$) and trapped gas volume (from 217 ± 124 mL to 98 ± 82 mL, $p < 0.001$). Jolliet et al concluded that heliox could "offer an attractive option in COPD patients with intrinsic PEEP/dynamic hyperinflation."

Lee et al studied the effects of heliox in a prospective interventional study of 25 consecutive mechanically ventilated patients with COPD and acute respiratory failure with systolic pressure variation (pulsus paradoxus) of at least 15 mm Hg.[20] Heliox improved intrinsic PEEP, reduced trapped lung volume, and decreased pulsus paradoxus (Fig. 2). In the patients with pulmonary artery catheters, heliox significantly increased cardiac index (Fig. 3). As did Jolliet et al, Lee et al concluded that heliox may be a useful adjunct therapy for acute respiratory failure in patients with severe COPD.

Diehl and colleagues investigated the role of heliox in reducing the work of breathing (WOB) at the time of extubation for COPD patients.[21] In a prospective randomized crossover trial, heliox and oxygen-enriched air were administered in random order for 20 min each, before and after extubation. Heliox reduced WOB by 21%, mainly by reducing the resistive component of WOB (Fig. 4). Heliox also decreased intrinsic PEEP. Thus, heliox may help transition COPD patients from mechanical ventilation to extubation.

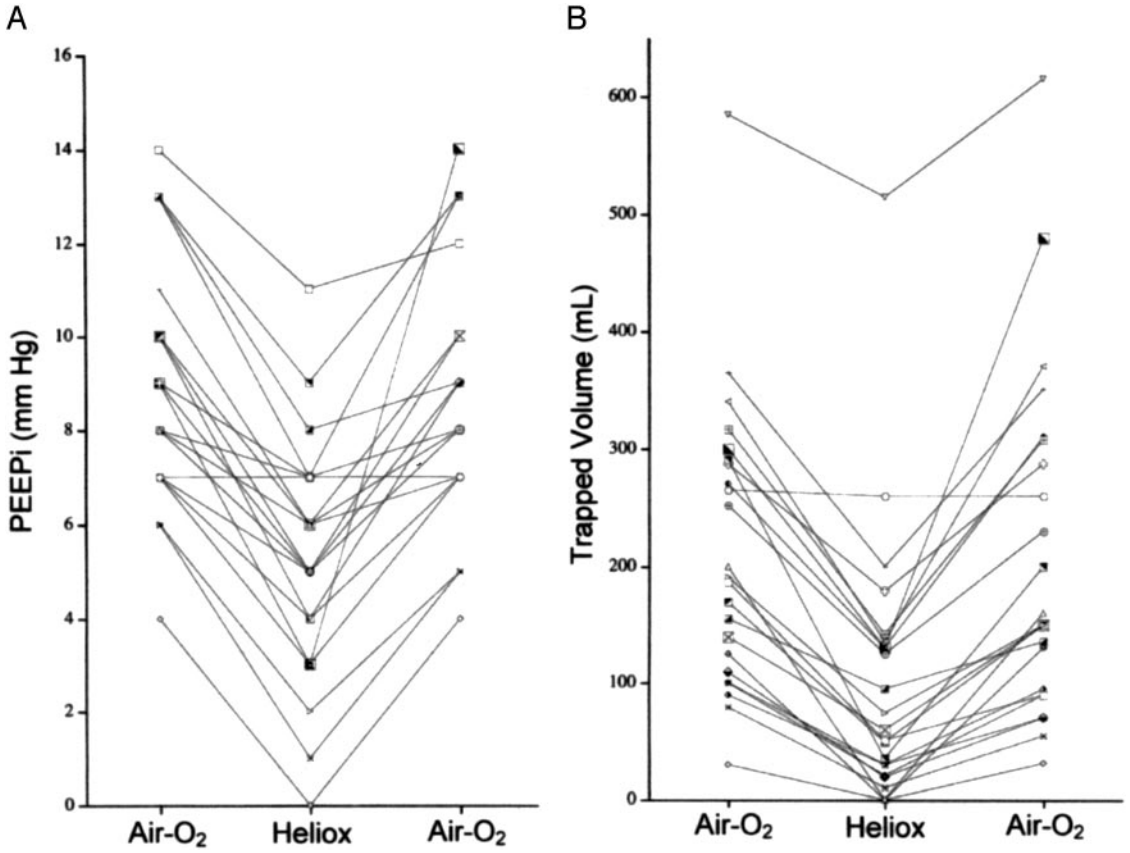

Fig. 1. Left: Individual measurements of intrinsic positive end-expiratory pressure (PEEPi) before, during, and after administration of helium-oxygen mixture (heliox). Right: Individual measurements of trapped end-expiratory lung volume before, during, and after administration of heliox. (Adapted from Reference 17, with permission.)

In a Cochrane review, Rodrigo et al identified only 4 studies that met their inclusion criteria.[22] Of those 4 studies, data could only be obtained for 2 of them. Thus it is not surprising that their conclusion was that there are currently insufficient data to support heliox use for COPD. Again, this type of statement does not indicate that heliox is contraindicated or nonuseful, but only that there are inadequate data to reach a firm conclusion.

Heliox and Nonconventional Ventilation

Heliox has been reported to be beneficial with various forms of nonconventional ventilation, including high-frequency oscillatory ventilation (HFOV),[23] high-frequency jet ventilation,[24] and high-frequency percussive ventilation.[25] Winters et al reported improved carbon dioxide elimination in a series of 5 children with acute respiratory distress syndrome when heliox was administered during HFOV.[23] P_{aCO_2} decreased 24% within 45 min of initiating heliox, and ultimately decreased 43%. Gupta et al reported the combined use of heliox and high-frequency jet ventilation to augment carbon dioxide clearance in a 5-month-old infant with acute respiratory failure associated with gas-trapping, hypercarbia, respiratory acidosis, and air leak.[24] Stucki et al reported successful use of heliox with high-frequency percussive ventilation in a 5-year-old boy with cystic fibrosis and severe acute respiratory failure.[25] Although no controlled studies have investigated the combined use of heliox and nonconventional ventilation, these case reports do demonstrate the technical feasibility of that combination. Based on the limited data, it is not possible to endorse this approach. However, for a patient in extremis, such a strategy might be reasonable. Careful attention must be given to the technical aspects of administering heliox through devices that were not designed for and have not been approved by the U.S. Food and Drug Administration (FDA) for delivering heliox.

Heliox during HFOV has been studied in a laboratory setting. A prospective crossover laboratory study compared heliox to oxygen-enriched air during HFOV in a model of acute lung injury.[26] Heliox improved oxygenation and CO_2 elimination. With further investigation it was found that that improvement was related to larger tidal volume (V_T) delivery by the oscillator with heliox. When

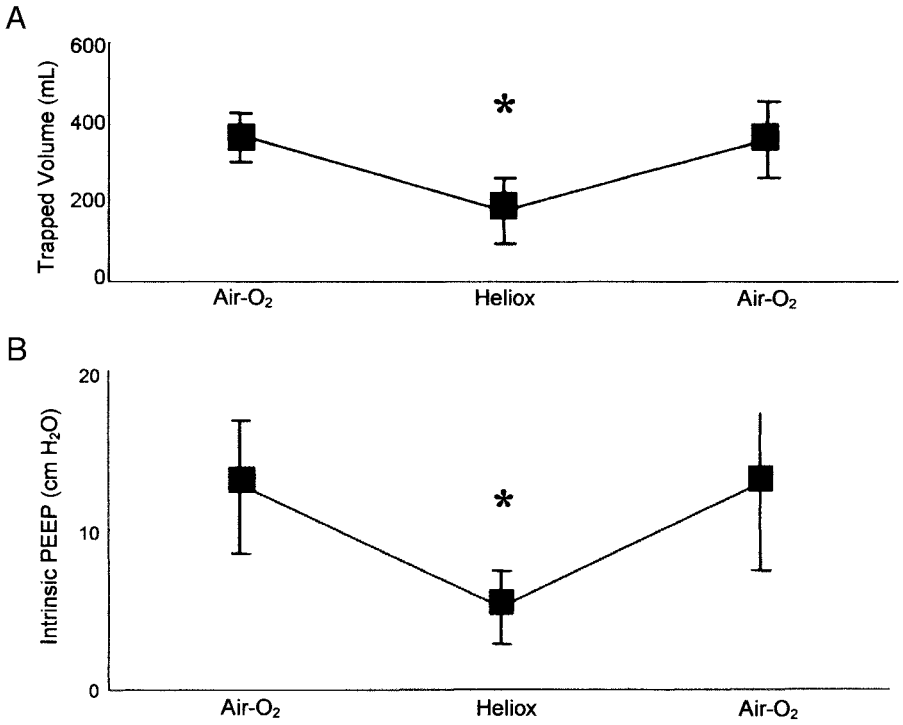

Fig. 2. Changes in trapped lung volume (top panel) and intrinsic positive end-expiratory positive pressure (PEEP) (bottom panel) during mechanical ventilation with heliox. * $p < 0.001$ versus air-oxygen mixture. (Adapted from Reference 20, with permission.)

V_T was maintained constant, there was no significant improvement in gas exchange.[27]

Based on these results, routine heliox use during nonconventional ventilation cannot be recommended. However, for a patient in extremis, who is at the limit of some of these devices, heliox may extend the device's gas-delivery capability. A trial of heliox may be attempted in very selected patients, using nonconventional ventilation, based on the clinician's assessment of the risk/benefit ratio. Since heliox administration with nonconventional ventilation modes is less reliable than with conventional modes, the need for continuous monitoring of gas exchange and oxygen delivery must be stressed.

Technical Considerations During Heliox Administration

Several studies have investigated the effects of heliox on mechanical ventilators, and it is clear that each ventilator behaves differently with heliox and that the behavior varies with changes in F_{IO_2} and helium concentration.[28–31] This knowledge should not necessarily dissuade the clinician from using heliox, but it is necessary to assess the risk/benefit ratio of heliox for each individual patient. It is very important for a clinician who administers heliox to know the performance of any ventilator through which heliox could be administered in their ICU.

FDA-approved and commercially available heliox-calibrated ventilators and stand-alone respiratory mechanics monitors are available. Recently, Fink published an excellent overview of the technical aspects of heliox administration.[32] It is important to stress that 100% helium tanks should never be used clinically. In the heliox tank, 20% is the minimum oxygen concentration in clinical use (ie, at least 80:20 heliox). One should not attempt to blend 100% helium with oxygen to create 80:20 heliox. Use continuous in-line monitoring of F_{IO_2} to ensure adequate oxygen delivery to the airways.

Summary of Pro Position

In a recent publication, Venkataraman concluded that, though the evidence is mostly low-level (grade III and IV), in selected situations heliox is indicated during mechanical ventilation.[33] These situations include: lower-airways obstruction, especially when associated with hypercapnia; the need to augment aerosol delivery; and the need to facilitate weaning from mechanical ventilation. As the effects of heliox are very rapid, the clinician will quickly know if the heliox will benefit the patient or should be abandoned.

As is the case for all therapies that have not been definitively studied, the risk/benefit ratio for the individual patient must be assessed by the clinical care

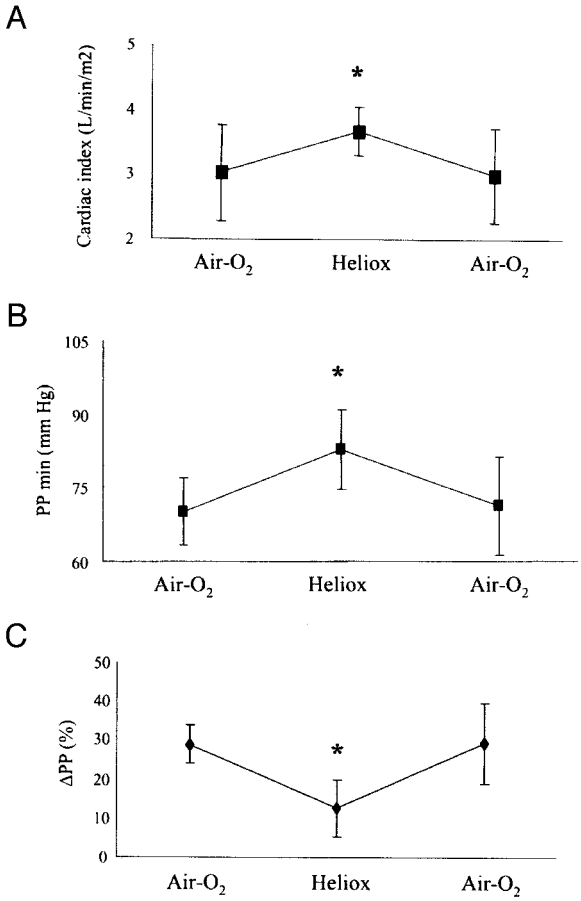

Fig. 3. Changes in cardiac index (top panel), pulse pressure during expiration (PP min) (middle panel), and respiratory changes in PP (ΔPP) (bottom panel) during heliox ventilation. ΔPP(%) = 100 × ([maximum PP – minimum PP]/0.5 × [maximum PP + minimum PP]). * $p < 0.001$ vs air-oxygen. For cardiac index, $n = 10$ patients who had pulmonary arterial catheterization. (From Reference 20, with permission.)

team. It is clear that no study has definitively shown improved outcomes from heliox in mechanically ventilated patients, but before concluding that heliox does not work, we must consider why heliox improves physiologic variables, including pulsus paradoxus (ie, patient WOB) and peak expiratory flow, but has not seemed to change more important outcomes. The answer is simply that no study has been appropriately powered to demonstrate a difference. Such a large-scale study has not been performed. In fact, even multicenter studies (of any size) on heliox are hard to find. Thus, until definitive data are available, heliox remains a reasonable management strategy for the ventilated patient with severe airway obstruction, as the clinical benefits can be very important. The risks of heliox therapy are negligible, as long as careful attention is paid to correct heliox delivery.

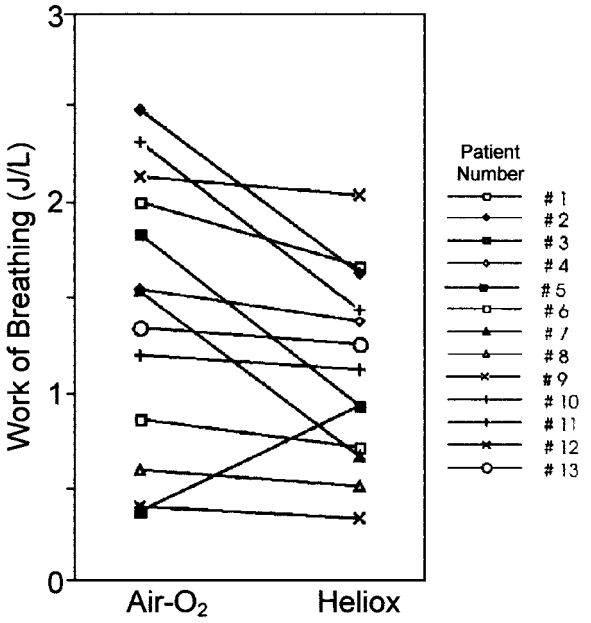

Fig. 4. Individual work of breathing measurements just before extubation in 13 patients with chronic obstructive pulmonary disease breathing either air-oxygen mixture (left) or helium-oxygen mixture (heliox) (right). (Adapted from Reference 21, with permission.)

Con: Heliox Should Not Be Used With Mechanically Ventilated Patients

Aerosol Delivery

Multiple small clinical and bench studies suggest that heliox improves aerosol delivery.[34,35] Heliox, because it is less dense than air, reduces turbulent flow and reduces deposition of MDI aerosol particles in the spacer.[6,7] Whether the improved lung deposition is sufficient to significantly improve pulmonary function is controversial. Henderson and co-workers noted similar improvements in 205 patients with mild-to-moderate exacerbations of asthma who received albuterol from either an air-powered or a 70:30 heliox-powered nebulizer.[36] deBoisblance and colleagues also noted no significant differences in clinical improvement in patients with exacerbations of chronic obstructive pulmonary disease (COPD) who received albuterol from either an air-powered or heliox-powered nebulizer.[37]

Changing the driving gas from air to heliox, however, alters the functioning of gas-powered nebulizers and can confound comparative studies of nebulized drug deposition. Hess and co-workers reported that particle size and inhaled mass of albuterol decreased significantly for a given gas flow when nebulizers were powered with heliox instead of air.[5] However, increasing the flow of heliox increased the particle size, inhaled mass of albuterol, and inhaled mass of particles to levels similar to when pow-

ering the nebulizer with air at the lower flow. Though there are theoretical advantages to using heliox during mechanical ventilation to improve the delivery of aerosolized medications, the clinical advantages, if present, are difficult to detect and may be due to alterations in nebulizer performance produced by changes in the driving gas.

Mechanical Ventilation of the Asthmatic Patient

The lower density of heliox should reduce airway resistance and provide symptomatic relief in patients with asthma exacerbation. Studies of heliox in mechanically ventilated patients with asthma, however, are limited. Gluck et al reported a case series of 7 mechanically ventilated patients with status asthmaticus.[10] Heliox was associated with a decrease in peak inspiratory pressure of 33 cm H_2O (peak pressure was initially $>$ 75 cm H_2O), and P_{aCO_2} decreased by 36 mm Hg). Regrettably, the study was not controlled for either the type or duration of concomitant therapies. Ventilator settings and performance during heliox administration were not fully described.

Kass and Castriotta studied 5 patients with asthma exacerbation who were mechanically ventilated, with and without heliox.[11] P_{aCO_2} decreased and arterial pH increased with heliox, but the ventilator settings and the performance of the ventilator that was used were not reported, and the case series was uncontrolled.

Schaeffer and colleagues retrospectively studied 11 patients who had been mechanically ventilated with heliox for status asthmaticus.[12] Though the alveolar-arterial oxygen difference decreased in these patients, there was no difference in the change in P_{aCO_2} or arterial pH between the patients ventilated with heliox and that in matched controls who were traditionally ventilated.

Gross and colleagues reported an uncontrolled case series of 10 infants (age range 1–9 months) mechanically ventilated because of bronchiolitis.[38] They compared heliox to traditional mechanical ventilation and found no statistical or clinically meaningful differences between the mean P_{aCO_2}, P_{aO_2}/F_{IO_2}, or the ratio of P_{aO_2} to alveolar partial pressure of oxygen.

Abd-Allah and colleagues retrospectively reviewed 28 pediatric patients who were mechanically ventilated for asthma exacerbation.[13] Mechanical ventilation with heliox decreased peak inspiratory pressure and P_{aCO_2} and increased arterial pH. However, no control measurements were performed, and there was no comparison group.

Overall, the evidence on heliox for asthma is limited. Rodrigo and colleagues, writing for the Cochrane Database, summarized 10 heliox trials that involved 544 nonintubated patients with acute asthma.[15] Though heliox occasionally improved pulmonary function, especially in those patients with the most severe impairments of pulmonary function, there was no difference in the risk of hospital admission (risk ratio 0.83, 95% confidence interval 0.66 to 1.08, $p = 0.17$). The authors concluded that existing evidence did not support heliox for all patients with acute asthma.

Mechanical Ventilation of the Patient With COPD

Studies of heliox use in patients with COPD exacerbations have often focused on whether heliox treatment can decrease the necessity for intubation or provide symptom relief during noninvasive mechanical ventilation. Jolliet and co-workers examined noninvasive pressure-support ventilation with and without heliox, in a randomized crossover study of 19 patients with severe COPD.[39] Heliox was associated with a lower Borg dyspnea score, duty cycle (ratio of inspiratory time to total respiratory cycle time), and P_{aCO_2}. However, there was no difference in respiratory rate, V_T, arterial pH, or alveolar-arterial oxygen difference.

Tassaux and colleagues reported a prospective case series of 23 patients with severe COPD who required sedation, neuromuscular paralysis, and mechanical ventilation.[17] A 45-min trial of 70:30 heliox ventilation was associated with decreases in trapped lung volume (from 215 mL to 99 mL), intrinsic PEEP (from 9 cm H_2O to 5 cm H_2O), and peak inspiratory pressure (from 30 cm H_2O to 25 cm H_2O). Hemodynamics and gas exchange, however, were unaffected. In a follow-up crossover study of 10 COPD patients who received pressure-support ventilation with either a nitrogen-oxygen mixture or heliox for 30 min, that research group confirmed a reduction in intrinsic PEEP, total WOB, and the number of ineffectively-triggered breaths.[40]

Lee and colleagues found that heliox improved hemodynamics and pulmonary mechanics in a study of 25 mechanically ventilated patients with severe COPD and systolic pressure variations $>$ 15 mm Hg.[20] During 30 min of mechanical ventilation with heliox, intrinsic PEEP, trapped lung volume, and systolic arterial pressure variations all decreased. In 10 patients who had pulmonary artery catheters in place, heliox decreased mean pulmonary arterial pressure, right atrial pressure, and pulmonary arterial occlusion pressure, and increased cardiac index.

All these trials, however, examined only short-term physiologic changes, and did not assess whether heliox meaningfully affected important clinical outcomes.

In 2003, Jolliet and co-workers published a multicenter randomized trial of heliox during noninvasive pressure-support ventilation with 123 patients with decompensated COPD.[19] Patients received noninvasive ventilation for 100-min periods and were randomized to be ventilated either with or without heliox during noninvasive ventilation. No heliox was administrated (1) when the patient was breathing unassisted, (2) if endotracheal intubation was required,

Table 1. Use of Helium-Oxygen Mixture (Heliox) in Mechanically Ventilated Patients

Heliox may increase delivered dose of bronchodilators and improve symptoms and physiologic variables such as dyspnea or pulsus paradoxus.
Heliox does not improve pulmonary function or the necessity for hospital admission.
There are insufficient data to determine whether heliox affects the necessity for intubation, the duration of mechanical ventilation, ICU or hospital stay, or mortality.

Table 2. Alternatives to Helium-Oxygen Mixture (Heliox) During Mechanical Ventilation

Benefits of Heliox	Alternatives to Heliox
Increased delivery of bronchodilator	Increase dose or frequency of bronchodilator
Reduced dyspnea, airway resistance, and work of breathing	Increase level of ventilatory support or change flow pattern. Heliox relieves symptoms only; it does not treat underlying the cause.
Reduced air trapping and positive end-expiratory pressure	Properly adjust ventilator settings; reduce respiratory rate; permit hypercapnia

(3) after the patient no longer required mechanical ventilation, or (4) after discharge from the ICU. By multiple logistic regression analysis, heliox was not associated with the need for endotracheal intubation. There were no differences between the groups in Borg dyspnea scale, respiratory rate, arterial blood gas tensions or pH, hemodynamics, necessity for endotracheal intubation (20% of controls vs 13% of heliox patients), duration of ICU stay (controls 6.2 d vs patients who received heliox 5.6 d), or improvement in respiratory or hemodynamic variables over time. The duration of stay following ICU discharge was shorter and hospital costs were lower among the patients who received heliox (controls 19 ± 12 d vs patients who received heliox 13 ± 6 d), but treatment assignments had not been blinded, there were no standardized discharge criteria from the ICU, and treatment was not standardized after discharge from the unit.

In a review of heliox treatment for exacerbations of COPD, Rodrigo and colleagues, writing for the Cochrane Database in 2002, found only limited data to support the use of heliox in either mechanically ventilated or nonventilated patients.[22] In review of more recent data, it is reasonable to conclude that heliox may increase the delivered dose of bronchodilator and improve secondary variables such as dyspnea or pulsus paradoxus (2 studies; one nonrandomized). Since heliox is inert, it does not provide primary treatment for any underlying disease and does not affect underlying pulmonary function or the necessity for hospital admission. No studies to date have been sufficiently powered to detect differences in clinical outcome. There are insufficient data to support that heliox affects the necessity for endotracheal intubation, duration of mechanical ventilation, ICU or hospital stay, or mortality. Appropriately designed prospective studies are certainly indicated.

Disadvantages and Risks of Heliox Administration

Heliox has risks and disadvantages (Table 1). Difficulties in patient care may arise if clinicians fail to fully understand how delivery devices may have been "jury-rigged" to administer heliox. They also may make well-meaning but incorrect adaptations of the equipment. Even when correctly adapted, V_T may be unpredictably altered by heliox.[33] Providing a clinically useful reduction in gas density requires a substantial helium concentration (usually at least 60%), which limits the F_{IO_2} that can be delivered while obtaining a benefit from the helium. Various concentrations of source gas are available (60:40, 70:30; 80:20, and 100:0), which can add to confusion. One should never use a tank that contains 100% helium, because of the risk of delivering a gas mixture that has less than 20% oxygen.[32] Heliox is more expensive than air (heliox $2.40/L vs air $0.07 per 100 L), though this difference is relatively minor when examined in light of the overall costs of hospitalization.[19]

Heliox can be difficult to administer properly with the currently available respiratory care equipment. The vast majority of mechanical ventilators are designed on the assumption that the gas is a mixture of oxygen and air. Helium's low density alters the flow through the valves, regulators, and tubing, and the flow differences can be difficult to predict.[41] Some of the physiologic changes attributed to heliox may in fact be due to unanticipated changes in ventilator flow and delivered V_T.[27] Experimentally derived conversion factors that attempt to correct for gas-flow differences with heliox have been published, but these conversion factors are cumbersome to use, are dependent on the device being employed, and have not been fully validated in clinical situations.[28,29,33] Most ventilators are not FDA-approved to deliver heliox, and making modifications that have not been approved by either the FDA or the manufacturer of these devices creates liability risk.[32]

Summary of Con Position

Overall, current evidence suggests that heliox administration during mechanical ventilation may benefit some patients with large airway obstruction or asthma. Heliox appears to be of limited utility for COPD patients, although it might be used to increase the amount of aerosolized medication delivered to the lungs. Nevertheless, since

Table 3. Pros and Cons of Helium-Oxygen Mixture (Heliox)

Factor	Pros	Cons
Equipment	Food and Drug Administration approved equipment now exist to facilitate safe and accurate delivery of heliox.	Most ventilators and monitors are not heliox-calibrated and are not approved for heliox. Modifying devices creates liability risk.
	Clinicians must know their equipment, which can be heliox-incompatible, heliox-compatible, and/or heliox-calibrated.	Clinicians might not understand jury-rigged devices and/or may make incorrect adaptations; the delivered tidal volume can be difficult to predict and measure.
Conversion factors	Conversion factors are unnecessary with heliox-calibrated equipment (ventilator, stand-alone monitor, and/or flow meter).	Experimentally derived conversion factors are cumbersome and unreliable.
Gas concentrations	Clinical benefit can be seen at any fraction of inspired oxygen, although the response is proportional to the helium concentration.	Clinical benefit may be limited with a high fraction of inspired oxygen, because the helium concentration is correspondingly low. The fraction of inspired oxygen is limited by the percentage of helium in the delivered gas.
		A confusing variety of helium-oxygen concentrations are available: 60:40, 70:30, 80:20, and 100:0. Tanks that contain 100% helium should *never* be used, because there is a risk of delivering gas that contains no oxygen. Only heliox tanks that have at least 20% oxygen (ie, 80:20 heliox) should be used.
Expense	Although heliox is more expensive than air, it is very inexpensive compared to another day in an ICU or a day on a ventilator.	Heliox is more expensive than air: $2.40/L versus $0.07/100 L.

helium is an inert, nonreactive gas, it is at best symptomatic therapy and does not address the patient's underlying pulmonary pathology. Further, heliox has been tested only in short-term applications. Substituting helium for air alters the performance of most respiratory care equipment. Jury-rigging of equipment that is not FDA-approved for heliox creates liability risk. Alternative therapies, such as increasing the dose of bronchodilator, providing an adequate level of mechanical ventilatory support, and adjusting the ventilator's flow pattern, can provide many, if not all, of the benefits attributed to heliox during mechanical ventilation (Table 2). No study has yet demonstrated improved clinical outcome for patients mechanically ventilated with heliox, compared to traditional nitrogen-oxygen mixtures.

Conclusion

The improved flow properties and higher CO_2 diffusion coefficient of heliox make it an interesting adjunct in the treatment of severe airway obstruction. It is imperative to keep in mind that heliox has no direct treatment effects and is only a temporizing measure until definitive therapies take effect or the disease process resolves. Various studies have supported and contested the value of heliox, but most studies agree that heliox is extremely safe; no adverse effects have been reported. Heliox must be administered with vigilance and continuous monitoring to avoid technical complications. Controversy over heliox in mechanically ventilated patients continues. The advantages and disadvantages of heliox must be considered before administering it to a patient (Table 3).

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Discussion

Fessler: I might be able to shed some light on that 1990 study by Gluck.[1] I was impressed by that study because heliox decreased P_{aCO_2} by over 33 mm Hg in patients who were paralyzed, with no change in their ventilator settings. I called Gluck to ask him what was going on, and he explained that, prior to heliox, the ventilators were all exceeding the pop-off pressure, so that much of the V_T was being vented into the room. With heliox the peak airway pressure went down, so the patients got their full, set V_T.

Obviously, peak airway pressure decreases when you use helium, because of the physics of turbulent flow, and I think it's inevitable that the plateau pressure, or any pressure that might cause barotrauma, increases with heliox. I think heliox is interesting and may be useful in nonintubated

patients, but once the patient is intubated, to me heliox becomes much less interesting. Heliox reduces the *ventilator* WOB, but not the *patient* WOB. And I'd agree that most of the minor benefits on hyperinflation that can be shown could be achieved with just a little sedative and decrease in respiratory rate.

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Cheifetz: I agree with Bill's presentation; I thought it was great. I agree that the evidence is very limited, and you can take these small studies, which are often not well-controlled, and pull them apart. My point is simply that there are some extreme patients who may benefit from heliox. It is not like most of the other topics we have discussed, where we have debated "all or none" perspectives. The focus of the argument for heliox is, I believe, "some."

There are some cases where, if you put heliox through a ventilator, you can help save a child or an adult. You may be able to minimize barotrauma, optimize gas exchange, and potentially optimize hemodynamics—in the extreme cases. There are technical limitations, but if you know how to use your equipment and technology correctly, you can deal with the technical hurdles. There has not been a single report of an adverse effect from heliox in any of the published trials, though some people don't publish a case report with a bad outcome.

Branson: I have a question that I want to be careful with. I see what might be called the "Duke Disconnect." Neil MacIntyre says, "Ventilate the lung gently; don't chase the P_{CO_2}. P_{O_2} is not important." But then another person from Duke says, "Heliox improves oxygenation, and high-frequency ventilation improves gas exchange." So on one hand they're saying that P_{O_2} is not important, while on the other hand they're saying that heliox improves P_{O_2} or V_T during high-frequency oscillation. So when are these therapies to be used? Which one is important?

Cheifetz: I think we are being misquoted. I don't think there is a disconnect. I agree with Neil's comments completely. With regard to oxygenation, I am not saying that heliox improves oxygenation. My point in showing the oxygenation data was simply to show that you *can* successfully use heliox despite a high F_{IO_2} in an individual patient. If a patient is on 70% oxygen and you believe that there is a clinical indication for heliox based on the patient's pathophysiology, you should still try it. A high F_{IO_2} does not *preclude* the use of helium. That's not saying that heliox improves oxygenation.

However, if you improve gas movement and, thus, gas exchange, so you can decrease the F_{IO_2}, then you will deliver a higher concentration of your therapy—additional helium to decrease the patient's WOB and to continue to improve gas exchange. It's a spiral effect in which improved gas exchange leads to the ability to offer more of your therapy and thus further improve gas exchange.

I also agree with Neil regarding P_{aCO_2}. I generally do not really care what the P_{aCO_2} is, except in extreme cases such as the 2-month-old patient I discussed who had a P_{aCO_2} of 160 mm Hg and a pH of 6.8. In that case I *have* to improve the CO_2 clearance because I can't sit at those levels and wait until the kidneys kick in and start buffering the pH. If the pH were 7.15 or 7.20 with a P_{aCO_2} of 90 mm Hg or so, I would be fine with that situation. It is just in the extreme cases where we have to do something to decrease P_{aCO_2}. Rich, does that dispel the appearance of a "disconnect"?

Branson: This happens at mechanical ventilation conferences, when Neil gives his very good lecture on ARDS [acute respiratory distress syndrome] and then somebody else says, whether it's heliox or high-frequency or the two together, how those 2 things together improve gas exchange. And I'm always trying to figure out why there seems to be a tendency to dismiss options for improving gas exchange during conventional mechanical support, but people are all for improving gas exchange with nontraditional ventilatory support.

MacIntyre: These things are connected because anything we can do that improves gas exchange is beneficial in that it allows us to turn down the V_T and/or the plateau pressure.

Deem: In that case, Neil, would you give inhaled nitric oxide to every patient?

MacIntyre: Over my dead body!

Cheifetz: No "Duke Disconnect." I agree.

Kacmarek: I agree with Neil. I think when you look at all the heliox data, you've got to exclude the patient with COPD from all the other indications. It's only the extreme asthmatic that you mentioned in whom I would *ever* consider heliox. With that patient, if you improve distribution of ventilation, decrease air trapping, and improve gas exchange at the same or lower plateau pressure, I think you've done the patient a favor for a very low level of overall risk—provided you have staff who understand how to operate the equipment, which is a big issue. We've done this very rarely over the years, and Dean Hess and I both get extremely nervous when we consider it, because it is difficult to do it safely with the available technology, and to make sure that from one clinician to another there is not a "disconnect" in the way things are accomplished.

Cheifetz: I definitely agree. I want to stress that the key here is that you have to administer heliox safely. You must know your equipment, and you must have the appropriate monitoring equipment. If you do not have the appropriate technology, you should not use heliox.

Kallet: We've been doing this at San Francisco General Hospital on a very sporadic basis for years. We do have a training program; we actually now have the newer ventilators, and some of them (Viasys and General Electric) actually are heliox-compatible, so a lot of the technical issues are disappearing. I would add to that, again, in extreme cases we had patients with horrible tracheal and bronchial stenosis who were basically in extremis, and heliox was the only way that we could keep these people alive. We have used it in status asthmaticus—*rarely*. We don't need to, but I think it's worth it to try it in extreme conditions. Whether we're ever going to get beyond Level 5 or Level 4 evidence is a different matter; but if you have the appropriate training and support for the staff, I think it can be done safely.

Hurford: If you take this discussion and substitute the term "nitric oxide" for "heliox," you all would be choking yourself. You now are advocating "ICU adventurism" in its finest of *n*-of-1 studies; no need to do any sort of study at all, but it will work for my one patient, and I can figure it out. Shouldn't we require the same level of evidence as we have been talking about for other studies?

Kallet: I think ethically in patients in extremis, no. How can you randomize a study, if you have someone who is in an extreme life-threatening situation? You ethically can't do a controlled study. That's always going to be the situation you face as a clinician: you're going to do what you need to do. I'm certainly not advocating making the therapy a standard of care, but in these rare *extreme* circumstances clinicians are always left with stark options.

Hurford: And the bronchial stenosis went away?

Kallet: Certainly not. But the heliox kept the patient alive and bought us some time.

Hurford: So you kept him alive for a few more hours or days?

Kallet: You know, as a clinician my responsibility is to keep that patient alive during my shift. The situation I referred to was someone for whom we had not made the ethical decision to withdraw or limit support. So, again, this is not something that you are ever going to be able to randomize, ethically, and we are talking about extreme circumstances.

Cheifetz: I agree with Rich about extreme circumstances. What heliox does in those situations is buy time. One example is a child with a foreign body obstructing the airway. Heliox can buy valuable time until the surgeon can remove the foreign body. In a patient with an airway or anterior mediastinal tumor, heliox facilitates gas exchange until a more therapeutic plan can be initiated. Heliox does not fix the underlying problem; it simply allows time for definitive therapies to work or for the natural resolution of the process.

Heliox is very different from nitric oxide. For acute lung injury in the adult and pediatric populations, inhaled nitric oxide does not change outcomes,[1–3] so it is generally not indicated for acute lung injury in the nonneonatal patient. For heliox, there are no data either way, so until data are available, it should be left to clinicians to determine if the risk/benefit ratio favors heliox for an individual patient.

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Kallet: I want to respond to the issue of nitric oxide. There is a legitimate indication for nitric oxide in ARDS as *rescue therapy* when your back is up against the wall and you are trying to buy time. That is the only situation in which we use aerosolized prostacyclin or inhaled nitric oxide in ARDS. That is a distinct application, as opposed to advocating it as a standard therapy to improve oxygenation in these patients. We wouldn't do that.

Hurford: Does that all mix together in one can? The nitric oxide, the heliox, and the aerosolized prostacyclin?

Kallet: We're working on it.

Hurford: Our vote* about ICU adventurism was split.[1]

1. Rubin BK, Steinberg KP. When caring for critically ill patients, do clinicians have a responsibility to be innovative and try unproven approaches when accepted approaches are failing? Respir Care 2007;52(4):408-413.

Pierson:† It seems to me that if heliox is going to have a role in the ICU,

* Editor's note: See Conference Summary.

† David J Pierson MD FAARC, Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, Washington.

it's going to be in the prevention of intubation. Inhaled nitric oxide is an easy "straw man." It has potentially fatal complications, it's extraordinarily expensive; and big trials have failed to document its theoretical promise. But as Ira was giving his presentation, the intervention I kept thinking about was not nitric oxide, but noninvasive ventilation.

Now look at the fervor with which we have embraced noninvasive ventilation—and for very good reason, because it has a solid database and so forth. But it shares important things with heliox: it's inexpensive; everybody can do it because it is readily available; and it has very few adverse affects, and those are by and large minor. I'm interested in the vigor with which people resist heliox, a quite benign therapy, and I think Bill's argument is compelling, along with the fact that the database is not there.

But maybe 10 years from now someone will have done randomized controlled trials that show that in a certain percentage of patients with acute respiratory distress who would otherwise be intubated despite all of the other things that we've been advocating, intubation could be avoided with heliox. And if that does prove to be the case, heliox may have the same benefit, albeit at a smaller scale, as noninvasive ventilation.

Kacmarek: It's going to be a tough sell. We have over 50 positive randomized controlled trials of noninvasive ventilation. The problem with heliox is that there are so few intubated asthmatic patients. The other therapy for asthma is changing so rapidly, and there's so few of these patients in any of our institutions who get intubated today, it would be tough to ever come up with the data needed. In the nonintubated patient I think we should use heliox even if we do not have a randomized trial. It's easy to do in the emergency room, it's not costly, and we can rapidly set up heliox for the asthmatic patient who isn't getting better, with little down side to heliox use, even without the randomized controlled trial!

Myers: I think the take-home message on heliox is that its benefit is that it may prevent intubation. After intubation, though, I think the situation is analogous to Woody Hayes's comment about passing the football: "There's 3 things that could happen when you pass the football, and 2 of them are bad." Same thing goes with delivering heliox through a ventilator: there are probably 3 or 4 things that could happen and potentially 3 of them are bad. So, I don't think the safety profile can be extrapolated from nonintubated patients to intubated patients. Although it wasn't reported in the literature, we're not really sure what the data was or what it showed.

Deem: In relation to your statement that we don't have any randomized controlled trials and so until then it's safe, I think that's an incorrect assumption, because many times over the years we've seen interventions that had unintended consequences that we didn't see until we obtained high-level evidence. A randomized controlled trial can reveal an outcome that was totally unexpected. I have nothing against using heliox for rescue therapy—I use inhaled nitric oxide in that setting—but I think as a standard therapy in ventilated patients there's no good rationale for applying heliox broadly.

Cheifetz: As Rich [Kallet] and I stated, we are talking about the extreme cases. There are no randomized controlled data on the safety of administering heliox through a ventilator. But in all the published papers so far, no one has documented any adverse effects from heliox. I am not saying there are none; I am just saying that no adverse effects have been reported yet.

It is also important to note that the FDA has approved at least one ventilator to safely deliver heliox, and they have approved monitors that can be used with heliox to accurately measure delivered V_T. The biggest risk in heliox administration is the technical gas delivery problem. Heliox is safe if correctly delivered with the correct equipment. But we do need a randomized controlled trial (in children and adults) to try to answer this question.