

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

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## Introduction

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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. © 2006 Daedalus Enterprises]**

## Introduction

In the United States, more than 16 million patients are diagnosed with chronic obstructive pulmonary disease

(COPD).<sup>1,2</sup> 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.<sup>3</sup>

Evidence-based respiratory therapy procedures for COPD exacerbation include oxygen, inhaled bronchodilators, and noninvasive positive-pressure ventilation (NPPV).<sup>2-5</sup> 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,<sup>6-9</sup> 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.<sup>10</sup> 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.<sup>11,12</sup> 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  $\Delta\dot{V}_{\max 50}$ . The volume at which the flows with heliox and air become the same is called the volume of isoflow ( $V_{\text{iso}\dot{V}}$ ). In normal persons,  $\Delta\dot{V}_{\max 50}$  is about 50% and  $V_{\text{iso}\dot{V}}$  is about 15%. In patients with COPD, maximum expiratory flow is often density-independent,

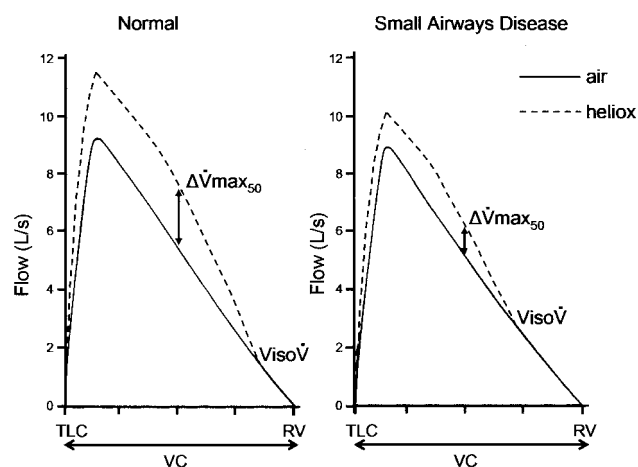


Fig. 1. Expiratory flow-volume loop while breathing air versus breathing heliox. In the normal case (left), note the greater increase in expiratory flow while breathing heliox at 50% of the vital capacity ( $\Delta\dot{V}_{\max 50}$ ) than in the case of small-airways disease. Also note that the volume of isoflow ( $V_{\text{iso}\dot{V}}$ ) 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.

due to disease predominantly of the small airways (see Fig. 1).

#### 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.<sup>13</sup> 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<sup>14</sup> randomized patients with severe COPD (mean forced expiratory volume in the first second [FEV<sub>1</sub>] 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

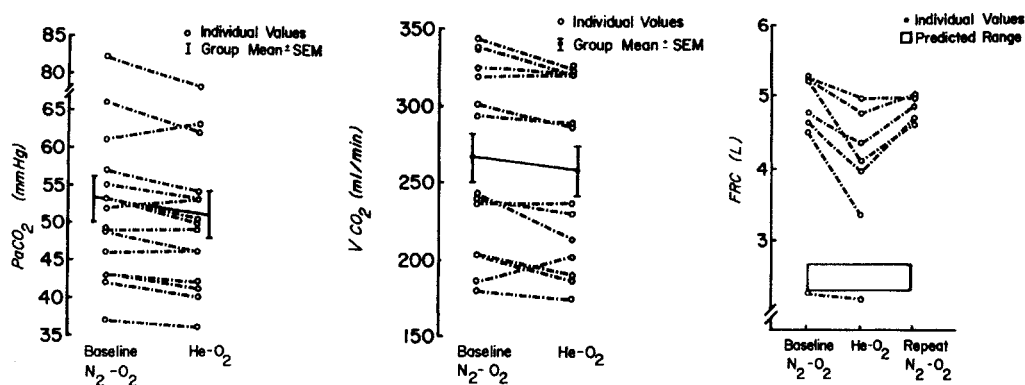


Fig. 2.  $P_{aCO_2}$ , carbon dioxide production ( $\dot{V}_{CO_2}$ ), and functional residual capacity (FRC) in patients with stable chronic obstructive pulmonary disease (COPD) breathing air-oxygen (N<sub>2</sub>-O<sub>2</sub>) and helium-oxygen mixture (He-O<sub>2</sub>). SEM = standard error of the 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<sup>15</sup> tested the hypothesis that heliox, by reducing dynamic hyperinflation and dyspnea, improves exercise endurance in patients with COPD ( $n = 12$ , FEV<sub>1</sub> = 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<sup>16</sup> 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<sup>17</sup> 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<sup>18</sup> 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<sup>19</sup> 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<sup>20</sup> 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-

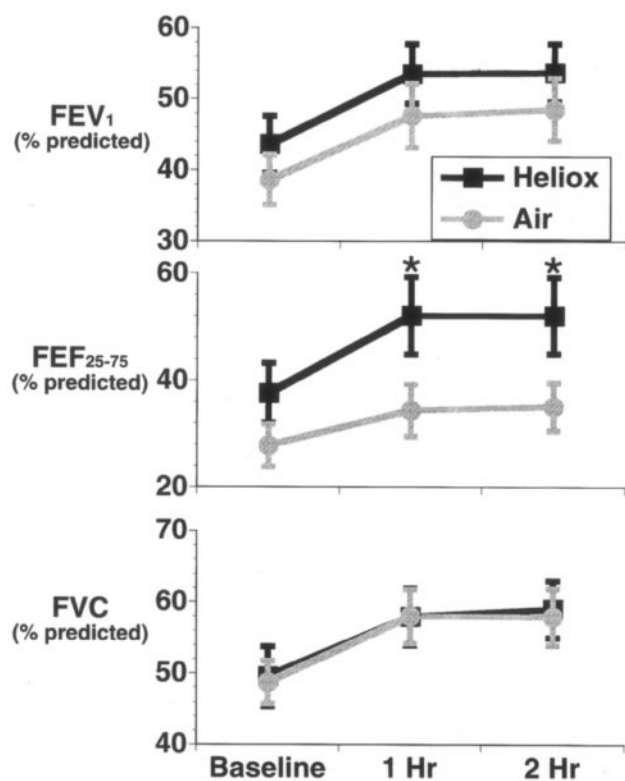


Fig. 3. Mean  $\pm$  SEM pulmonary function values in patients with exacerbation of chronic obstructive pulmonary disease, receiving inhaled bronchodilator therapy, with the nebulizer powered by either air or helium-oxygen mixture (heliox). There were no significant differences between the treatment groups in forced expiratory volume in the first second (FEV<sub>1</sub>) 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<sub>25-75</sub>) 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<sup>21</sup> 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 in-

tensive-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.<sup>22</sup> 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<sub>1</sub> 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<sub>25-75</sub>) 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<sup>23</sup> 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<sup>24</sup> 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<sup>25</sup> 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-

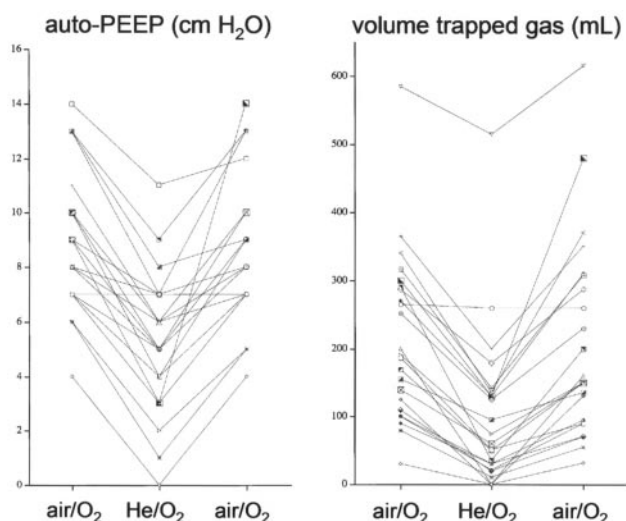


Fig. 4. Left: Individual levels of intrinsic positive end-expiratory pressure (auto-PEEP) before, during, and after administration of helium-oxygen mixture (He/O<sub>2</sub>). Right: Volume of trapped gas before, during, and after administration of helium-oxygen mixture. (Adapted from Reference 25, with 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<sup>26</sup> 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 ( $4 \pm 5$  breaths/min vs  $9 \pm 5$  breaths/min), auto-PEEP ( $3.1 \pm 2$  cm H<sub>2</sub>O vs  $4.8 \pm 2$  cm H<sub>2</sub>O), the magnitude of negative esophageal pressure swings ( $6.7 \pm 2$  cm H<sub>2</sub>O vs  $9.1 \pm 4.9$  cm H<sub>2</sub>O), pressure-time product ( $42 \pm 37$  vs cm H<sub>2</sub>O · s/min  $67 \pm 65$  cm H<sub>2</sub>O · s/min), and work of breathing ( $11 \pm 3$  J/min vs  $18 \pm 10$  J/min).

Gannier et al<sup>27</sup> 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  $2.34 \pm 1.04$  J/L to  $1.85 \pm 1.01$  J/L,  $p < 0.001$ ). This was accompanied by significant reductions in auto-PEEP and inspiratory resistance. Respiratory-system compliance was unchanged with heliox.

Joliet et al<sup>28</sup> 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)

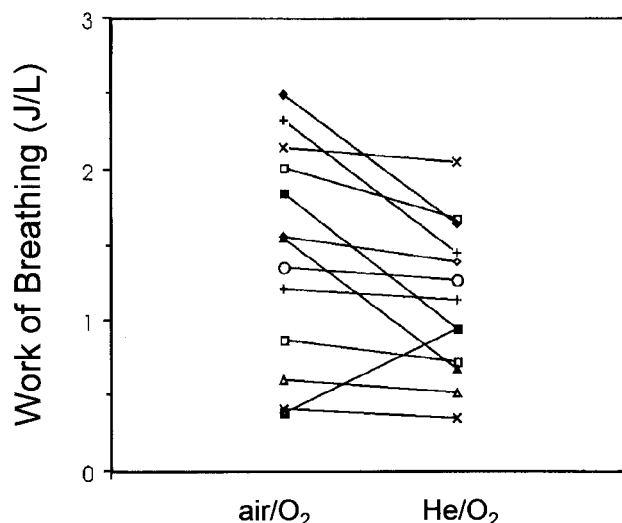


Fig. 5. Individual values of work of breathing, measured just before extubation, in 13 patients with chronic obstructive pulmonary disease (COPD) breathing either air-oxygen mixture (air/O<sub>2</sub>) or helium-oxygen mixture (He/O<sub>2</sub>). (From Reference 29, with permission.)

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 ( $4.2 \pm 4$  cm H<sub>2</sub>O vs  $7.7 \pm 4$  cm H<sub>2</sub>O, and  $98 \pm 82$  mL vs  $217 \pm 124$  mL, respectively) and by applied PEEP ( $4.4 \pm 1.3$  cm H<sub>2</sub>O vs  $7.8 \pm 3.6$  cm H<sub>2</sub>O, and  $120 \pm 107$  mL vs  $216 \pm 115$  mL, respectively). Heliox reduced inspiratory and expiratory resistance ( $15.5 \pm 4.4$  cm H<sub>2</sub>O/L/s vs  $20.7 \pm 6.9$  cm H<sub>2</sub>O/L/s, and  $19 \pm 9$  cm H<sub>2</sub>O/L/s vs  $28.8 \pm 15$  cm H<sub>2</sub>O/L/s, respectively) and plateau pressure ( $13 \pm 4$  cm H<sub>2</sub>O vs  $17 \pm 6$  cm H<sub>2</sub>O). PEEP increased airway pressures and decreased compliance. The ratio of P<sub>aO<sub>2</sub></sub> to fraction of inspired oxygen was slightly reduced by heliox ( $225 \pm 83$  mm Hg vs  $245 \pm 82$  mm Hg), without a significant ventilation/perfusion ratio change.

The effect of heliox on work of breathing was evaluated by Diehl et al,<sup>29</sup> 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  $1.4 \pm 0.7$  J/L to  $1.1 \pm 0.5$  J/L ( $p < 0.05$ ). This was due mainly to a reduction in the resistive component of the work of breathing, from  $0.7 \pm 0.4$  J/L to  $0.5 \pm 0.3$  J/L ( $p < 0.01$ ). There was also a slight reduction in auto-PEEP, from  $2.9 \pm 2.1$  cm H<sub>2</sub>O to  $2.1 \pm 1.8$  cm H<sub>2</sub>O ( $p < 0.05$ ). The effect, however, was not consistent

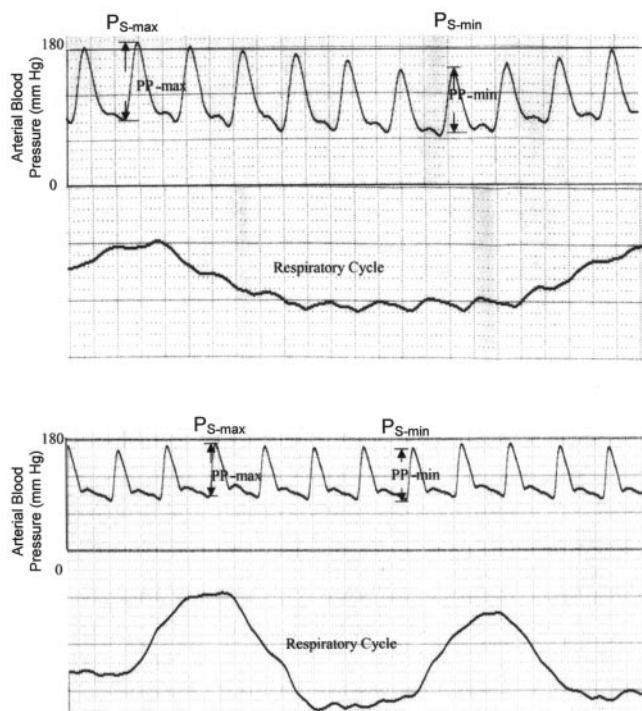


Fig. 6. Tracings of pulse pressure within a respiratory cycle during mechanical ventilation with air-oxygen mixture (air/O<sub>2</sub>) (top panel) and helium-oxygen mixture (heliox) (bottom panel). Maximum systolic pressure (P<sub>S-max</sub>) and maximum pulse pressure (P<sub>P-max</sub>) occur during inspiration. Minimum systolic pressure (P<sub>S-min</sub>) and minimum pulse pressure (P<sub>P-min</sub>) occur during exhalation.  $\Delta P_p$  (%) =  $100 \times [(P_{P-max} - P_{P-min}) / 0.5 \times (P_{P-max} + P_{P-min})]$ . (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<sup>30</sup> 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<sub>2</sub>O to  $5 \pm 2$  cm H<sub>2</sub>O ( $p < 0.05$ ), 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.

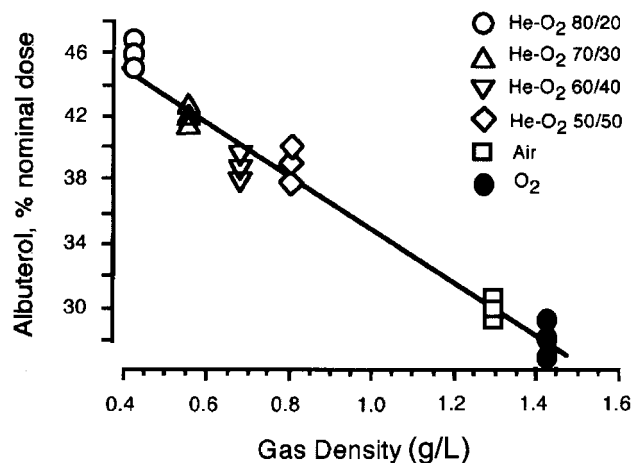


Fig. 7. Albuterol delivery (percent of the nominal dose) from a metered-dose inhaler to filters placed at the ends of simulated bronchi, as a function of gas density. Eight puffs (720 mg) of albuterol were administered into a chamber spacer during controlled ventilation in an unheated, dry ventilator 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<sup>31</sup> 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<sup>32</sup> 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,

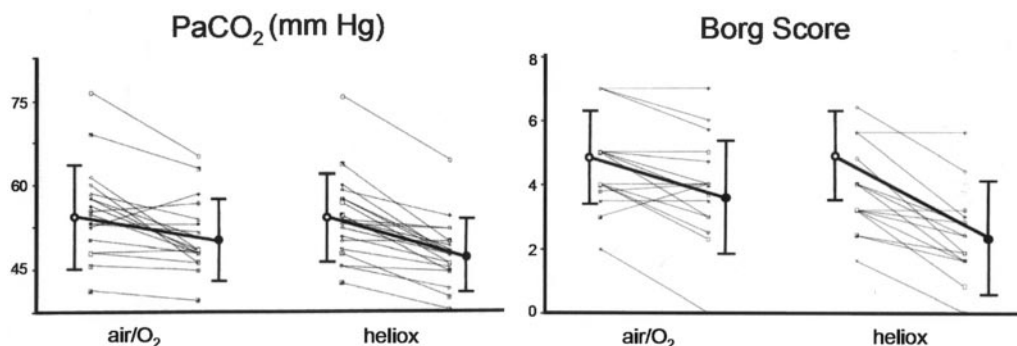


Fig. 8. Individual differences with noninvasive positive-pressure ventilation and air-oxygen mixture (air/O<sub>2</sub>) or helium-oxygen mixture (heliox). The mean  $\pm$  standard deviation values are represented by the larger circles and thicker lines. Left: P<sub>aCO<sub>2</sub></sub> differences. 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.<sup>33</sup> 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<sub>aCO<sub>2</sub></sub> decreased more with heliox (Fig. 8). When P<sub>aCO<sub>2</sub></sub> was  $> 56$  mm Hg, P<sub>aCO<sub>2</sub></sub> decreased by  $\geq 7.5$  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<sup>34</sup> 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:  $9 \pm 2$  cm H<sub>2</sub>O and  $18 \pm 3$  cm H<sub>2</sub>O. Significant reductions in pressure-time index were observed with heliox (versus air-oxygen), at both the low pressure-support level ( $160 \pm 58$  cm H<sub>2</sub>O  $\cdot$  s/min vs  $198 \pm 78$  cm H<sub>2</sub>O  $\cdot$  s/min,  $p < 0.05$ ) and the high pressure-support level ( $100 \pm 45$  cm H<sub>2</sub>O  $\cdot$  s/min vs  $150 \pm 82$  cm H<sub>2</sub>O  $\cdot$  s/min,  $p < 0.01$ ). Work of breathing was also significantly lower with heliox ( $7.8 \pm 4.1$  J/min vs  $10.9 \pm 6.1$  J/min at the low pressure-support level,  $p < 0.05$ , and  $5.7 \pm 3.3$  J/min vs  $9.2 \pm 5$  J/min at the high pressure-support level,  $p < 0.01$ ) (Figs. 9 and 10). Heliox reduced P<sub>aCO<sub>2</sub></sub> at both the low pressure-support level and the high pressure-support level, without significantly changing breathing pattern or oxygenation.

Jolliet et al<sup>35</sup> conducted a prospective randomized multicenter study to determine whether NPPV with heliox

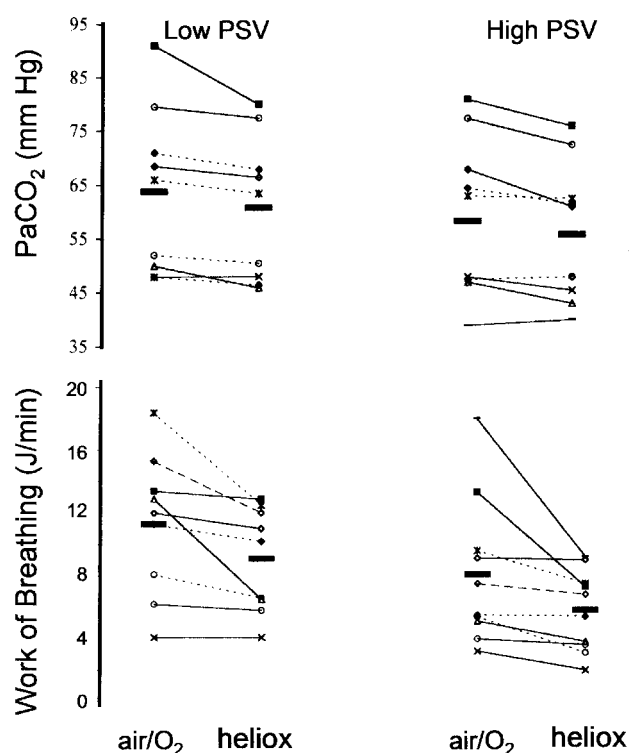


Fig. 9. Individual differences in P<sub>aCO<sub>2</sub></sub> and work of breathing between air-oxygen mixture (air/O<sub>2</sub>) and helium-oxygen mixture (heliox) with low and high levels of pressure support during pressure-support ventilation (PSV). The horizontal bars indicate the mean values ( $p < 0.05$ ). (From Reference 34, with permission.)

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  $6.2 \pm 5.6$  d vs heliox  $5.1 \pm 4$  d) were not significantly different. The post-ICU hospital stay was shorter with heliox (air-oxygen  $19 \pm 12$  d vs heliox  $13 \pm$

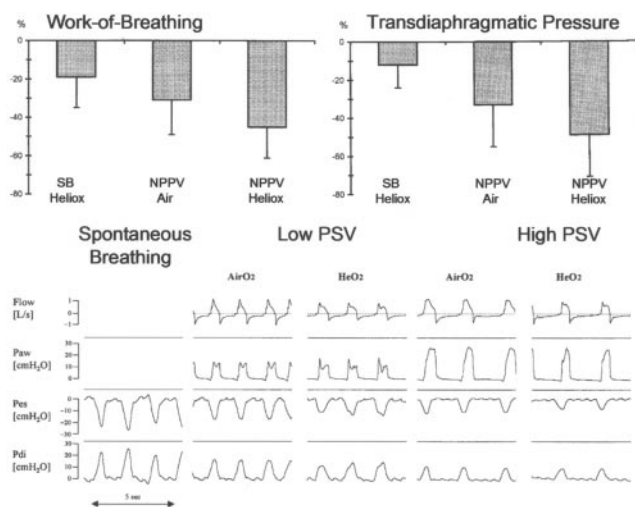


Fig. 10. Top left: Relative changes in work of breathing. Top right: Relative changes in tidal transdiaphragmatic pressure swings. Bottom: These patient tracings show that the esophageal pressure ( $P_{es}$ ) and diaphragmatic pressure ( $P_{di}$ ) swings were smaller with helium-oxygen mixture ( $He/O_2$ ) 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.)

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.<sup>36–38</sup>

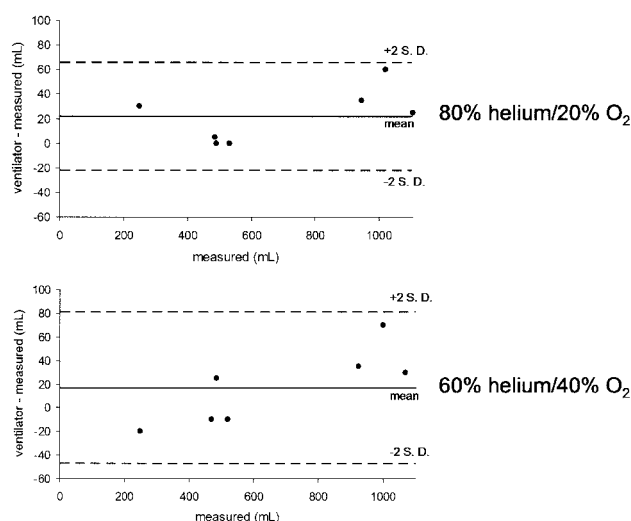


Fig. 11. Bland-Altman plots of bias and limits of agreement between exhaled tidal volume measured on the ventilator and that delivered to the test lung for mixtures of 80% helium/20% oxygen and 60% helium/40% oxygen. (From Reference 39, with permission.)

The only ventilator that can be used for invasive and noninvasive ventilation that is approved by the United States 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.<sup>39</sup> 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 ( $6 \pm 31$  mL vs  $22 \pm 22$  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 ( $14 \pm 22$  mL vs  $17 \pm 32$  mL,  $p = 0.63$ ) (Fig. 11). The bias for  $V_T$  delivered to the test lung with 80% helium versus air was  $37 \pm 43$  mL. The bias for  $V_T$  delivered to the test lung for 60% helium/40% oxygen versus 60% nitrogen/40% oxygen was  $20 \pm 27$  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<sup>40</sup> 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



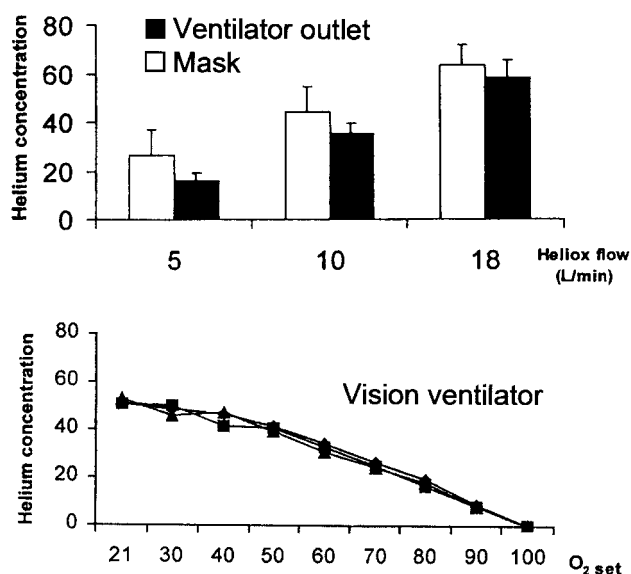


Fig. 12. Helium concentration when helium-oxygen mixture (heliox) was infused into 4 ventilator brands (Knightstar, Quantum, BiPAP S/T-D30, and Sullivan) at the mask and at the ventilator outlet with heliox flows of 5, 10, and 18 L/min. The leak port is in the circuit, near the mask position. (From Reference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

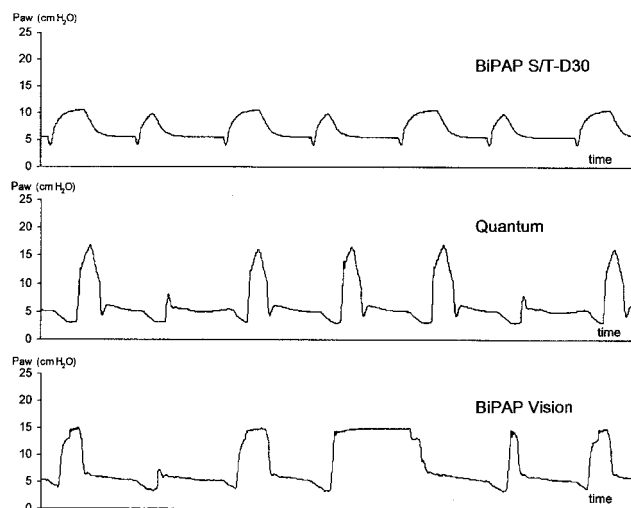


Fig. 13. Airway pressure waveforms showing erratic performance (top panel) with the BiPAP S/T-D30 ventilator when helium-oxygen mixture (heliox) flow of 10 L/min was titrated into the system at the mask position with a noninvasive positive-pressure ventilation (NPPV) setting of 10/5 cm H<sub>2</sub>O; (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<sub>2</sub>O 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<sub>2</sub>O. (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 Aptaer 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<sub>2</sub>O. 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<sub>2</sub>O), trigger sensitivity (–0.1 to –1.5 cm H<sub>2</sub>O), rise time, and cycle sensitivity (5–75% of peak inspiratory flow). It incorporates an Aeroneb Pro vibrating-mesh nebulizer (Nektar Therapeutics, Mountain View, California),<sup>41</sup> which, by its design, should not be affected by gas density, as occurs with jet nebulizers.<sup>42</sup> Aside from a few abstracts,<sup>43–47</sup> 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<sub>IO<sub>2</sub></sub> 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,<sup>35</sup> 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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