Heliox and Noninvasive Positive-Pressure Ventilation: A Role for Heliox in Exacerbations of Chronic Obstructive Pulmonary Disease?

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Evidence-based respiratory therapy for exacerbations of chronic obstructive pulmonary disease (COPD) includes oxygen, inhaled bronchodilators, and noninvasive positive-pressure ventilation. Examining the physics of gas flow, a case can be made either for or against the use of helium-oxygen mixture (heliox) in the care of patients with COPD. The evidence for the use of heliox in patients with COPD exacerbation is not strong at present. Most of the peer-reviewed literature consists of case reports, case series, and physiologic studies in small samples of carefully selected patients. Some patients with COPD exacerbation have a favorable physiologic response to heliox therapy, but predicting who will be a responder is difficult. Moreover, the use of heliox is hampered by the lack of widespread availability of an approved heliox delivery system. Appropriately designed randomized controlled trials with patient-important outcomes, such as avoidance of intubation, decreased intensive-care-unit and hospital days, and decreased cost of therapy, are sorely needed to establish the role of heliox in patients with COPD exacerbation, including those receiving noninvasive positive-pressure ventilation. Lacking such evidence, the use of heliox in patients with COPD exacerbation cannot be considered standard therapy. *Key words: chronic obstructive pulmonary disease, heliox, mechanical ventilation, noninvasive positive-pressure ventilation.* [Respir Care 2006;51(6):640–650.

Introduction

In the United States, more than 16 million patients are diagnosed with chronic obstructive pulmonary disease (COPD).[1,2] COPD accounts for approximately 110,000 deaths per year, making it the 4th leading cause of death. It annually accounts for 16,367,000 office visits and 500,000 hospitalizations. The mortality rate of COPD is

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rising. The estimated direct and indirect costs of COPD were $30.4 billion in 1998. On average, COPD patients experience 2 or 3 exacerbations per year.[3]

Evidence-based respiratory therapy procedures for COPD exacerbation include oxygen, inhaled bronchodilators, and noninvasive positive-pressure ventilation (NPPV).[2–5] In patients with severe exacerbation, invasive mechanical ventilation may be necessary. It is common that, once intubated, the patient with COPD will proceed to tracheostomy and prolonged mechanical ventilation. Although Barach many years ago described the use of heliox (usually 70–80% helium and 20–30% oxygen) in managing patients with airflow obstruction,[6–9] the precise role of heliox in COPD exacerbation remains unclear. This paper reviews the current evidence on heliox in patients with COPD, specifically addressing the role of heliox with NPPV.

Making the Case for Heliox in COPD Using the Physics of Gas Flow

Examining the physics of gas flow, a case can be made either for or against the use of heliox in the care of patients with COPD. Various effects are simultaneously at play, and this may explain the variable responses reported for heliox in patients with COPD.

Why Heliox Might Not Help Patients With COPD Exacerbation

COPD is characterized by disease of small airways, where flow is laminar. Laminar flow is density-independent and viscosity-dependent.[10] Thus one would predict that changing the gas density is not likely to affect flow in patients with COPD. If expiratory flow is measured while breathing gases with different densities, the flow will remain stable if there is laminar flow in the flow-limiting segment. If flow in the flow-limiting segment is turbulent, breathing a gas of lower density (ie, heliox) should increase flow. This has been used as a test of small-airways disease.[11,12] Because the viscosity of heliox is similar to that of air but its density is much lower, it is expected that higher expiratory flow will be achieved if flow in the flow-limiting segment is turbulent. In normal persons, in whom the flow-limiting segment is in the central airways, where flow is turbulent, there is an increase in expiratory flow when breathing heliox (Fig. 1). The increase in expiratory flow while breathing heliox at 50% of the vital capacity is called $\Delta\dot{V}_{max50}$. The volume at which the flows with heliox and air become the same is called the volume of isoflow ($V_{iso\dot{V}}$). In normal persons, $\Delta\dot{V}_{max50}$ is about 50% and $V_{iso\dot{V}}$ is about 15%. In patients with COPD, maximum expiratory flow is often density-independent, due to disease predominantly of the small airways (see Fig. 1).

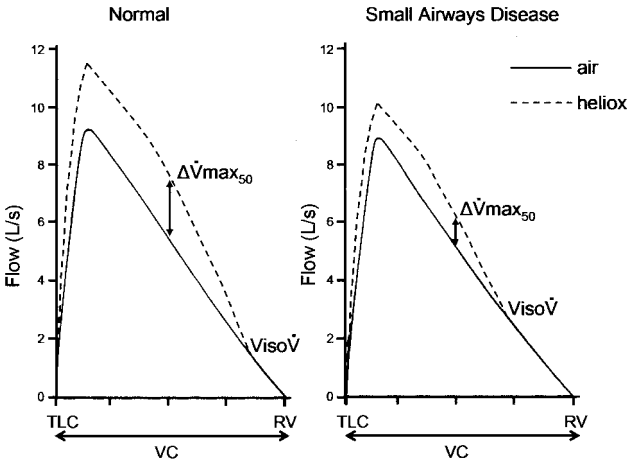

Fig. 1. Expiratory flow-volume loop while breathing air versus breathing heliox. In the normal case (left), note the greater increase in expiratory flow while breathing heliox at 50% of the vital capacity ($\Delta\dot{V}_{max50}$) than in the case of small-airways disease. Also note that the volume of isoflow ($V_{iso\dot{V}}$) is larger in the case of small-airways disease than in normal. In small-airways disease, gas flow is laminar in the flow-limiting segment, which is density-independent. TLC = total lung capacity. RV = residual volume. VC = vital capacity.

Why Heliox Might Help Patients With COPD Exacerbation

Although expiratory flow is often density-independent in patients with COPD, in some patients expiratory flow retains its density dependence, and heliox might be of value in these patients.[13] Moreover, according to wave speed theory, $\Delta\dot{V}_{max}$ increases as gas density decreases. Wave speed theory predicts that, in patients with flow limitation (eg, COPD), breathing a gas with lower density (heliox) might improve expiratory flow and thus decrease dynamic hyperinflation.

Heliox in Spontaneously Breathing Patients With COPD

Stable COPD

Johnson et al[14] randomized patients with severe COPD (mean forced expiratory volume in the first second [FEV_1] 33.5% of predicted) to air ($n = 11$), heliox ($n = 10$), or NPPV ($n = 11$) during 6 weeks of exercise training. They found no training advantage in the heliox group, compared to the group breathing air without NPPV. NPPV produced a small increase in exercise time. These authors concluded

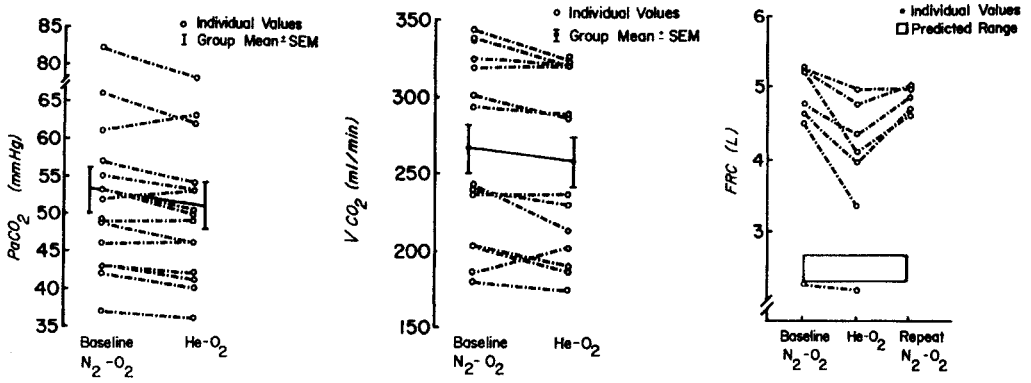

Fig. 2. P_{aCO_2}, carbon dioxide production ($\dot{V}_{CO_2}$), and functional residual capacity (FRC) in patients with stable chronic obstructive pulmonary disease (COPD) breathing air-oxygen (N_2-O_2) and helium-oxygen mixture (He-O_2). SEM = standard error of the mean. (From Reference 18, with permission.)

that heliox does not offer a training advantage in patients with COPD, but NPPV may confer a training advantage.

Palange et al[15] tested the hypothesis that heliox, by reducing dynamic hyperinflation and dyspnea, improves exercise endurance in patients with COPD (n = 12, FEV_1 = 1.15 ± 0.32 L). Each patient underwent cycle-ergometer high-intensity constant-work exercises to exhaustion while breathing either air or heliox. Exercise endurance time was significantly greater with heliox (9.0 ± 4.5 min vs 4.2 ± 2.0 min, $p < 0.001$). Heliox was associated with a significant reduction in dynamic hyperinflation, as reflected by an increase in inspiratory capacity (1.97 ± 0.40 L vs 1.77 ± 0.41 L, $p < 0.001$) and a decrease in dyspnea score (6 ± 1 vs 8 ± 1, $p < 0.001$). Heliox also induced a state of relative hyperventilation, as reflected by an increase in minute volume ($\dot{V}_E$) and $\dot{V}_E/CO_2$ output at peak exercise, and by a reduction in P_{aCO_2}. The authors concluded that heliox improved high-intensity exercise endurance in patients with COPD, by increasing the maximum ventilatory capacity and by reducing dynamic hyperinflation and dyspnea.

In 8 patients with severe COPD, Oelberg et al[16] used incremental cycling tests while the subjects breathed air or heliox. Compared to air, heliox resulted in a higher peak exercise $\dot{V}_E$ (25.5 ± 2.2 L/min vs 19.3 ± 1.5 L/min, $p = 0.002$), lower P_{aCO_2} (42 ± 2 mm Hg vs 46 ± 2 mm Hg, $p = 0.0003$), and higher maximum oxygen consumption ($\Delta\dot{V}_{O_{2max}}$) (594 ± 75 mL/min vs 514 ± 54 mL/min, $p = 0.04$). Cardiac output, however, did not improve with heliox. The increased $\dot{V}_E$ and reduced P_{aCO_2} suggest that respiratory muscle unloading occurred with heliox at peak exercise, but this was not associated with improved oxygen transport or utilization.

Pecchiari et al[17] explored the effects of heliox on breathing pattern, expiratory flow limitation, and dynamic hyperinflation in 22 patients with COPD. During air-breathing, 13 of the patients were flow-limited in the sitting position and 18 were flow-limited in the supine position. In both positions, inspiratory capacity increased significantly in most flow-limited patients after administration of inhaled albuterol, but not after heliox administration. The investigators concluded that heliox had no effect on dynamic hyperinflation and did not appear to benefit stable patients with COPD at rest.

Swidwa et al[18] evaluated the effect of heliox in 15 patients with severe COPD. Functional residual capacity decreased significantly with heliox (Fig. 2). There was no significant change in $\dot{V}_E$, tidal volume (V_T), or respiratory rate. In the majority of patients (11/15), P_{aCO_2} decreased. Carbon-dioxide production also decreased, which was attributed to a lower work of breathing. Expiratory flow also increased during heliox breathing. These short-term physiologic effects support the use of heliox in COPD but provide little insight into the use of heliox during COPD exacerbations.

COPD Exacerbation

There have been several impressive case reports of the use of heliox in patients with COPD exacerbation. Polito and Fessler[19] reported a patient with COPD receiving invasive mechanical ventilation who self-extubated. While breathing 40% oxygen, she developed progressive hypercapnia and somnolence. With administration of heliox via face mask, the patient's respiratory rate immediately fell, she became alert, and her P_{aCO_2} decreased from about 90 mm Hg to about 50 mm Hg. An attempt to remove the heliox resulted in a worsening of her hypercapnia. It was possible to discontinue the heliox after 24 hours of therapy, re-intubation was avoided, and she was discharged on the 10th day.

Gerbeaux et al[20] reported the case of a patient with COPD exacerbation who presented to the emergency department with altered mentation, paradoxical diaphragmatic motion, tachypnea, and hypercarbia. With heliox admin-

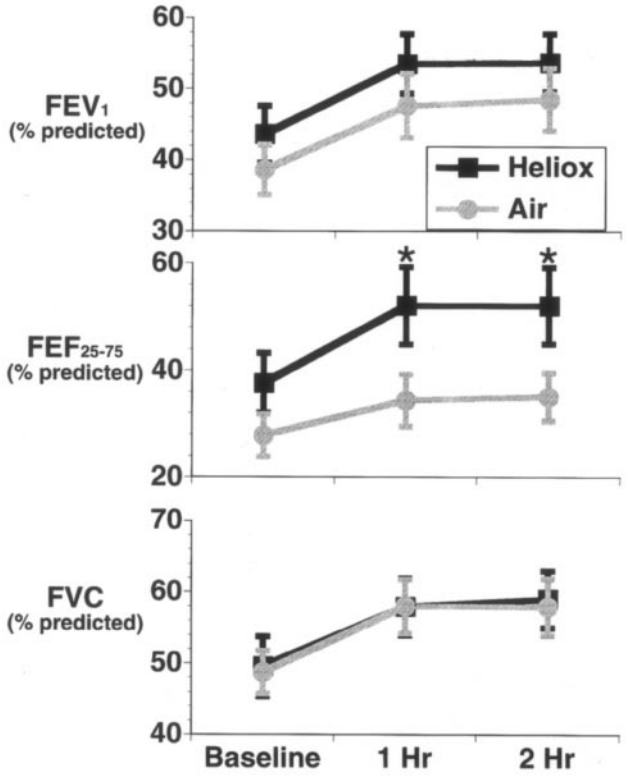

Fig. 3. Mean ± SEM pulmonary function values in patients with exacerbation of chronic obstructive pulmonary disease, receiving inhaled bronchodilator therapy, with the nebulizer powered by either air or helium-oxygen mixture (heliox). There were no significant differences between the treatment groups in forced expiratory volume in the first second (FEV_1) or forced vital capacity (FVC) at any of the sampled time points. However, the improvement in forced expiratory flow in the middle half of the FVC ($FEF_{25–75}$) was significantly greater in the heliox group (squares) than in the air group (circles) ($p < 0.05$) at both the 1-hour and 2-hour measurement points. (From Reference 22, with permission.)

istered via face mask there was marked improvement in the respiratory acidosis and mentation. Attempts to discontinue the heliox resulted in a return of hypercapnia. Heliox was continued for 4 days, after which it was successfully discontinued, and the patient was discharged from the hospital 1 week later.

In a retrospective study, Gerbeaux et al[21] assessed whether patients with COPD treated with heliox have a better prognosis than those treated with standard therapy. Over a period of 18 months, 81 patients admitted with exacerbation of COPD and respiratory acidosis were placed into 2 groups, according to whether heliox was used as a therapeutic agent (heliox group, $n = 39$) or not (standard group, $n = 42$). Age, gender, medical history, vital signs, initial arterial blood gas values, and emergency-room treatment were similar for the 2 groups. Intubation and mortality were significantly lower in the heliox group. The survivors in the heliox group had significantly shorter intensive-care-unit (ICU) and hospital stays. This study supports a benefit from heliox in COPD exacerbation, but as a retrospective analysis the study is methodologically weak.

Patients with COPD exacerbation benefit from inhaled bronchodilators. A randomized trial of the use of heliox as the driving gas for nebulization of bronchodilators in the treatment of COPD exacerbation was conducted by deBoisblanc et al.[22] Over a 12-month period, 50 patients who presented with COPD exacerbation were evenly randomized to receive either heliox or air as the driving gas for the nebulizer to deliver albuterol and ipratropium bromide. There were no significant differences in the FEV_1 change between the 2 groups, at either the 1-hour or 2-hour time points (Fig. 3). The improvement in forced expiratory flow in the middle half of the FVC ($FEF_{25–75}$) was significantly greater in the heliox group than in the air group at both time points, the clinical importance of which is unclear. Although the results of this study were negative, there is an important methodological issue that might have affected these results. That is, heliox was used to power the nebulizer at a flow of 11 L/min, but the gas-delivery system was not closed and additional gas entrained by the patient was air (not heliox). Thus, the helium concentration in the inspired gas may have been sufficiently diluted to negate the potential benefits of the heliox. This study should be repeated using a gas-delivery system that does not allow heliox dilution.

Two meta-analyses of the use of heliox for COPD exacerbation have been published. A Cochrane review[23] concluded that there is insufficient evidence to support the use of heliox to treat COPD exacerbations. This Cochrane review recommended that suitably designed randomized controlled trials be designed, with the end point being the avoidance of mechanical ventilation.

Andrews and Lynch[24] conducted a meta-analysis to determine if heliox in nonintubated patients with COPD exacerbation reduces P_{aCO_2} or the odds of intubation. They concluded that definitive evidence of a beneficial role of heliox in treatment of severe COPD is lacking and its widespread use cannot be recommended. They did find that heliox may reduce the odds of intubation, and they suggested that, in the individual case of severe COPD where intubation is required but would be undesirable, heliox is a treatment worthy of consideration.

Heliox in Invasively Ventilated Patients With COPD

Using a prospective crossover design, Tassaux et al[25] tested the hypothesis that replacing a 70:30 nitrogen-oxygen mixture with 70:30 heliox can reduce dynamic hyperinflation in mechanically ventilated patients with COPD. Intubated, sedated, and paralyzed patients ($n = 23$) were enrolled within 36 hours after intubation. Trapped gas volume, intrinsic positive end-expiratory pressure (auto-

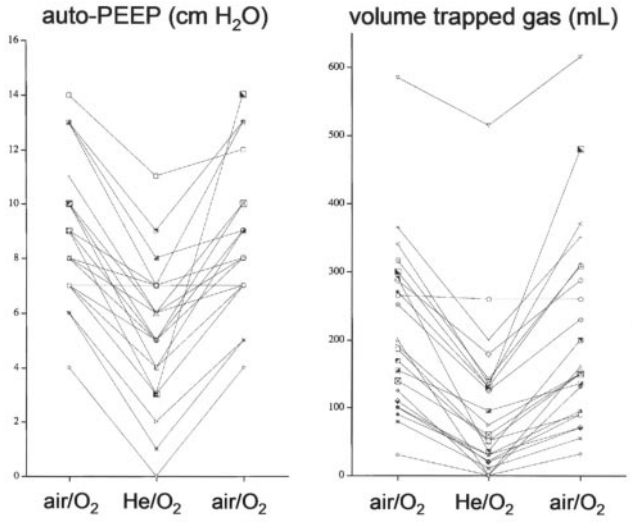

Fig. 4. Left: Individual levels of intrinsic positive end-expiratory pressure (auto-PEEP) before, during, and after administration of helium-oxygen mixture (He/O_2). Right: Volume of trapped gas before, during, and after administration of helium-oxygen mixture. (Adapted from Reference 25, with permission.)

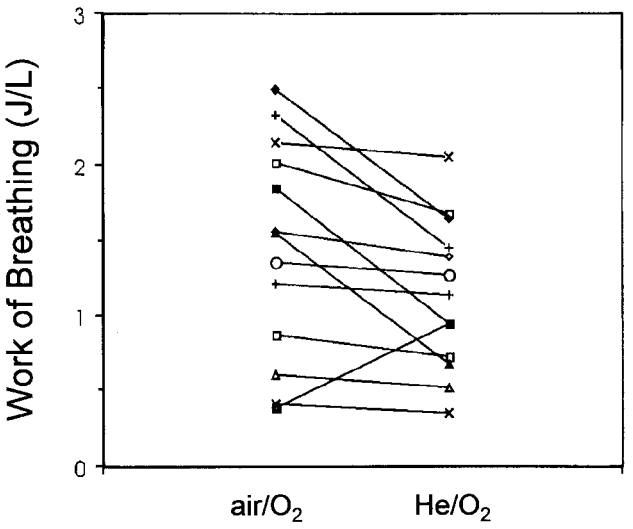

Fig. 5. Individual values of work of breathing, measured just before extubation, in 13 patients with chronic obstructive pulmonary disease (COPD) breathing either air-oxygen mixture (air/O_2) or helium-oxygen mixture (He/O_2). (From Reference 29, with permission.)

PEEP), and peak airway pressure were significantly lower with heliox ($p < 0.05$). However, the effect was quite variable between patients (Fig. 4). Breathing heliox had no effect on arterial blood gases, heart rate, arterial blood pressure, pulmonary artery pressure, right- or left-ventricular filling pressures, cardiac output, pulmonary or systemic vascular resistance, or venous admixture.

In another prospective crossover study, the same investigators[26] evaluated the impact of heliox on inspiratory effort and work of breathing in 10 intubated patients with COPD receiving pressure-support ventilation. Heliox reduced the number of ineffective triggers (4 ± 5 breaths/min vs 9 ± 5 breaths/min), auto-PEEP (3.1 ± 2 cm H_2O vs 4.8 ± 2 cm H_2O), the magnitude of negative esophageal pressure swings (6.7 ± 2 cm H_2O vs 9.1 ± 4.9 cm H_2O), pressure-time product (42 ± 37 vs cm $H_2O \cdot$ s/min 67 ± 65 cm $H_2O \cdot$ s/min), and work of breathing (11 ± 3 J/min vs 18 ± 10 J/min).

Gainnier et al[27] evaluated whether heliox reduces inspiratory work of breathing in 23 sedated, paralyzed, and mechanically ventilated patients with COPD exacerbation. It was a prospective randomized crossover study. Work of breathing significantly decreased with heliox (from 2.34 ± 1.04 J/L to 1.85 ± 1.01 J/L, $p < 0.001$). This was accompanied by significant reductions in auto-PEEP and inspiratory resistance. Respiratory-system compliance was unchanged with heliox.

Jolliet et al[28] compared the effects of heliox and applied PEEP on auto-PEEP, respiratory mechanics, gas exchange, and ventilation/perfusion ratio in 10 mechanically ventilated patients with COPD. The patients were studied (1) without heliox and without applied PEEP, (2) with heliox and without applied PEEP, and (3) without heliox but with applied PEEP set at 80% of auto-PEEP. Measurements at each condition included ventilation/perfusion ratio, measured via the multiple-inert-gas-elimination technique. Auto-PEEP and trapped gas volume were comparably reduced by heliox (4.2 ± 4 cm H_2O vs 7.7 ± 4 cm H_2O, and 98 ± 82 mL vs 217 ± 124 mL, respectively) and by applied PEEP (4.4 ± 1.3 cm H_2O vs 7.8 ± 3.6 cm H_2O, and 120 ± 107 mL vs 216 ± 115 mL, respectively). Heliox reduced inspiratory and expiratory resistance (15.5 ± 4.4 cm H_2O/L/s vs 20.7 ± 6.9 cm H_2O/L/s, and 19 ± 9 cm H_2O/L/s vs 28.8 ± 15 cm H_2O/L/s, respectively) and plateau pressure (13 ± 4 cm H_2O vs 17 ± 6 cm H_2O). PEEP increased airway pressures and decreased compliance. The ratio of P_{aO_2} to fraction of inspired oxygen was slightly reduced by heliox (225 ± 83 mm Hg vs 245 ± 82 mm Hg), without a significant ventilation/perfusion ratio change.

The effect of heliox on work of breathing was evaluated by Diehl et al,[29] in 13 mechanically ventilated patients with COPD. Heliox and air-oxygen mixtures were administered in random order, for 20 min each, just before extubation. The study was repeated after extubation in 5 patients. Heliox reduced the work of breathing from 1.4 ± 0.7 J/L to 1.1 ± 0.5 J/L ($p < 0.05$). This was due mainly to a reduction in the resistive component of the work of breathing, from 0.7 ± 0.4 J/L to 0.5 ± 0.3 J/L ($p < 0.01$). There was also a slight reduction in auto-PEEP, from 2.9 ± 2.1 cm H_2O to 2.1 ± 1.8 cm H_2O ($p < 0.05$). The effect, however, was not consistent

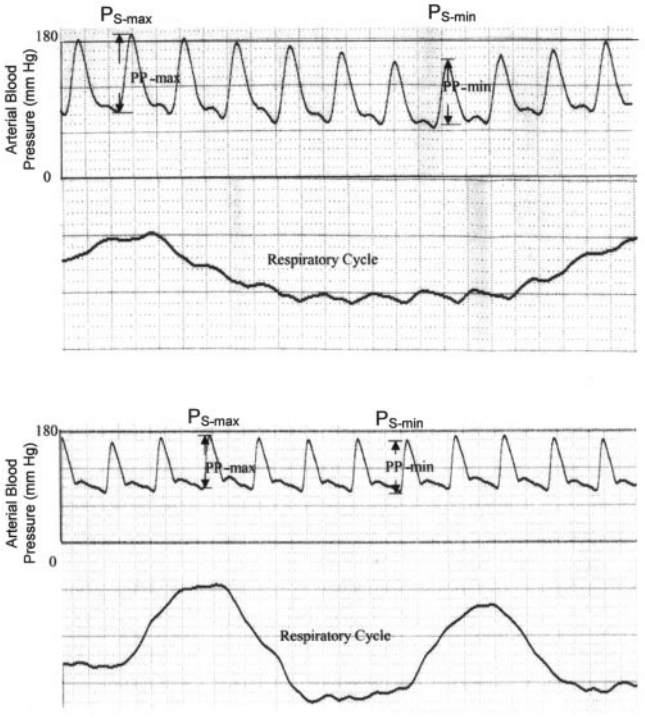

Fig. 6. Tracings of pulse pressure within a respiratory cycle during mechanical ventilation with air-oxygen mixture (air/O_2) (top panel) and helium-oxygen mixture (heliox) (bottom panel). Maximum systolic pressure ($P_{S\text{-}max}$) and maximum pulse pressure ($P_{P\text{-}max}$) occur during inspiration. Minimum systolic pressure ($P_{S\text{-}min}$) and minimum pulse pressure ($P_{P\text{-}min}$) occur during exhalation. ΔP_P (%) = $100 \times ([P_{P\text{-}max} - P_{P\text{-}min}]/0.5 \times [P_{P\text{-}max} + P_{P\text{-}min}])$. (From Reference 30, with permission.)

among patients (Fig. 5). In some patients, there was a large decrease in work of breathing, whereas in others the effect was much less, and in one patient the work of breathing increased with heliox. Similar results were observed after extubation in the 5 patients in whom the study was repeated after extubation.

Lee et al[30] compared the effect of heliox versus air-oxygen mixture on cardiac performance in 25 mechanically ventilated patients with severe COPD and systolic pressure variations $>$ 15 mm Hg. Respiratory and hemodynamic measurements were taken at baseline ventilator settings, after 30 min with heliox, and 30 min after return to air-oxygen. Heliox decreased auto-PEEP from 13 $\pm$ 4 cm H_2O to 5 $\pm$ 2 cm H_2O ($p < 0.05$), trapped gas volume from 362 $\pm$ 67 mL to 174 $\pm$ 86 mL ($p < 0.05$), and respiratory variations in systolic pressure from 29 $\pm$ 5% to 13 $\pm$ 7% ($p < 0.05$) (Fig. 6). In 10 patients with pulmonary arterial catheters, heliox decreased mean pulmonary arterial pressure, right atrial pressure, and pulmonary arterial occlusion pressure, and increased cardiac index. Pre-heliox variations in systolic pressure correlated with the magnitude of reduction in auto-PEEP with heliox.

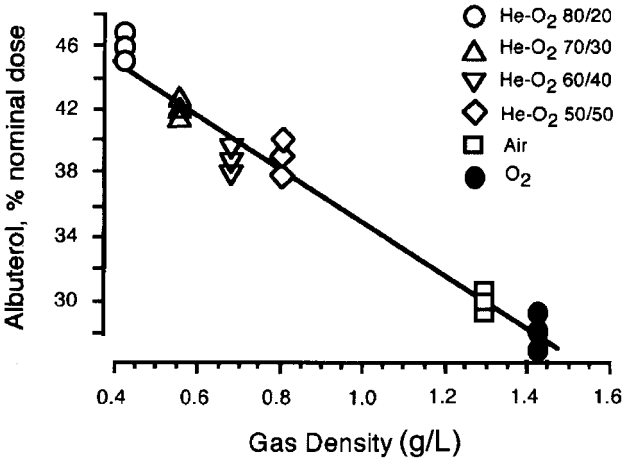

Fig. 7. Albuterol delivery (percent of the nominal dose) from a metered-dose inhaler to filters placed at the ends of simulated bronchi, as a function of gas density. Eight puffs (720 mg) of albuterol were administered into a chamber spacer during controlled ventilation in an unheated, dry ventilator circuit containing air, oxygen, or one of several helium-oxygen mixtures (80%/20%, 70%/30%, 60%/40%, 50%/50%). Albuterol delivery was inversely related to gas density in the ventilator circuit. The highest aerosol delivery occurred with the lowest-density gas (80%/20%). (From Reference 31, with permission.)

Goode et al[31] evaluated the effect of heliox on albuterol delivery from metered-dose inhalers and jet nebulizers in an in vitro model of mechanical ventilation. Albuterol delivery with the metered-dose inhaler was greater when the ventilator circuit contained heliox (versus air) (Fig. 7). The difference was mainly due to decreased drug deposition in the spacer chamber. Nebulizer efficiency at a flow of 6 L/min was 5 times lower with heliox than with oxygen, and the amount of nebulized drug was inversely correlated with gas density. When the nebulizer was operated with oxygen, greater albuterol delivery was achieved when the ventilator circuit contained heliox rather than oxygen. Because patients with COPD benefit from inhaled bronchodilators, these results may be important in mechanically ventilated patients receiving albuterol therapy. As this was a bench study, it is important for these results to be confirmed in patients.

Heliox in Patients With COPD Receiving NPPV

Austan and Polise[32] reported the case of a patient with COPD exacerbation who had minimal clinical improvement with NPPV, oxygen, and inhaled bronchodilators. A 70:30 heliox mixture was delivered into the nasal mask during NPPV with a Respironics S/T-D ventilator, and within 20 min there was marked improvement in arterial blood gases, and a reduction in respiratory rate and accessory muscle use were noted. The patient reported less dyspnea and remained on the heliox therapy for 80 min,

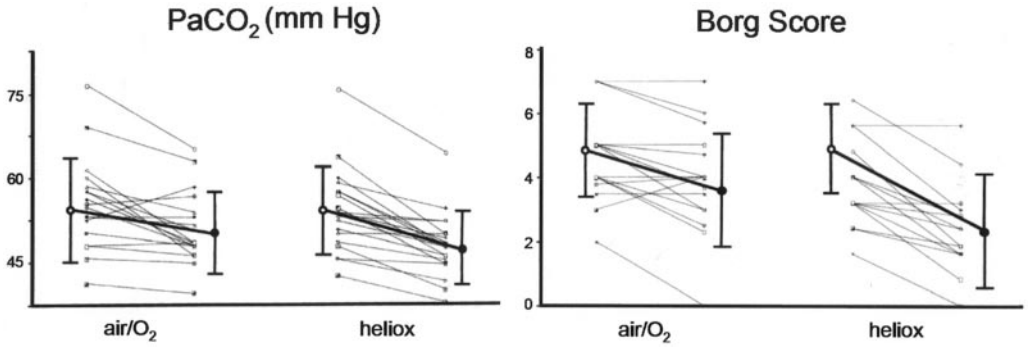

Fig. 8. Individual differences with noninvasive positive-pressure ventilation and air-oxygen mixture (air/O_2) or helium-oxygen mixture (heliox). The mean ± standard deviation values are represented by the larger circles and thicker lines. Left: P_{aCO_2} differences. Right: Dyspnea differences (measured with the Borg scale). (From Reference 33, with permission.)

after which the patient was placed on a 50% oxygen mask. He was discharged 6 days later.

In a randomized crossover study, Jolliet et al evaluated whether using 70:30 heliox instead of 70:30 air-oxygen could reduce dyspnea and improve ventilatory variables, gas exchange, and hemodynamic tolerance in 19 patients with COPD exacerbation.[33] A Hamilton Veolar ventilator was used to provide NPPV. Patients were studied within 24 hours of ICU admission. Patients received 45 min of NPPV with air-oxygen or heliox, then no ventilation for 45 min, and then 45 min with air-oxygen or heliox. P_{aCO_2} decreased more with heliox (Fig. 8). When P_{aCO_2} was > 56 mm Hg, P_{aCO_2} decreased by ≥ 7.5 mm Hg in 6 of 7 patients with heliox, and in 4 of 7 patients with air-oxygen. Dyspnea score decreased more with heliox than with air-oxygen. Mean arterial blood pressure decreased with air-oxygen but remained unchanged with heliox.

In 10 patients with COPD exacerbation, Jaber et al[34] compared the effort to breathe, as assessed by the respiratory-muscle pressure-time index, work of breathing, and gas exchange during NPPV with heliox or air-oxygen mixture. A prototype specially designed ventilator that functions correctly in the presence of heliox was used. Two levels of pressure-support ventilation were used: 9 ± 2 cm H_2O and 18 ± 3 cm H_2O. Significant reductions in pressure-time index were observed with heliox (versus air-oxygen), at both the low pressure-support level (160 ± 58 cm $H_2O \cdot$ s/min vs 198 ± 78 cm $H_2O \cdot$ s/min, $p < 0.05$) and the high pressure-support level (100 ± 45 cm $H_2O \cdot$ s/min vs 150 ± 82 cm $H_2O \cdot$ s/min, $p < 0.01$). Work of breathing was also significantly lower with heliox (7.8 ± 4.1 J/min vs 10.9 ± 6.1 J/min at the low pressure-support level, $p < 0.05$, and 5.7 ± 3.3 J/min vs 9.2 ± 5 J/min at the high pressure-support level, $p < 0.01$) (Figs. 9 and 10). Heliox reduced P_{aCO_2} at both the low pressure-support level and the high pressure-support level, without significantly changing breathing pattern or oxygenation.

Jolliet et al[35] conducted a prospective randomized multicenter study to determine whether NPPV with heliox would benefit outcome or cost in patients with COPD exacerbation. Patients ($n = 123$) were randomized to NPPV with air-oxygen or heliox. All patients were ventilated with a Hamilton Veolar or Siemens Servo 300 ventilator. Intubation rate (air-oxygen 20% vs heliox 13%) and ICU stay (air-oxygen 6.2 ± 5.6 d vs heliox 5.1 ± 4 d) were not significantly different. The post-ICU hospital stay was shorter with heliox (air-oxygen 19 ± 12 d vs heliox 13 ±

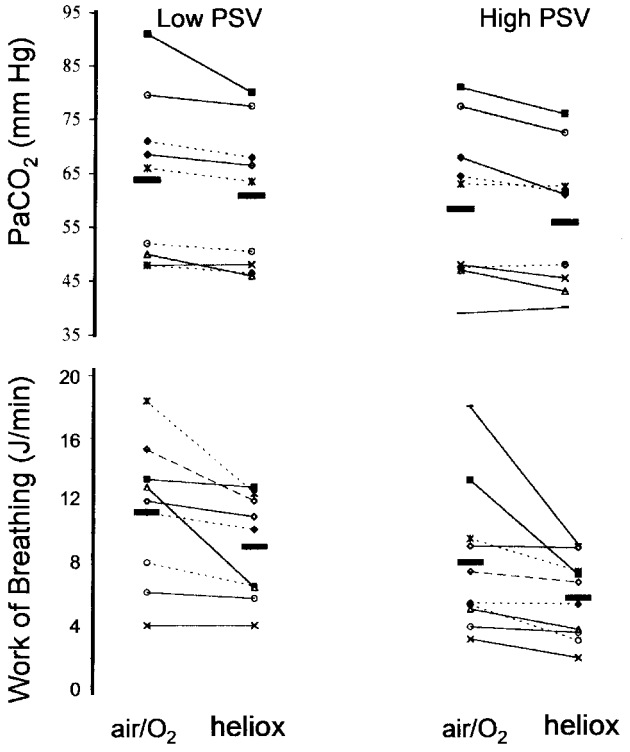

Fig. 9. Individual differences in P_{aCO_2} and work of breathing between air-oxygen mixture (air/O_2) and helium-oxygen mixture (heliox) with low and high levels of pressure support during pressure-support ventilation (PSV). The horizontal bars indicate the mean values ($p < 0.05$). (From Reference 34, with permission.)

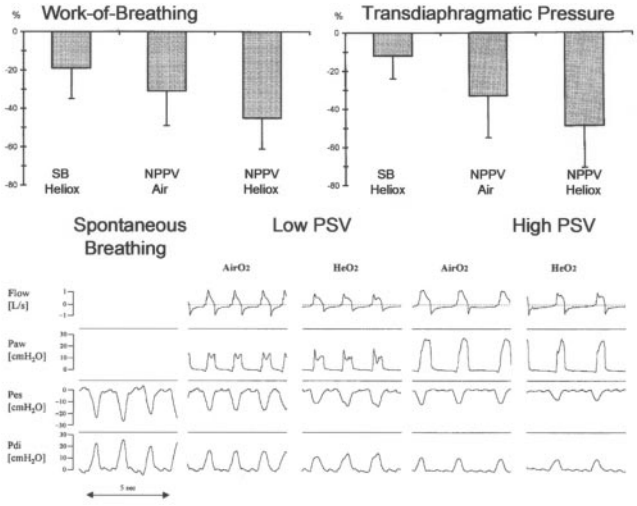

Fig. 10. Top left: Relative changes in work of breathing. Top right: Relative changes in tidal transdiaphragmatic pressure swings. Bottom: These patient tracings show that the esophageal pressure (P_{es}) and diaphragmatic pressure (P_{di}) swings were smaller with helium-oxygen mixture (He/O_2) than with air-oxygen mixture (air/O_2) during both low and high levels of pressure support during pressure-support ventilation (PSV). SB = spontaneous breathing. NPPV = noninvasive positive-pressure ventilation. (From Reference 34, with permission.)

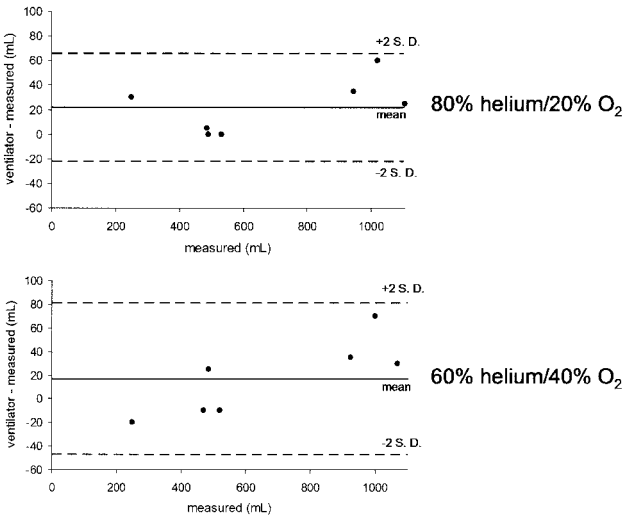

Fig. 11. Bland-Altman plots of bias and limits of agreement between exhaled tidal volume measured on the ventilator and that delivered to the test lung for mixtures of 80% helium/20% oxygen and 60% helium/40% oxygen. (From Reference 39, with permission.)

6 d, $p < 0.002$). Gas cost was higher with heliox, but total hospitalization costs were lower, by $3,348 per patient, with heliox. No complications were associated with the use of heliox. The authors concluded that heliox with NPPV can be safely administered and might be a cost-effective strategy. The results of this study are difficult to interpret. It is difficult to reconcile the shorter post-ICU hospital stay and lower costs with the fact that the intubation rate and ICU stay were not significantly different. However, this may be due to the study being underpowered. A reduction in intubation rate from 20% to 13% is clinically important, but would require a sample size of about 450 patients (4 times the sample size in this study) to be statistically significant. Similarly, a sample size of about 400 patients would be necessary to demonstrate a 1-day reduction in ICU stay. Thus, unfortunately, the discouraging results of this study might be the result of an insufficient sample size.

Effect of Heliox on the Performance of the Ventilator Used for NPPV

Respiratory care equipment, including the ventilator, is calibrated to operate with a gas mixture containing air and oxygen. The low density and high thermal conductivity of helium can adversely affect ventilator functioning. This has been reported in several evaluations of ventilator functioning with heliox.[36–38]

The only ventilator that can be used for invasive and noninvasive ventilation that is approved by the United Stated Food and Drug Administration for heliox delivery is the Viasys Avea. Using "Smart" connector technology, the Avea can deliver heliox blended gas instead of air. By changing a connector on the back panel, the ventilator identifies the gas input and adjusts to accommodate the change. All volumes are automatically compensated for the presence of heliox. Using a lung model, we evaluated the accuracy of the volume displays of the Avea with volume-controlled, pressure-controlled, and pressure-support ventilation.[39] We found no significant difference for the bias between exhaled V_T measured on the ventilator and that delivered to the test lung for air and 80:20 heliox (6 ± 31 mL vs 22 ± 22 mL, $p = 0.19$) (Fig. 11). Similarly, there was no significant difference for the bias between exhaled V_T measured on the ventilator and that delivered to the test lung for 40% oxygen/balance nitrogen and 40% oxygen/balance helium (14 ± 22 mL vs 17 ± 32 mL, $p = 0.63$) (Fig. 11). The bias for V_T delivered to the test lung with 80% helium versus air was 37 ± 43 mL. The bias for V_T delivered to the test lung for 60% helium/40% oxygen versus 60% nitrogen/40% oxygen was 20 ± 27 mL. For the pressure-supported breaths, triggering was identical with and without helium. We concluded that the accuracy of volume delivery with heliox is clinically acceptable with the Avea.

NPPV is usually applied using ventilators designed specifically for mask ventilation. We[40] studied helium concentration when 80:20 heliox was used with 5 NPPV ventilators (Knightstar, Quantum, BiPAP S/T-D30, Sullivan, and BiPAP Vision). A lung model simulating spontaneous

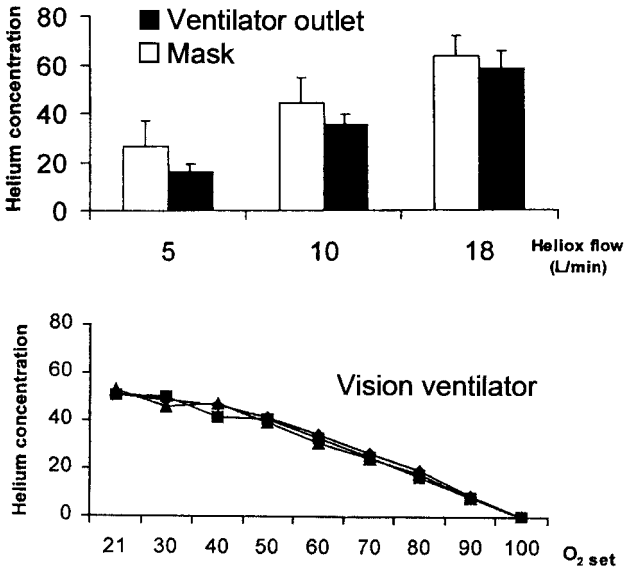

Fig. 12. Helium concentration when helium-oxygen mixture (heliox) was infused into 4 ventilator brands (Knightstar, Quantum, BiPAP S/T-D30, and Sullivan) at the mask and at the ventilator outlet with heliox flows of 5, 10, and 18 L/min. The leak port is in the circuit, near the mask position. (From Reference 40, with permission.)

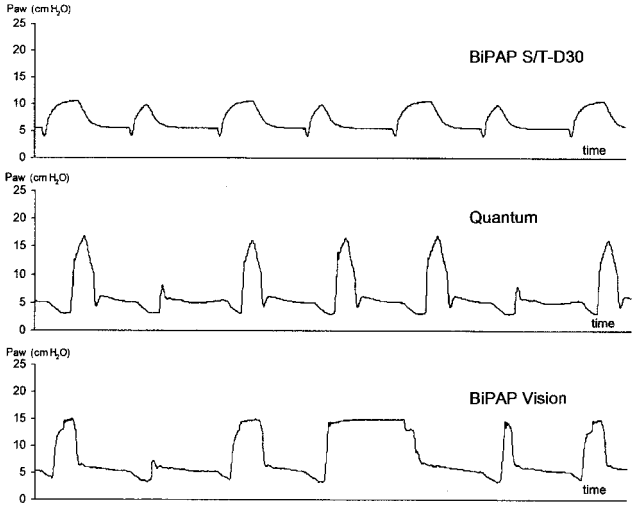

Fig. 13. Airway pressure waveforms showing erratic performance (top panel) with the BiPAP S/T-D30 ventilator when helium-oxygen mixture (heliox) flow of 10 L/min was titrated into the system at the mask position with a noninvasive positive-pressure ventilation (NPPV) setting of 10/5 cm H_2O; (middle panel) with the Quantum ventilator when heliox flow of 18 L/min was titrated into the system with an NPPV setting of 20/5 cm H_2O at the ventilator outlet; and (bottom panel) with the BiPAP Vision ventilator with heliox delivered via the external blender with an NPPV setting of 15/5 cm H_2O. (From Reference 40, with permission.)

breathing was connected to the ventilator with a circuit that incorporated a standard leak. Heliox flows of 0, 5, 10, and 18 L/min and oxygen flows of 0 and 10 L/min were

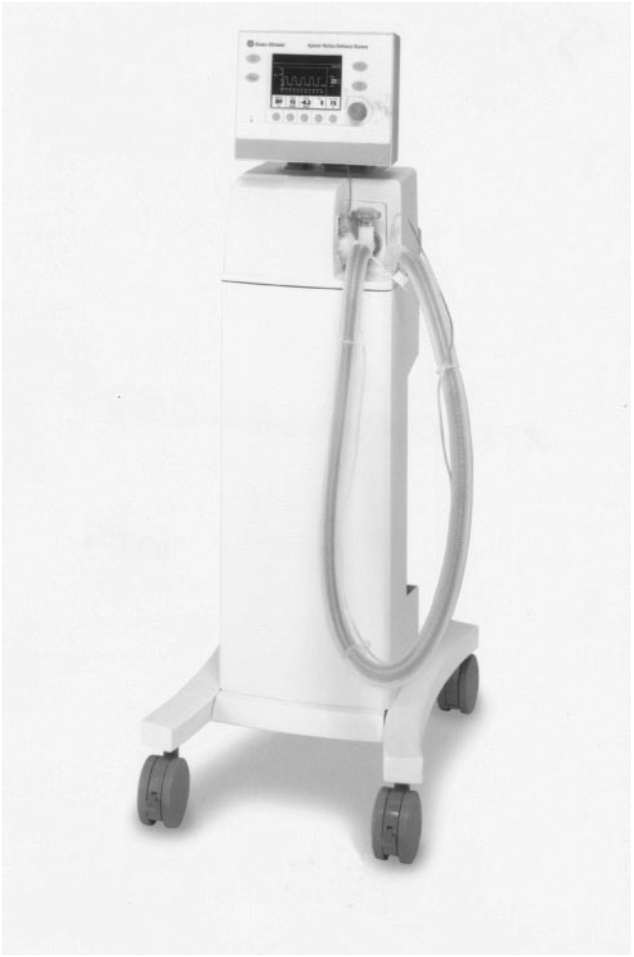

Fig. 14. The Aptaér heliox delivery system. (Courtesy of GE Healthcare, Madison, Wisconsin.)

titrated into the system at either a proximal position near the lung model or a distal position near the ventilator (titration method). Because the BiPAP Vision has an oxygen-delivery module, we also studied using heliox connected to the air inlet of an oxygen blender, with the blender outlet connected to the oxygen module of the ventilator (blender method). All ventilators were evaluated in spontaneous/timed mode at inspiratory/expiratory pressures of 10/5, 15/5, and 20/5 cm H_2O. Heliox flow, NPPV settings, site of heliox infusion, and type of ventilator significantly ($p < 0.05$) affected helium concentration. Helium concentration was $> 60\%$ when heliox flow was 18 L/min in some combinations of settings (Fig. 12). The BiPAP S/T-D30 and Quantum occasionally functioned erratically. The BiPAP Vision (blender method) performed erratically with heliox unless the exhalation-port test was bypassed on startup (Fig. 13). The addition of heliox flow had no important effect on inspiratory or expiratory positive airway pressure on those breaths during which the ventilators functioned correctly. We concluded that there was a potential

for ventilator malfunction in some conditions with heliox use in ventilators designed specifically for NPPV.

The Aptaér heliox delivery system (GE Healthcare, Madison, Wisconsin) recently became available to administer heliox with NPPV (Fig. 14). It uses a premixed blend of heliox from a source gas cylinder and delivers it to a spontaneously breathing patient through a sealed face mask. The Aptaér allows the clinician to adjust the level of pressure support (3–20 cm H_2O), trigger sensitivity (-0.1 to -1.5 cm H_2O), rise time, and cycle sensitivity (5–75% of peak inspiratory flow). It incorporates an Aeroneb Pro vibrating-mesh nebulizer (Nektar Therapeutics, Mountain View, California),[41] which, by its design, should not be affected by gas density, as occurs with jet nebulizers.[42] Aside from a few abstracts,[43–47] little has been published on the performance of the Aeroneb Pro. Using a commercially available heliox-delivery system improves the safety of heliox administration. Improvements in the device could include an oxygen blender (so that the tank does not need to be changed for an F_{IO_2} change) and the ability to apply PEEP. Titration of applied PEEP might be particularly important to counterbalance auto-PEEP in the patient with COPD.

Comment and Conclusions

The evidence for the use of heliox in patients with COPD exacerbation is not robust or mature. Most of the peer-reviewed literature consists of case reports, case series, and physiologic studies in small samples of carefully selected patients. Only one multicenter randomized controlled trial has been reported,[35] and that study was flawed by a too-small sample size. Even in the physiologic studies, a consistent response in not reported in all patients. It seems that some patients with COPD exacerbation have a favorable physiologic response to heliox therapy, whereas others do not, and it is not clear how to predict who will respond to heliox and who will not. Finally, the use of heliox is hampered by the lack of widespread availability of an approved heliox-delivery system. Homemade systems are often used for heliox administration, which, at the least, do not deliver a helium concentration sufficient to produce a physiologic benefit and, at worst, have the potential for patient harm.

The following questions remain unanswered about the use of heliox in patients with COPD exacerbation.

1. Which patients are most likely to benefit from heliox?
2. Is there a role for heliox combined with aerosol bronchodilator delivery?
3. Is there a role for heliox combined with NPPV?
4. Is there a role for heliox in the invasively ventilated patient?
5. What is the best delivery system for heliox?

These questions should be addressed in appropriately designed randomized controlled trials with patient-important outcomes such as avoidance of intubation, decreased ICU and hospital days, and decreased cost of therapy. Lacking such evidence, the use of heliox in patients with COPD exacerbation cannot be considered standard therapy.

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Opportunities and Risks of Using Heliox in Your Clinical Practice

James B Fink MSc RRT FAARC

Helium-oxygen mixture (heliox) has been advocated for clinical use since 1934, and there has been a growing array of clinical applications. Until recently, administering heliox has required jury-rigging by modifications and/or extension of available devices not designed for use with heliox. This paper reviews devices required to administer heliox and considers how devices designed to deliver air and/or oxygen have been adapted for use with heliox. Use of devices outside of their design limits adds risk and liability, whereas using Food-and-Drug-Administration cleared devices for heliox administration reduces the risk and liability. *Key words: helium, heliox, nebulizer, ventilator, regulator, analyzer, blender, risk.* [Respir Care 2006;51(6):651–660.

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Table 1. Devices Commonly Used With Heliox

Device Type	Available Devices Designed for Use With Helium?
Regulators	Yes
Flow meters	Yes
Masks	No
Catheters	No
Hoods	No
Tents	No
Blenders	No
Analyzers	Yes
Monitors	Yes
Nebulizers	Yes
Ventilators	Yes

heliox = helium-oxygen mixture

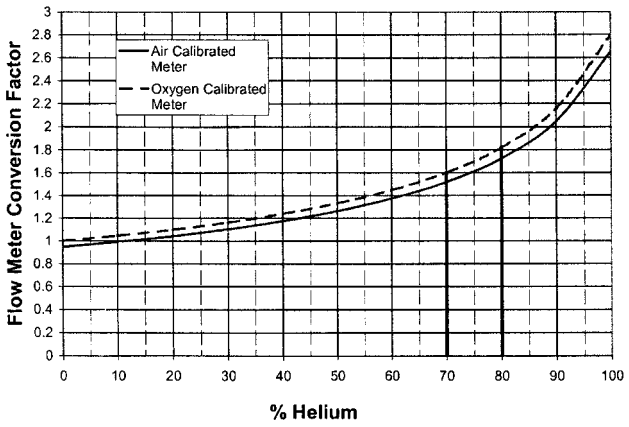

Fig. 1. Diagram from which conversion factors are derived for calculating actual heliox flow rate from readings from flow meters calibrated for air or oxygen. (From Reference 5, with permission.)

Introduction

Since 1934, when Barach first reported clinical use of helium,[1–4] clinicians have faced the necessity to improvise, jury-rig, and kluge delivery systems for helium and helium-oxygen mixture (heliox), using components that were not designed for those gases. Until very recently, clinicians had to develop their own methods to deliver and monitor heliox, using technology and specific devices that had primarily been designed for use with air or oxygen (Table 1). Some of these methods have incorporated intuitive innovations that have ranged from brilliant success to catastrophic failure.

While heliox has considerable potential to benefit patients in various settings, the success of heliox therapy depends on the methods and devices used. Innovation has been key to introducing heliox into clinical practice, but the practice of modifying commercially available devices to function outside of their intended design constraints creates considerable risk and liability for the patient, clinician, and institution. The risks include anoxia (by inadvertently administering an anoxic 100% helium) and delivering a dangerously high lung volume (because flow meters designed to measure air or oxygen flow give incorrect readings with heliox). Only by understanding how helium affects devices and by becoming familiar with how a device or system performs with heliox can researchers and clinicians safely administer heliox. One of the best ways to minimize risk is to use devices that are designed for heliox and cleared by the Food and Drug Administration (FDA) for use with heliox, as they become available on the market. This paper explores key considerations in devices used for administering heliox, and discusses reducing risk by using devices designed and cleared for heliox delivery.

Devices Used With Heliox

Regulators

The most readily available component specifically designed for use with heliox, the regulator, is required to transition the compressed gas into the breathing system. Currently, regulators are commercially produced to deliver pure helium or heliox. Heliox is commonly available in concentrations of 80% helium/20% oxygen (80:20 heliox) and 70% helium/30% oxygen (70:30 heliox), and in various cylinder sizes. Both single-stage and 2-stage regulators are available. Concern has been raised that the threaded connections of the regulator-to-cylinder connectors are the same for heliox and carbogen (a mixture of 95% oxygen and 5% carbon dioxide). Both heliox and carbogen regulators use Compressed-Gas-Association 280 threaded inlet and Diameter-Index Safety System 1020/1180/1200 outlets, so there is a risk of accidentally administering carbogen instead of heliox. Therefore it is important that clinicians double-check before administering carbogen or heliox by documenting that they have read the cylinder label *and* analyzed the cylinder contents for oxygen.

Flow Meters

Helium and heliox flow through an orifice faster than do air or oxygen. Consequently, when using a flow meter calibrated for oxygen or air, a correction factor (based on the helium concentration) must be applied to correct for the difference in flow rate (Fig. 1).[5] The heliox correction factors are generally rounded off to 1.4 for 60:40, 1.6 for 70:30, and 1.8 for 80:20. Thus, when an oxygen flow meter delivering 80:20 heliox reads 10 L/min, it is actually delivering 18 L/min (ie, 10×1.8).

Back-pressure-compensated flow meters have been designed for delivery of helium and several specific concentrations of heliox. These devices are commercially available from several manufacturers, at prices similar to those for air and oxygen flow meters of similar design. However, many clinicians persist in using readily available air or oxygen flow meters when delivering heliox.

Accessories for Delivery

Helium has a very high diffusion coefficient and can escape from all but the most tightly sealed containers. This creates particular problems in administering heliox to the patient's airway, especially in nonintubated patients. The most effective heliox systems appear to be closed systems, but, except for invasive mechanical ventilation, a closed system is relatively difficult to accomplish.

To achieve a sufficient helium concentration ($> 50\%$) to gain mechanical advantage from the helium, the system needs to be "helium tight," which requires considerably less leak than "air tight." The system should be high-flow, with sufficient flow to meet or exceed the patient's requirements for minute volume and peak inspiratory flow, to minimize dilution with ambient air.

Helium is relatively rare on the Earth, and an H-size cylinder typically costs more than $80. Flushing a high flow of heliox into the patient's airway to meet the peak inspiratory flow requirement is expensive and can be wasteful. The delivery method should include a reservoir and an on-demand delivery system that minimize total flow and helium requirements.

Masks

Several studies have used valved nonrebreather oxygen masks with reservoirs. The problem is that most of these commercial masks are not designed to provide a sufficiently snug fit to minimize heliox leakage. A disposable nonrebreathing oxygen mask that rarely delivers $> 60\%$ oxygen will not be sufficient to consistently deliver an adequate heliox concentration to the patient. Typically, ambient gas enters the system between the mask and the reservoir with all but the best-fitting masks, and this dilution may be an even greater problem with heliox. To be successful, the mask must have a tight fit and a competent valve, or a valved exhalation port. Unfortunately, properly sealing, tight-fitting masks (such as those used for anesthesia or mask continuous-positive-airway-pressure systems) are more expensive and may be less comfortable when properly seated, especially with infants and small children.

Catheters and Cannulas

In adults, both catheters and cannulas are low-flow devices that do not deliver sufficient concentrations for reliable heliox administration. However, in infants cannulas made for nasal continuous positive airway pressure may provide an adequate seal and maintain pressure at the nares and might therefore be effective with heliox.[6]

Tents and Hoods

Tents and hoods have been suggested for use with infants and small children. These may appear to provide a closed system conducive to heliox administration, but studies suggest that hoods and tents are less effective than tight-fitting masks. It has been hypothesized that helium rises to the top of the enclosure, above the nares and mouth.[7] As with oxygen, leaks are very difficult to control if you do not get a good seal around the perimeters of the enclosure.

Hypothermia with hood or tent heliox administration has been anecdotally reported. Helium's thermal conductivity is 6 times that of nitrogen, so the risk of hypothermia should be considered before using a hood or tent. Inside a diving helmet filled with heliox, the diver can lose body heat 6 times faster than with compressed air or nitrogen-oxygen mixture, which increases the risk of hypothermia.[8] Heating the heliox before the diver inhales it is one strategy used to combat hypothermia. Some clinicians have cautioned against administering heliox at temperatures less than 36°C to infants and small children contained in hoods or tents.

Artificial Airways

For patients with artificial airways, closed systems with demand valves and reservoirs continue to be the commonly used systems. Open T-tubes, even with attached open reservoir tubing, will not adequately contain the helium. A valved reservoir with a valved exhalation port may be more effective in maintaining the desired concentration. An alternative to the reservoir is a demand regulator that provides adequate and immediate gas flow in response to the patient's inspiratory effort, as does the Aptaér heliox administration system (GE Healthcare, Madison, Wisconsin).

Analyzers

Clinicians commonly use oxygen analyzers to monitor heliox concentration "by exclusion," based on the assumption that the delivered gas is either helium or oxygen; if you know the oxygen concentration, then the remaining gas is helium. This assumes that there are no leaks in the

system and no opportunity for air or other gases to enter the system at the point of measurement. An oxygen analyzer cannot detect any addition or leak of air into the system.

Although rarely advertised for use in respiratory care applications, helium analyzers have been available for various commercial applications for many years. These analyzers enable leak detection in industrial applications ranging from pharmaceutical manufacturing to food-processing to tracing leaks in home floor radiant heating systems. Multiple companies market helium analyzers for gas mixtures used for diving. Most analyzers operate by comparing the thermal conductivity of the sample gas to the thermal conductivity of a reference gas housed in a sealed cell, using a temperature-sensitive heated filament mounted in each cell. These filaments are part of a Wheatstone Bridge circuit. Thermal-conductivity gas analysis is also used to measure oxygen, hydrogen, carbon dioxide, and other gases. These gases are normally measured in a background of air, but the sensors operate just as well in a background of nitrogen or when monitoring 2 inert gases. There generally is a quick ($<$ 15 s) response to any change in gas composition. The helium concentration reading can be updated about every 1 second.

The basic assumption on which these analyzers work is that the gases in the mixture are known (eg, oxygen, nitrogen, and/or helium). Minor amounts ($<$ 1% total) of trace gases will not significantly alter the readings and can be ignored. The sensor is nonspecific; it will not indicate if the test gas has carbon monoxide, argon, or any other gas in the mix. It will only determine the relative difference in thermal conductivity of the test gas to the reference cell. It is assumed that the difference is the result of the addition of helium to the gas mixture.

While few respiratory services have a helium analyzer for use in the emergency department or intensive care unit, many have one in the pulmonary function laboratory, although many of these helium analyzers have a range limited to 0–15% helium. The FDA has provisions for approving helium analyzers for use with pulmonary-function-testing devices, defining a helium gas analyzer as a device intended to determine the concentration of helium in a gas mixture during pulmonary function testing. The device may use techniques such as thermal conductivity, gas chromatography, or mass spectrometry.

Blenders

While heliox blenders abound in the diving community, they appear to be rare in the medical community. Consequently, clinicians either entrain oxygen into a pre-set heliox concentration, or use blenders designed for oxygen and air. There is limited published evidence on which, if any, blenders are satisfactory for use with heliox. Typically, the 80:20 heliox is attached to the air inlet of the blender, and an oxygen analyzer is placed immediately downstream to monitor the blended gas.

Table 2. Actual F_{IO_2} During Heliox Administration With 7 Ventilators

Set F_{IO_2}	Ventilator						
	Veolar FT	Galileo	Evita 2	Evita 4	Servo 900C	Servo 300	7200 Series
0.21	0.22	0.22	0.22	0.22	0.22	0.22	0.22
0.25	0.25	0.25	0.24	0.24	0.25	0.26	0.56
0.3	0.31	0.31	0.28	0.27	0.33	0.33	0.73
0.35	0.37	0.35	0.31	0.3	0.35	0.38	0.83
0.4	0.4	0.41	0.35	0.34	0.46	0.43	0.88
0.5	0.51	0.5	0.42	0.41	0.51	0.52	0.95
0.6	0.61	0.6	0.52	0.5	0.62	0.63	0.99
1.0	0.98	1.0	0.98	0.97	0.99	0.99	1.0

*The set F_{IO_2} is the fraction of inspired oxygen blender setting (as opposed to the actual F_{IO_2}).
heliox = heliox-oxygen mixture
(Data from Reference 9.)

Tassaux and colleagues evaluated the fraction of inspired oxygen (F_{IO_2}) delivered through 7 commercially available ventilators and found that all but one provided $\pm$ 10% of the set F_{IO_2} (Table 2).[9]

Before using a blender with or without a ventilator, test the accuracy and reliability of the system's F_{IO_2} readings and know the difference between the set F_{IO_2} and the actual F_{IO_2}.

Monitors

There are a number of ventilation monitors, both integrated in and independent of mechanical ventilators. Few are designed specifically for use with heliox. Monitors that are not designed for use with heliox may behave erratically, providing inconsistent and unreliable volume and flow readings. Monitors designed for use with heliox may allow for specifying the fraction of inspired helium and other gases being monitored.

As a general guide, any monitor or test lung that measures displaced volume should accurately measure the volume and flow of heliox. Unfortunately, no systems are currently commercially available that provide volumetric bedside monitoring for mechanically ventilated patients. There are several test lungs that use volume displacement, which simplifies in vitro testing of a ventilator's performance with heliox (Fig. 2).

Nonvolumetric monitors usually use pressure-differential transducers or hot-wire anemometers to measure flow through the circuit. The 5-fold greater thermoconductivity of helium affects anemometer readings, whereas density

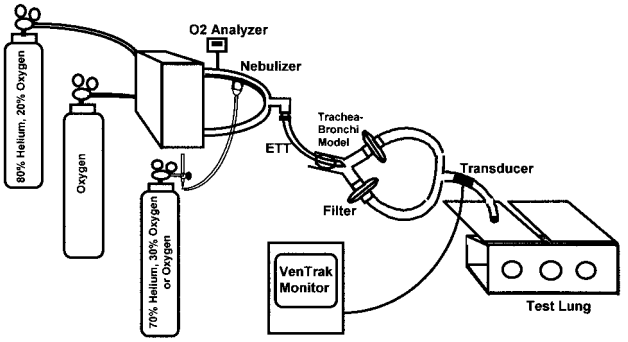

Fig. 2. In vitro test setup with a volumetric test lung. This setup has a monitor in the circuit, which allows comparison of the reading from the volumetric test lung. ETT = endotracheal tube. (Adapted from Reference 12, with permission.)

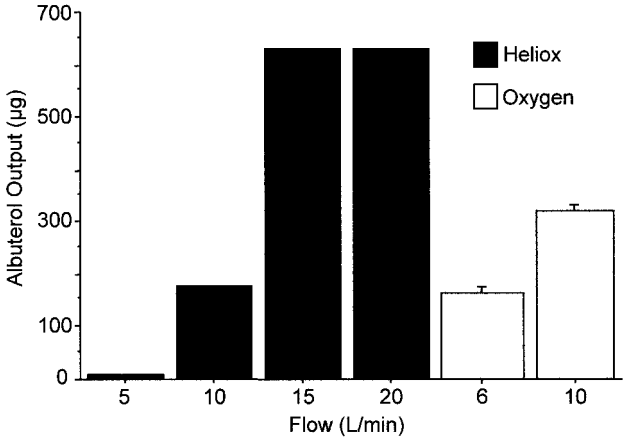

Fig. 3. Output of aerosolized albuterol from an AeroTech II nebulizer driven with various flow rates of oxygen or helium-oxygen mixture (heliox). Note that at a given driving-gas flow, aerosol output with heliox is substantially less than with oxygen. The maximum output with heliox was at 15 L/min. (Adapted from Reference 12, with permission.)

affects pressure-differential transducers. To determine how a monitor works with heliox, test inline with a volumetric monitor, considering the volumetric device the standard (see Fig. 2).

Nebulizers

Heliox improves aerosol deposition, with up to 50% more drug delivered, primarily because helium's density is lower than air or oxygen, and the lower density means less gas turbulence and less aerosol-particle-impaction loss in the tubing and airways. The lower gas density of helium also affects pneumatic (jet) nebulizers. At a given gas flow, a jet nebulizer produces less aerosol output per unit time with heliox than with air or oxygen. Hess et al found a smaller particle size and lower aerosol output rate with jet nebulizers (all operated at 8 L/min) with 80:20 heliox than with air.[10] Increasing the heliox flow rate to 11 L/min increased the particle size and the output rate to values similar to those achieved with air at 8 L/min.

Corcoran and colleagues also found lower aerosol output with heliox, but they did not find a comparable difference in particle size.[11] They attributed this to a difference in methods; they used a Doppler method of aerosol characterization, whereas Hess et al used the cascade impactor method.[10]

Goode et al found a similar heliox-flow-related impact on nebulizer output (Fig. 3). In their experiments, 10 L/min of heliox generated similar output to 6 L/min of oxygen, but 15 L/min of heliox generated 2-fold more aerosol than did 10 L/min of oxygen.[12] Aerosol output is directly correlated to the density of the driving gas (Fig. 4).

It is important to recognize that when delivering 80:20 heliox through a flow meter that is calibrated to measure air or oxygen flow, a reading of 6 L/min indicates an actual flow of $>$ 10 L/min of heliox, which is sufficient to produce a similar nebulizer output to air at 6 L/min. Volu-

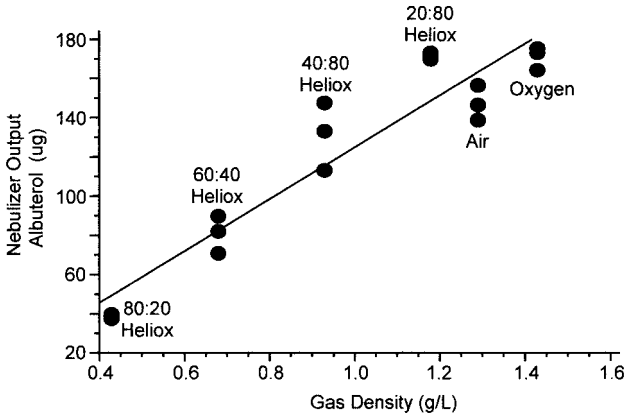

Fig. 4. The output of aerosol from an AeroTech II nebulizer (operated at the same driving-gas flow rate [6 L/min] with each gas mixture) is positively correlated with gas density. $Y = -7.849 + 132.715X$, $r^2 = 0.891$, $r = 0.944$, $p < 0.001$. Heliox = helium-oxygen mixture (heliox ratio values [eg, 80:20] indicate percentages of helium and oxygen, respectively). (Adapted from Reference 12, with permission.)

metric and corrected flow at 8 L/min with oxygen and heliox has been reported to provide similar inhaled aerosol mass (Fig. 5).[13]

The output of aerosol-generation technologies other than pneumatic (jet) nebulizers, such as pressurized metered-dose inhalers and vibrating-mesh nebulizers, is not changed by heliox.[12,14] However, heliox reduces turbulence (with a linear correlation to gas density), which reduces aerosol-particle-impaction loss to the walls of the tubing and airways. A comparison of deposition from a pressurized metered-dose inhaler with spacer chamber in a ventilator circuit with oxygen versus 80:20 heliox showed a $>$ 50% in-

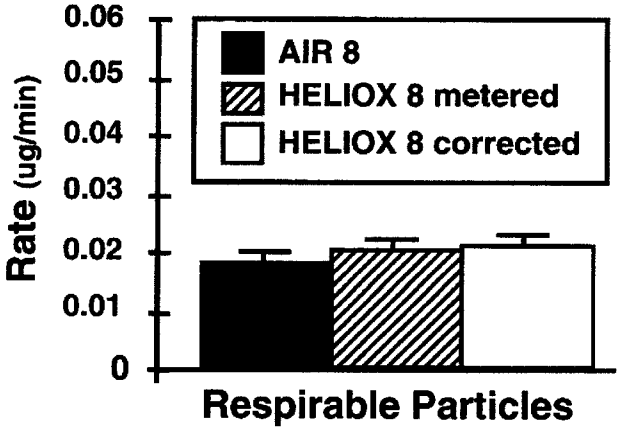

Fig. 5. Rate of generation of respirable albuterol particles, assessed in vitro. The nebulizer was driven with: air at 8 L/min (AIR 8); helium-oxygen mixture (heliox) at a flow-meter reading of 8 L/min (actual flow rate 11 L/min, measured volumetrically) (Heliox 8 metered); or heliox at an actual flow of 8 L/min volumetrically corrected (Heliox 8 corrected). There were no significant differences between the groups. (From Reference 13, with permission.)

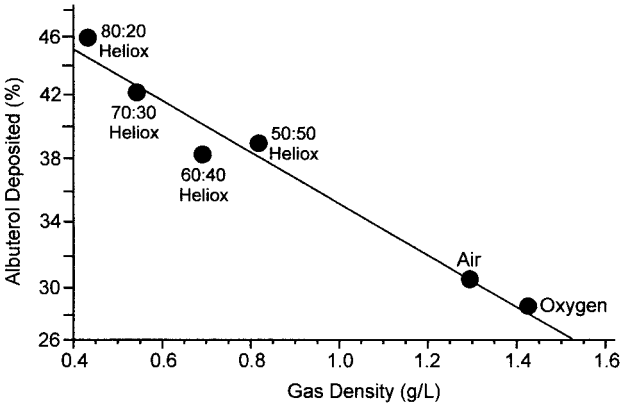

Fig. 6. Deposition of albuterol from a pressurized metered-dose inhaler increases as gas density decreases. $Y = 51.667 - 16.77X$, $r^2 = 0.965$, $p < 0.005$. Heliox = helium-oxygen mixture (heliox ratio values [eg, 80:20] indicate percentages of helium and oxygen, respectively). (Adapted from Reference 12, with permission.)

crease of aerosol delivered to a filter beyond the endotracheal tube (Fig. 6).[12]

Nebulizers Cleared for Use With Heliox

The Hope nebulizer (B&B Medical Technologies, North Highlands, California) was the first large-volume pneumatic nebulizer cleared by the FDA for administration of aerosol with heliox. In this device, the primary gas inlet, which generates the aerosol, is driven by air or oxygen; a secondary inlet allows heliox to be added, with flows > 40 L/min, without affecting aerosol-particle size or output.[15] Other pneumatic nebulizers, such as the Flo-Mist (DHD Healthcare, Wampsville, New York), which has a similar dual-gas-inlet design, are entering the marketplace.

A vibrating-mesh nebulizer (Aeroneb Pro, Nektar Therapeutics, Mountain View, California) has been FDA-cleared for use with the Aptaér heliox delivery system (GE Healthcare, Madison, Wisconsin), based on evidence that the aerosol output and particle size was consistent with oxygen or heliox (Table 3).[14] The Aptaér system is a pressure-support device for use with a sealed mask, with an integrated vibrating-mesh nebulizer. The use of a coaxial circuit and placement of the nebulizer proximal to the delivery system increased aerosol deposition to 35% of nominal dose, compared to 18–22% with a standard ventilator circuit and placement proximal to the patient, at the Y-piece.[14] Deposition of aerosol in an in vitro model with an unobstructed airway was similar with air and heliox, at 35% inhaled mass. Only when a partially obstructed airway was simulated was a 50% increase in deposition observed with heliox (Fig. 7 and Table 4).[14]

Mechanical Ventilators

Until recently, no ventilators were FDA-cleared for heliox. Tassaux and colleagues[9] evaluated the functioning of 7 ventilators with heliox, some of which worked well with heliox, and some of which did not (Table 5). Ventilators that work with heliox may require a conversion factor to adjust settings (Fig. 8).[9] The 80:20 heliox is typically attached to the air inlet.

The Puritan Bennett 700 series ventilator (Puritan Bennett, Pleasanton, California), which incorporates a frictionless piston, provides accurate volume and flow measurements and monitoring in vitro, but the oxygen sensor alarm must be disabled.

The eVent ventilator (eVent Medical, Vista, California) also works well with heliox, but the Puritan Bennett 7200 and 800 series, the Dräger Evita 2 and 4 (Dräger Medical, Telford, Pennsylvania), and the Engström Carestation ventilator (GE Healthcare, Madison, Wisconsin) do not work with heliox.

Berkenbosch and colleagues found considerable differences between displayed and delivered tidal volume (Fig. 9 and Table 6) and consumption rates of heliox among various modes of ventilation and ventilator brands.[16] Some bi-level devices have been reported to perform erratically with heliox.[17]

Ventilators Cleared for Delivery of Heliox

The Avea ventilator (Viasys Healthcare, Conshohocken, Pennsylvania) was the first ventilator cleared for use with air, oxygen, and heliox. Several other ventilators will probably receive approval soon.

Table 3. Volume Median Diameter of Aerosol Particles Generated by a Vibrating-Mesh Aerosol Generator at 3 Flow Rates of Oxygen and Heliox*

	Gas Type and Flow					
	O_2 at 5 L/min	O_2 at 10 L/min	O_2 at 15 L/min	Heliox at 5 L/min	Heliox at 10 L/min	Heliox at 15 L/min
		Aerosol Particle Volume Median Diameter (μm)				
Measurement 1	2.95	3.16	3.14	3.12	3.08	3.14
Measurement 2	2.94	3.19	3.1	3.14	3.09	3.09
Measurement 3	2.84	3.17	3.2	3.17	3.06	3.05
Mean ± SD	2.94 ± 0.05	3.17 ± 0.01	3.14 ± 0.04	3.14 ± 0.02	3.08 ± 0.01	3.09 ± 0.04

*The nebulizer was operated with gas flows of 5, 10 and 15 L/min, with either oxygen or heliox (mixture of 80% helium and 20% oxygen) passing through the T-piece connector. Aerosol in the gas mixture was measured by laser diffraction as it exited the T-piece and passed into the Spraytech aerosol particle sizer (Malvern Instruments, Worcestershire, United KIngdom).
(Data from Reference 14.)

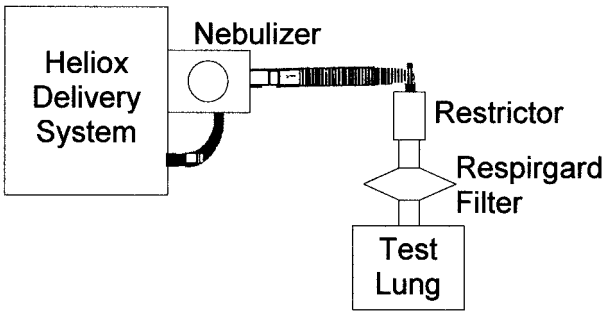

Fig. 7. Aerosol deposition is higher with heliox than with air when a fixed obstruction is added to the model. See Table 4. (Adapted from Reference 14.)

Risks of Using Heliox

The greatest risk with heliox is in the use of a jury-rigged device operated by a person who does not understand the implications of the device or the gas being administered.

For many years, respiratory therapists have prided themselves on their ability to modify, extend, or jury-rig available components and adapters to create effective devices for "off-label" applications. This was how technical innovations such as intermittent mandatory ventilation and continuous positive airway pressure were initiated. In today's risk-averse environment, the hospital risk manager would be at risk for apoplexy upon finding unproven, jury-rigged devices being applied to critically ill patients.

The safety and effectiveness of jury-rigged devices are only as good as the ingenuity and diligence of the clinician who rigs them. Some of these devices are brilliant and innovative, whereas some are not so good, and some are downright dangerous. Few clinicians are trained to design medical devices, just as few engineers are trained to provide respiratory care. The formal device-development process occurs with teams of competent engineers and designers working for months or years to be sure that the device works as intended to meet each specification, with extensive real-life testing to minimize unanticipated variations in performance. On the clinical side, we rarely spend more than a few hours developing a device modification, and we rarely spend adequate time with in vitro performance analysis prior to patient application.

If an institution decides to use heliox device configurations that are not within the intended use of the devices, 2 safeguards should be strongly encouraged. First, comprehensive and detailed policies and procedures should be written, reviewed, and taught to all relevant staff. Second, extensive bench testing should be undertaken to confirm the consistent functioning and operation of the device.

Hazards of Heliox Use

Anoxia

One of the greatest hazards with helium administration is the possibility of delivering a gas mixture that contains $< 21\%$ oxygen. This risk is reduced by never administering 100% helium to a closed system, and always using heliox that contains at least 20% oxygen in clinical applications. The use of an oxygen analyzer in line with the gas output provides some assurance that sufficient oxygen is present in the gas mixture delivered to the patient.

In 1990, a hospital that used a medical gas cylinder labeled "certified mixture of 30% oxygen and 70% helium" and intended for patient inhalation found, after beginning administration of the gas to a patient, that the cylinder delivered an $F_{IO_2} < 0.21$, because the gases in the cylinder had not been mixed before delivery to the hospital, even though the mixture had been labeled as certified. Following this discovery, the remaining cylinders in the lot were tested, and some of them contained unmixed gases.

Table 4. Aerosol Deposition With Heliox Versus Air, With and Without a Fixed Obstruction in the Model

Gas	Mean ± SD Deposition Percent at Resistance of 20 cm H_2O/L/s	V_T (mL)	Mean ± SD Deposition Percent at Resistance of 50 cm H_2O/L/s	V_T (mL)
Air	36.8 ± 1.9	410	32.2 ± 1.8	330
70:30 heliox	47.8 ± 2.5	535	44.3 ± 1.1	430

70:30 heliox = mixture of 70% helium and 30% oxygen
V_T = tidal volume
(Data from Reference 9.)

Table 5. Correction Factors for Inspiratory and Expiratory Volumes With 7 Ventilators

	Ventilator Model													
	Veolar FT		Galileo		Servo 900C		Servo 300		Evita 2		Evita 4		7200 Series	
	Volume-Correction Factor													
Set F_{IO_2}	Insp	Exp	Insp	Exp	Insp	Exp	Insp	Exp	Insp	Exp	Insp	Exp	Insp	Exp
0.21	1.68	1.70	1.68	1.70	1.38	1.34	1	1.34	1.83	Inop	NL	Inop	0.1	Inop
0.25	1.60	1.60	1.60	1.60	1.36	1.34	1	1.34	1.75	Inop	NL	Inop	0.14	Inop
0.30	1.51	1.50	1.51	1.50	1.35	1.33	1	1.33	1.73	Inop	NL	Inop	0.19	Inop
0.35	1.44	1.47	1.44	1.47	1.33	1.23	1	1.33	1.66	Inop	NL	Inop	0.25	Inop
0.40	1.37	1.40	1.37	1.40	1.31	1.22	1	1.22	1.60	Inop	NL	Inop	0.3	Inop
0.45	1.31	1.33	1.31	1.33	1.29	1.20	1	1.20	1.55	Inop	NL	Inop	0.35	Inop
0.50	1.28	1.30	1.28	1.30	1.26	1.17	1	1.17	1.48	Inop	NL	Inop	0.4	Inop
0.60	1.20	1.26	1.20	1.26	1.24	1.13	1	1.13	1.40	Inop	NL	Inop	0.5	Inop
1.0	0.97	1.01	0.97	1.01	0.97	1.09	0.99	1.09	0.98	1.09	0.99	1.09	1.05	1.05

F_{IO_2} = fraction of inspired oxygen
Insp = inspiratory volume correction factor, calculated as delivered V_T divided by set V_T
Exp = expiratory volume correction factor, calculated as V_T reported by the ventilator divided by actual measured expired V_T
Inop = inoperative
NL = nonlinear relationship
(Data from Reference 9.)

Suppliers add pure gases to a cylinder one at a time, using a gravimetric method (weighing the cylinder and contents during filling) to provide the most accurate gas mixture.

However, the gases are stratified and do not quickly mix. Highly compressed gases behave almost like liquids, and they mix slowly if diffusion is the only mixing process and no additional mixing method (such as rotating the cylinder on rollers until the components are thoroughly mixed) is used. Once the mixture is homogenized, it will not stratify again at room temperature and can be delivered to the user.

Health Devices journal recommends that users always verify the contents of a cylinder of mixed gases when it is received and again before connecting it into a system and administering gas to a patient. Always use an oxygen monitor in a breathing system.[18]

Hypoxia has been reported with heliox in preterm infants who have a history of bronchopulmonary dysplasia and subglottic stenosis.[19] It has been hypothesized that hypoxia in preterm infants secondary to heliox adminis-

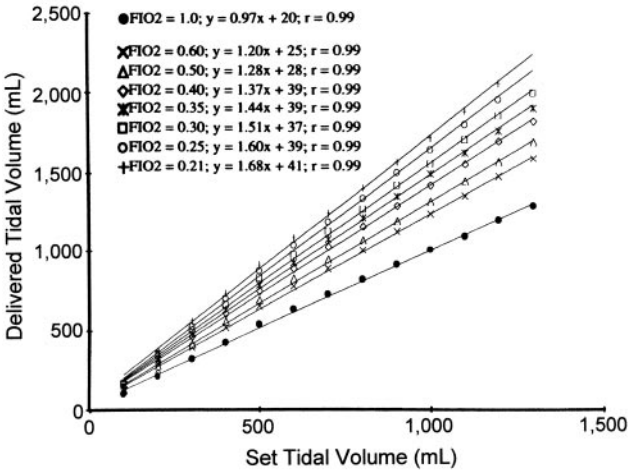

Fig. 8. Relationship between the tidal volume set on the ventilator and the tidal volume actually delivered by the ventilator, at various fractions of inspired oxygen (F_{IO_2}), with corresponding regression equations, for 3 ventilators: Veolar FT, Galileo, and Evita 2. (Adapted from Reference 9.)

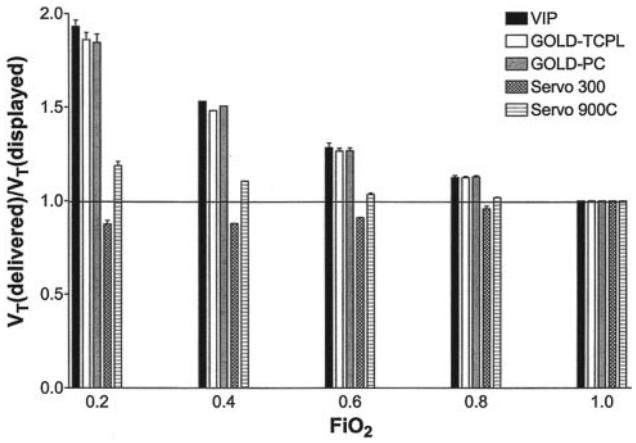

Fig. 9. Difference between displayed and delivered tidal volume (V_T) during pressure-controlled ventilation with 4 ventilators: Bird VIP, Bird VIP Gold, Servo 900C, and Servo 300. The data are presented as mean ± SD of the ratio of delivered V_T to displayed V_T at each fraction of inspired oxygen (F_{IO_2}). $V_T$delivered = tidal volume delivered to the test lung. $V_T$displayed = inspiratory V_T displayed by the ventilator. TCPL = time-cycled, pressure-limited mode. PC = pressure-control mode. (From Reference 16, with permission.)

Table 6. Relative Rates of Helium Consumption During Pressure-Controlled and Volume-Controlled Ventilation*

Ventilator	VC	PC
Bird VIP	8	17
Bird VIP Gold	9	9
Servo 900C	4	7
Servo 300	1	1

*The values are the relative rates of helium consumption compared with the usage rate of the Servo 300.
VC = volume-controlled ventilation
PC = pressure-controlled ventilation
(Data from Reference 16.)

tration is related to the reduction of lung volume and the increase of intrapulmonary shunt.[20]

Delivery of Too Much Volume

If the mechanical ventilator delivers more than the set volume, there is a risk of volume-induced injury, pressure-induced injury, or hypocarbia. This is of particular concern with ventilators not designed for heliox administration.

Delivery of Too Much or Too Little Bronchodilator

Running a jet nebulizer with too low a flow of heliox can result in inadequate aerosol delivery to the patient at a time when aerosol delivery is critical. On the other extreme, heliox can increase the lung delivery to well above the intended dose, though relatively few adverse effects have been reported in the literature.

Hypothermia

Hypothermia has been associated with hood administration of heliox to infants. Heliox must be used with caution because of its high thermal conductivity and the consequent risk of hypothermia when the gas temperature is $< 36°C$, especially when heliox is administered for long periods. The risk of hypothermia can be avoided with adequate warming and humidification of the heliox, using standard devices.[21]

Liability With Heliox Devices

When devices are used outside their intended "labeled" design limits, liability shifts from the device manufacturer to the institution and clinician. As devices designed for and cleared by the FDA for use with heliox become available, integrating those devices into your practice reduces risk for the patient, clinician, and institution. Continued use of jury-rigged systems places patients and institutions at risk.[22] It is always better policy to use a device that has FDA approval for a specific application, irrespective of price. Continued use of a jury-rigged setup would be very difficult to justify to a jury if there were a catastrophic device failure and resulting lawsuit, and such use would almost certainly be considered negligence.[22]

Summary

Evidence continues to evolve that heliox can effectively reduce airway resistance and work of breathing in patients with severe airway obstruction and can improve delivery of aerosol by reducing turbulence and aerosol-particle-impaction en route to the lungs. As the practice of heliox administration continues to evolve, it is very important for clinicians to understand how heliox works, what it can and cannot do, and how it will affect devices and patients. No heliox-administration device should be used clinically without ample training and bench testing. As FDA-cleared devices are introduced in the market, jury-rigged devices must be eliminated to reduce risk for patients, clinicians, and institutions.

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Heliox Redux

Helium is an inert, colorless gas. It was discovered by spectroscopic methods during an eclipse of the sun in India in 1868 and, thus, was named from the Greek word *helios*, which means *sun*. It was not isolated until 1895 by Sir William Ramsey, and by Nils Langlet and P.T. Cleve. Its first major uses in the first third of the 20th century were for filling airships and balloons during World War I and for divers in a mixture with oxygen. Alvan Barach[1] first used it for medical purposes in 1934 and confirmed the biological inertness of helium by exposing mice to 79% helium and 21% oxygen for 2 months without deleterious effects.[2] He reported the successful usage of helium-oxygen mixtures in four cases of asthma in adults and two cases of upper airway obstruction in infants.[3] Of interest, the patients were relieved of their dyspnea in 6 to 10 breaths, and when the helium was removed the dyspnea came back in 3 or 4 breaths. After the explosion of the dirigible Hindenburg in 1937, Congress regulated the sale of helium, and its availability was further reduced during World War II. After the war, with the advent of pharmacologic bronchodilators with improving side-effect profiles, helium was cast aside as a treatment for asthma. It was relegated back to filling balloons at parties, where its effect on the voice, making one sound like "Donald Duck," was its main notoriety. There were a few reports of its respiratory usage showing the lack of significant improvement in asthmatic patients[4] and in patients with emphysema.[5] Helium-oxygen was shown to be an effective treatment of upper airway obstruction in 1976,[6] and there were scattered reports for this usage until 1986.[7–9]

In 1987, the use of helium-oxygen in the treatment of patients with asthma resurfaced in Hartford, CT, and in France, and it became known as *heliox*. Within a few years, its use spread to Camden, NJ, Chicago, IL, Houston, TX and then to many other sites. Despite anecdotal reports of its efficacy,[10–14] heliox therapy for asthma patients continued to be viewed as experimental because of the lack of randomized controlled trials.[15,16]

The theoretical basis behind the use of helium in asthma patients mainly relates to its low density. It has the lowest density of any gas except hydrogen. Asthma is a disorder of airways obstruction, and the pathophysiology includes an increased turbulent flow in the airways. Since airway resistance in turbulent flow is directly related to the density of a gas, helium with its lower density results in a lower airway resistance. It also reduces the Reynolds number, converting turbulent flow to laminar flow and further decreasing airway resistance. These effects result in a decreased work of breathing. Helium also increases the diffusion of carbon dioxide and may improve alveolar ventilation, resulting in improved gas exchange. Helium is an inert element and does not interact with any biochemical process. It is noncombustible, nonexplosive, and nondetectable by taste and smell. Its effect on the airways occurs and goes away within a few breaths. In summary, it is an extremely safe and rapid-acting therapeutic agent that reduces airway resistance, decreases the work of breathing, and may improve gas exchange.

So what is its downside? The cost for heliox is in the range of $30 to $70 for 8 h of usage, making it a rather low-cost medical modality.[17] However, its usage takes a little knowledge and work. Heliox needs to be dispensed via a nonrebreathing mask, so it is not diluted with room air. The heliox tanks have to be obtained and, despite their large size, have to be easily accessible to the emergency department and/or ICU. Educational sessions have to be set up with respiratory therapists and with the staffs of the emergency department and ICU. There are few guidelines in the medical literature on optimal patient selection and usage.

In cases in which it has been beneficial, the rapidity and power of the therapeutic effect can be truly amazing. Two cases that I was involved with come to mind. In 1987, a young asthmatic patient went into respiratory failure and, despite all known treatments including halothane general anesthesia, was unable to be adequately ventilated. With heliox, the peak airway pressure and the $Paco_2$ markedly dropped in only a few minutes. Another young asthmatic patient, who had a pH of 6.95, refused endotracheal intubation. As with the prior patient, only a few minutes after initiating heliox, the patient had dramatic relief of dyspnea and the $Paco_2$ markedly diminished toward the normal range. However, not all asthmatic patients have such profound response to heliox. This anecdotal use of heliox in asthma patients led to three clinical studies[11–13] at Hartford and Mount Sinai hospitals (Hartford, CT), which were published between 1989 and 1995. These studies, in patients with acute ventilatory failure who were and were not receiving mechanical ventilation, demonstrated a dramatic decrease in $Paco_2$ in a great majority of patients, but not all. Heliox was still not accepted as a therapeutic choice for the treatment of acute severe asthma and was relegated to a grab bag of unconventional treatments due to the lack of a randomized controlled study demonstrating its efficacy.[15,16] However, this interest in heliox spawned other clinical trials across the country in patients with stridor,[18,19] bronchiolitis,[20] croup,[21] and COPD,[22,23] as well as investigations of its effect on nebulizer and ventilator function.[24–28]

In the article in this issue of *CHEST* (see page 882), Ho et al reviewed eight randomized controlled trials[29–36] of heliox in acute severe asthma published between 1996 and 2002. Five of these studies used peak expiratory flow rate (PEFR) as the main variable.[29–33] Two trials studied only children,[29,30] two trials studied only adults,[31,32] and one trial included both children and adults.[33] One trial[30] with children was excluded because it did not include percent predicted PEFR values. The data from the remaining four studies were pooled and evaluated with a meta-analysis. The authors found a small benefit in PEFR and dyspnea index with heliox and commented that the difference may have been even greater if the fifth study had been included. They also suggested that patients with more severe asthma might benefit more from heliox.

Markedly successful anecdotal reports of heliox treatment in asthma patients have been both a blessing and a curse for heliox. They have led to a wider but indiscriminate usage of heliox. In both of the hospitals where I have conducted clinical trials with heliox in asthma patients, its use in treating a small number of patients who had rapid and marked improvement with heliox has led to its regular use in patients with severe asthma. In reviewing the medical literature on heliox in asthma, Ho et al found that of the 13 randomized and nonrandomized clinical trials, 10 showed a benefit with heliox and 3 did not. However, even after the publication of randomized controlled trials of heliox in asthmatic patients, there was no widespread acceptance of heliox therapy. Despite the fact that heliox does not lead to improvement in every patient, it still has clinical value when used with the appropriate patients.

So who should receive heliox? Presently, it should be reserved for the "brittle" asthmatic patient who does not quickly respond to inhaled β-agonist therapy and who has any of the following characteristics:

1. Severe airflow obstruction (*ie*, PEFR, $< 30\%$ predicted) and a rapid onset of exacerbation of symptoms preferably over < 24 h but no > 72 h;

2. A history of labile asthma and/or previous tracheal intubation for asthma; and
3. The inability to be adequately ventilated on mechanical ventilation.

How should heliox be used?

1. It should be started as soon as possible.
2. If there is no subjective or objective improvement within a few minutes, alternative therapies should sought out. The main danger of heliox is continuing it too long when there is no benefit.
3. It should be used for at least 1 h but usually is not needed beyond 8 h. Every hour or two, the heliox can be removed and the patient can be assessed for deterioration over a few minutes.
4. The more severe the patient's condition is, the higher the percentage of helium should be, with a maximum of 80% and a minimum of 60%.

As stated by Ho et al, further studies are needed, specifically to ascertain whether heliox reduces the incidence of endotracheal intubation. Since it is but a therapeutic bridge until the effect of corticosteroids occurs, it is unlikely that it will reduce hospital admissions, hospital or ICU length of stay, or hospital mortality. It will provide rapid and marked relief of dyspnea to many patients without any detrimental effects. Since its therapeutic index is so high and its onset and offset of action are so rapid, it may find a useful niche in the prehospital setting when used by emergency medical technicians and possibly by an occasional labile asthmatic patient at home.

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