Helium–oxygen: A versatile therapy to “lighten the load” of chronic obstructive pulmonary disease (COPD)

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Abstract
Breathing helium–oxygen mixtures has a number of favorable physiological effects that could be beneficial in the treatment of both stable and unstable patients with chronic obstructive pulmonary disease (COPD). Helium–oxygen breathing reduces airway resistance, duty cycle, end-expiratory lung volume and intrinsic positive end-expiratory pressure, all leading to a reduction in the work of breathing in patients with airflow limitation. Important hemodynamic effects directly related to the reduction in the work of breathing also occur through enhanced lung–heart interaction. In the unstable patient, these physiological effects may decrease the need for intubation, reduce extubation failure and improve patient outcome. In the stable patient, similar effects lead to reduced dyspnea and improved exercise capacity, potentially enhancing the outcomes of exercise rehabilitation. To date, studies frequently include small sample sizes and less than rigorous methodology, so conclusive evidence regarding the effectiveness of breathing helium–oxygen mixtures for improving health outcomes in patients with COPD remains limited.

Introduction
Helium is a non-toxic, odorless, colorless gas that is non-reactive with biological membranes and virtually insoluble in tissue. First discovered in 1868 by the French astronomer Pierre Janssen (who detected an unknown yellow line in the sun’s spectrum during a total solar eclipse) it was first isolated on Earth in 1895 by both Sir William Ramsey and the Swedish chemists Per Teodor Cleve and Nils Langlet. The density of helium is approximately one-seventh that of nitrogen and when combined with 21% oxygen results in a gas that is approximately three times less dense than air.1 Although helium has a viscosity only 8% higher than air, the reduced density results in a kinematic viscosity approximately eight times greater than air.2 The physical properties of helium, especially the reduced density, help maintain laminar flow through the complex dichotomous branching airways of the lung. Even in the presence of turbulent or transitional flow, the benefits of helium–oxygen gases are preserved2 and as a result the pressure gradient needed to produce flow is reduced and airway resistance is decreased.3

Chronic obstructive pulmonary disease (COPD) is a complex, heterogeneous, chronic inflammatory disorder leading to increased airway resistance and loss of parenchymal elastance (alveoli destruction).4 These changes lead to ventilatory limitation worsened by inflammatory exacerbations or exercise. In fact, inflammatory exacerbations result in similar physiological changes to that observed during exercise.5 Any therapy that alters the ventilatory limitation such as helium–oxygen breathing, bronchodilators, oxygen or...
non-invasive positive-pressure ventilation will change the physiological impairment, leading to improved outcomes and a reduction in symptoms.

During an acute inflammatory exacerbation of COPD, ventilatory demand increases respiratory rate, which shortens expiratory time and results in an insufficient emptying of the lungs. As a result end-expiratory lung volume rises, causing dynamic hyperinflation (often confused with increased trapped air volume). This increases inspiratory muscle work through both a decrease in lung compliance and an increase in the intrinsic positive inspiratory pressure (PEEPi). In combination with increased airway resistance, both the elastic and resistive work of breathing are increased while the respiratory muscles ability to produce work is compromised. As the lungs dynamically hyperinflate in an ineffective attempt to increase ventilation, a vicious cycle develops and eventually the elevated work of breathing can cause the respiratory muscles to fatigue, which is one of the primary reasons for acute respiratory failure and the need for endotracheal intubation. Similar changes in lung mechanics to that observed during an exacerbation of COPD occur when ventilatory demand is increased due to exercise. In this scenario, the resulting increase in the work of breathing caused by dynamic hyperinflation in combination with a reduced ventilatory output causes severe dyspnea, which is the most common exertional symptom reported to limit exercise capacity in these patients.

Helium–oxygen was first used in clinical practice by Barach in 1934. In these initial studies he documented the benefits of helium for the therapeutic treatment of a number of obstructive disorders including asthma, upper airway obstruction and emphysema. Dean and Visscher confirmed these early findings and demonstrated that airway resistance was decreased in the presence of turbulent flow compared to air in an in-vivo animal lung preparation. Other early studies reported that helium–oxygen needed less pressure to generate a given flow velocity and decreased pulmonary resistance in emphysema patients. Recently, a number of studies have also demonstrated that the physical properties of helium–oxygen gas mixtures reduce airway resistance, dynamic hyperinflation and PEEPi, leading to a decreased work of breathing. This may be advantageous for treating patients with acute inflammatory exacerbations of COPD or for improving exercise tolerance in this population. Additionally, increasing the fraction of inspired oxygen (FIO2) in combination with helium maintains the benefits of both gases and has been shown to have additional benefits in the stable COPD patient during exercise.

**Helium–oxygen in combination with mechanical ventilation**

**Non-invasive ventilation**

In the last 20 years, the use of non-invasive ventilation (NIV) during acute exacerbation of COPD has been demonstrated to be an effective technique for decreasing the work of breathing and the need for intubation. NIV has also been shown to reduce the total duration of mechanical ventilation required, the time spent in hospital and mortality. Therefore, an intervention such as helium–oxygen that can reduce airway resistance and the work of breathing has the potential to further minimize the need for intubation and the complications associated with this procedure.

The few studies that have investigated whether helium–oxygen in combination with NIV can improve the effectiveness of mechanical ventilation are summarized in Table 1. Jolliet et al. were first to utilize helium–oxygen with NIV and supplied the first evidence for the use of this gas in the treatment of patients with COPD exacerbations. Helium–oxygen resulted in a significant increase in peak inspiratory flow, which shortened inspiratory time and duty cycle (Ti/Ttot). They also reported a decreased Paco2 with helium–oxygen, which was markedly decreased in the more hypercapnic patients. Dyspnea was also significantly reduced with helium–oxygen compared to baseline (2.8 ± 1.6 vs. 4.6 ± 1.5 Borg units) and air–oxygen (2.8 ± 1.6 vs. 3.7 ± 1.6 Borg units). The findings of increased peak inspiratory pressure and shortened Ti have a number of implications for improving the effectiveness of the pressure support ventilator for reducing dynamic hyperinflation through an increased expiratory time. This change in the pattern of breathing likely explains the beneficial reductions in Paco2 and dyspnea observed.

These initial findings were corroborated by Jaber et al., who measured the work of breathing in 10 patients with COPD receiving NIV in combination with helium–oxygen. Low-level pressure support was used to simulate unassisted spontaneous breathing and high-level pressure support was used as effective NIV treatment. Their findings demonstrated that helium–oxygen enhanced the efficacy of NIV by producing a larger increase in pH as well as greater decreases in Paco2 and inspiratory effort than NIV alone. Helium–oxygen also reduced total work of breathing and transdiaphragmatic pressure at both levels of pressure support ventilation.

Two studies have investigated the beneficial effect of helium–oxygen in combination with NIV on patient outcome as well as health care utilization. Esquinas et al. demonstrated that helium–oxygen in combination with NIV improved acidoses (p = 0.08), reduced the average length of stay in the ICU from 6.4 ± 9.9 to 3.56 ± 1.0 days (p = 0.08) and significantly improved the simplified acute physiology score II (p = 0.02) (a scale used to predict mortality). In contrast, Jolliet et al. reported no significant difference in terms of intubation rate (13.5% vs. 20.3% with helium–oxygen and air–oxygen, respectively) or length of stay in the ICU (5.1 ± 4 vs. 6.2 ± 5.6 days, respectively). However, the length of stay in the hospital post-ICU and the total hospitalization costs were lower in patients who were not intubated and received helium–oxygen.

The findings from these initial trials appear promising but their translation into standard practice is limited as the majority were inadequately blinded or were underpowered to accurately assess the additional benefit of helium–oxygen to patients receiving NIV. A recent systematic review of acute exacerbation of asthma and COPD by Colebourn et al. failed to demonstrate any benefit of using helium–oxygen in conjunction with NIV. They reported the mean reductions in...
\(P_{\text{a}CO_2} (0.29 \text{ kPa})\) and respiratory rate (1.6 breaths) across the available studies\(^\text{23,33,34,37}\) to be clinically and statistically insignificant. However, these small changes may well be physiologically important; it is not known how much the pattern of breathing needs to change to alter dynamic hyperinflation. There is a need for larger, fully powered, non-invasive ventilation

<table>
<thead>
<tr>
<th>Source</th>
<th>Participants</th>
<th>Study design</th>
<th>Interventions</th>
<th>Primary findings</th>
<th>Secondary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jolliet et al.(^\text{33})</td>
<td>19 COPD FEV(_1) = 0.83 L</td>
<td>Randomized crossover</td>
<td>NIV administered for 45 min with Air–O(_2) or He–O(_2) separated by 45 min of no NIV</td>
<td>↑ Inspiratory flow rate, ↓ (T_i/T_{TOT}) dyspnea and (P_{\text{a}CO_2}) with He–O(_2)</td>
<td>↔ Systemic blood pressure</td>
</tr>
<tr>
<td>Jaber et al.(^\text{23})</td>
<td>10 COPD FEV(_1) = 0.8 L</td>
<td>Randomized crossover</td>
<td>Air–O(_2) low PS (5–10 cm H(_2)O) He–O(_2) low PS (5–10 cm H(_2)O) Air–O(_2) high PS (15–25 cm H(_2)O) He–O(_2) high PS (15–25 cm H(_2)O)</td>
<td>↓ Respiratory muscle PTI, WOB and (P_{\text{a}CO_2}) with He–O(_2) with both high and low PSV</td>
<td>↔ Breathing pattern ↔ Oxygenation</td>
</tr>
<tr>
<td>Esquinas et al.(^\text{34})</td>
<td>50 COPD FEV(_1) = NR</td>
<td>Randomized controlled</td>
<td>NIV administered with:</td>
<td>↓ ICU stay ((P = 0.08)) ↓ (\text{pH} (p = 0.08)) ↑ SAPS II</td>
<td>↓ Length of hospital stay and post-ICU total hospitalization costs for non-intubated patients in He/O(_2) group</td>
</tr>
<tr>
<td>Jolliet et al.(^\text{37})</td>
<td>123 COPD FEV(_1) &lt;750 mL</td>
<td>Randomized crossover</td>
<td>Patients randomized to NIV with air–O(_2) or He–O(_2)</td>
<td>↔ Intubation rates or length of stay in ICU between groups</td>
<td></td>
</tr>
<tr>
<td>Tassaux et al.(^\text{41})</td>
<td>23 COPD FEV(_1) = 0.86 L</td>
<td>Randomized crossover</td>
<td>45 min on He–O(_2) 45 min on air–O(_2)</td>
<td>↓ EELV ↓ PEEPi ↓ Peak and mean airway pressures</td>
<td>↔ Pulmonary artery pressures, ventricular pressures, cardiac output or pulmonary vascular resistance</td>
</tr>
<tr>
<td>Jolliet et al.(^\text{24})</td>
<td>10 COPD FEV(_1) = NR</td>
<td>Non randomized crossover</td>
<td>30 min of He–O(_2) 30 min of air–O(_2) 30 min of air–O(_2) PEEPi 80% of PEEPe</td>
<td>Comparable ↓ in PEEPi and EELV with He–O(_2) and PEEPe</td>
<td>↓ Inspiratory and expiratory airway resistance and intrathoracic pressures compared to PEEPe ↓ Oxygenation with He–O(_2) ↔ Breathing pattern</td>
</tr>
<tr>
<td>Diehl et al.(^\text{46})</td>
<td>13 COPD (SB) FEV(_1) = 0.92 L</td>
<td>Randomized crossover</td>
<td>20 min of He–O(_2) or air–O(_2) mixtures immediately before extubation</td>
<td>↓ Total and resistive work of breathing in the He–O(_2) group ↓ PEEPi in He–O(_2) ↓ Total, elastic and resistive WOB ↓ Work to overcome PEEPi</td>
<td>↓ PEEPi, ↓ inspiratory resistance, ↓ (T_i) and (T_e), ↔ static respiratory system compliance</td>
</tr>
<tr>
<td>Gainier et al.(^\text{44})</td>
<td>23 COPD FEV(_1) = NR</td>
<td>Randomized crossover</td>
<td>45 min of either He–O(_2) and air–O(_2) breathing</td>
<td>↓ EELV in He–O(_2) ↓ Total, elastic and resistive WOB ↓ Work to overcome PEEPi</td>
<td>↓ PEEPi, ↓ inspiratory resistance, ↓ (T_i) and (T_e), ↔ static respiratory system compliance</td>
</tr>
<tr>
<td>Lee et al.(^\text{42})</td>
<td>25 COPD FEV(_1)/FVC = 0.37</td>
<td>Non-randomized crossover</td>
<td>30 min on He–O(_2) 30 min in air–O(_2)</td>
<td>↓ PEEPi in He–O(_2) ↓ EELV with He–O(_2) ↓ Changes in systolic pressure variations</td>
<td>↓ Mean pulmonary artery pressure ↓ Right atrial pressure ↓ Pulmonary artery occlusion pressure ↑ Cardiac index ↑ Total, elastic and resistive WOB</td>
</tr>
<tr>
<td>Tassaux et al.(^\text{43})</td>
<td>10 COPD FEV(_1) = 0.69 L</td>
<td>Non-randomized crossover</td>
<td>30 min air–O(_2) at constant (F_iO_2) and PS 30 min He–O(_2) at constant (F_iO_2) and PS 30 min air–O(_2) at constant (F_iO_2) and PS</td>
<td>↓ PEEPi, ineffective breaths, and inspiratory effort with He–O(_2)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; FEV\(_1\), forced expired volume in 1 s; NIV, non-invasive ventilation; \(P_{\text{a}CO_2}\), partial pressure of arterial CO\(_2\); \(T_i/T_{TOT}\), inspiratory time/total time (Duty cycle); SB, spontaneously breathing; PS, pressure support; PTI, pressure time index; WOB, work of breathing; ICU, intensive care unit; EELV, end expired lung volume; PEEPi, intrinsic positive end-expiratory pressure; \(T_i\), inspiratory time; \(T_e\), expiratory time; PEEPe, extrinsic positive end-expiratory pressure.
well-designed, randomized controlled trials to further investigate the mechanisms responsible for the improvements observed and their potential benefits.

Invasive mechanical ventilation

Dynamic hyperinflation and PEEPi can also adversely affect lung mechanics, gas exchange and hemodynamics in COPD patients intubated for acute respiratory failure. Any treatment that can reduce dynamic hyperinflation and PEEPi such as external PEEP (PEEPe) or continuous positive airway pressure should lead to positive outcomes for these patients. However, PEEPe may be difficult to titrate and can increase lung volume and PEEPi if the pressures administered are too high. The ability of helium–oxygen to reduce airway resistance, increase expiratory flow rates, and decrease dynamic hyperinflation could be of benefit for reducing PEEPi in the mechanically ventilated patient (Table 1).

Tassaux et al. were the first to investigate whether helium–oxygen could reduce dynamic hyperinflation and PEEPi in 23 decompensated patients. Helium–oxygen significantly reduced dynamic hyperinflation, decreased PEEPi (9 ± 3 cm H2O vs. 5 ± 3 cm H2O) and reduced peak and mean airway pressures by 17% and 13%, respectively. Interestingly, even with the reduction in PEEPi, helium–oxygen was reported to have no effect on any measure of hemodynamics in the 12 patients who had an indwelling pulmonary arterial catheter. In a second study by the same group, the effect on PEEPi of helium–oxygen or PEEPe was investigated. The primary findings of this study were that both helium–oxygen and PEEPe reduced PEEPi and end-expiratory lung volume to a similar extent. However, helium–oxygen reduced airway pressures and airway resistance, while these were increased with PEEPe. The authors also measured gas exchange and demonstrated no clinically important differences between helium and oxygen, air–oxygen and PEEPe. A small statistically significant reduction in oxygenation was observed with the helium–oxygen gas but care should be taken in interpreting these data as there were differences reported in alveolar \(\text{FIO2}\) was not matched across conditions. No other study of mechanically ventilated patients has demonstrated this change in oxygenation with helium–oxygen.

Gainnier et al. investigated the effect of helium–oxygen on the work of breathing in 23 intubated mechanically ventilated COPD patients and demonstrated that helium–oxygen reduced the work to overcome airway resistance, decreased the elastic work of breathing and the work to overcome PEEPi. As a result, the total work of breathing was also significantly reduced by 21%. These findings could be important for reducing the load on the respiratory muscles during mechanical ventilation but could also have a number of practical applications including successful withdrawal from ventilatory support because of an improved matching of respiratory muscle function to ventilatory demand seen in these patients. Diehl et al. studied this interesting application for helium–oxygen and demonstrated a reduction in the work of breathing and PEEPi in 13 spontaneous breathing patients just before extubation. This finding was especially true in the patients with the highest work of breathing, suggesting that helium–oxygen may be a useful intermediate step in the extubation process for these patients. Unfortunately, the same measurements could only be performed on five patients in the post-extubation period so no definite conclusion could be made.

In the latest investigation to be published in this area, Tassaux et al. investigated whether helium–oxygen in combination with pressure support could improve PEEPi in 10 intubated COPD patients. While all ventilator settings were kept constant throughout the protocol, the combination of helium–oxygen and pressure support ventilation reduced PEEPi (4.8 ± 2.7 vs. 3.1 ± 2.7 cm H2O), the number of effective inspiratory attempts and the magnitude of inspiratory efforts compared to pressure support alone. The combination of helium–oxygen and pressure support also reduced the resistive, elastic and total work of breathing.

Concomitant to the increased work of breathing caused by dynamic hyperinflation and PEEPi, the increase in lung volume can also compromise heart function. Dynamic hyperinflation and PEEPi increase right ventricular venous return through greater negative inspiratory pressure swings, increase right ventricular impedance through lung hyperinflation and reduce left ventricular filling and output due to ventricular interaction and septal shift. To assess whether helium–oxygen could reduce the influence of PEEPi on hemodynamics, Lee et al. administered helium–oxygen or air–oxygen to 25 mechanically ventilated patients with systolic pressure variations >15 mmHg but no systemic hypotension. Helium–oxygen reduced PEEPi which was directly related to the decreased respiratory changes in pulse pressure \(r = 0.84, p < 0.001\). They also reported significant reductions in mean pulmonary artery pressure, right atrial pressure and improvements in pulmonary artery occlusion pressure while cardiac index was increased. The difference between the findings of this study and those of Tassaux et al. could be explained by patient selection (known PEEPi associated hemodynamic instability in the Lee et al. study).

In summary, helium–oxygen breathing consistently reduces PEEPi and the work of breathing and may improve hemodynamic abnormalities associated with respiratory pressure swings in intubated, mechanically ventilated COPD patients. To date, there are no data available to determine whether these beneficial changes lead to other important clinical outcomes such as length of time patients require mechanical ventilation, successful extubation, length of stay in hospital or survival. In the systematic review of Colebourn et al., it was reported that helium–oxygen reduced mean PEEPi by 2.2 cm H2O during mechanical ventilation, although they point out that this only occurred in those with high PEEPi before helium–oxygen administration. This highlights that it may be possible to identify patients who could benefit from helium–oxygen breathing due to elevated PEEPi, hemodynamic abnormalities or reduced respiratory muscle weakness, which could help optimize treatment for these patients.

**Helium–oxygen for reducing exercise limitation in patients with COPD**

As helium has the ability to reduce airway resistance and increase flow rates it is logical that helium–oxygen could...
reduce dynamic hyperinflation, work of breathing and dyspnea during exercise, which would improve exercise tolerance. The studies that investigated these changes are summarized in Table 2. This postulate was first investigated in 1970 by Raimondi et al.\(^{47}\) who examined whether a 79:21 helium-oxygen mixture could improve incremental and constant load exercise time in eight patients with chronic bronchitis. Interestingly, even though peak expiratory flow rates were shown to increase with the helium-oxygen gas the authors reported no effect on exercise time or ventilation in any test performed. A decade later, Bradley et al.\(^{48}\) also demonstrated that helium–oxygen had no effect on peak O\(_2\) uptake (VO\(_{2\text{peak}}\)) or peak ventilation in seven patients with severe COPD. As these were the first studies in this area a

<table>
<thead>
<tr>
<th>Source</th>
<th>Participants</th>
<th>Study design</th>
<th>Exercise tests</th>
<th>Gas interventions</th>
<th>Primary findings</th>
<th>Secondary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heliox studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raimondi et al.(^{47})</td>
<td>8 COPD</td>
<td>Randomized crossover</td>
<td>Three incremental cycle tests and three constant load cycle trials (at 70% WL max) to symptom limitation</td>
<td>Oxygen(<em>{21}), heliox(</em>{21}), oxygen(_{35})</td>
<td>→ Exercise time with heliox(_{21}), ↑ with 100% O(<em>2) → Ventilation → Heart rate → VO(</em>{2\text{peak}}) → Ventilation</td>
<td>↑ Peak expiratory flow with heliox(_{21})</td>
</tr>
<tr>
<td>Bradley et al.(^{48})</td>
<td>7 COPD</td>
<td>Randomized crossover</td>
<td>Two incremental cycling tests to symptom limitation</td>
<td>Oxygen(<em>{21}) and heliox(</em>{21})</td>
<td>↑ VO(_{2\text{peak}}), ↑ peak ventilation and ↓ P(_a)CO(<em>2) with heliox(</em>{21})</td>
<td>→ Cardiac output ↔ Pulmonary artery pressure ↔ Right atrial pressure ↓ Pulmonary vascular resistance with heliox(_{21}) ↔ S(<em>O_2) and dyspnea at peak exercise with heliox(</em>{21})</td>
</tr>
<tr>
<td>Olberg et al.(^{50})</td>
<td>8 COPD</td>
<td>Non randomized</td>
<td>Two incremental cycling tests to symptom limitation</td>
<td>Oxygen(<em>{21}) and heliox(</em>{21})</td>
<td>↑ Endurance time, ↓ DH and dyspnea at isotime</td>
<td>↑ Ventilation ↓ P(_a)CO(_2)</td>
</tr>
<tr>
<td>Richardson et al.(^{50})</td>
<td>10 COPD</td>
<td>Balanced orderuai</td>
<td>Three incremental cycling tests to symptom limitation</td>
<td>Oxygen(<em>{21}), heliox(</em>{21}), oxygen(_{100})</td>
<td>Heliox(<em>{21}) and oxygen(</em>{100}) — ↑ peak WL Heliox(<em>{21}) — ↑ VO(</em>{2\text{peak}}) and ventilation</td>
<td></td>
</tr>
<tr>
<td>Palange et al.(^{55})</td>
<td>12 COPD</td>
<td>Randomized crossover</td>
<td>Two constant load cycling trials (at 80% WL max) to symptom limitation</td>
<td>Oxygen(<em>{21}) and heliox(</em>{21})</td>
<td>↑ Endurance time, ↓ DH and dyspnea at isotime</td>
<td>↑ Ventilation ↓ P(_a)CO(_2)</td>
</tr>
<tr>
<td><strong>Helium-hyperoxia studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laude et al.(^{53})</td>
<td>82 COPD</td>
<td>Randomized crossover</td>
<td>Four shuttle walk tests (at 85% estimated VO(_{2\text{peak}}))</td>
<td>Oxygen(<em>{21}), oxygen(</em>{28}), heliox(<em>{21}) and heliox(</em>{28})</td>
<td>Heliox(<em>{28}) ↑ walking distance and ↓ dyspnea more than oxygen(</em>{28}) or heliox(_{28})</td>
<td>At isotime only heliox(<em>{40}) ↓ the resistive and total WOB and the WOB to overcome PEEPi ↓ PEEPi with heliox(</em>{21}) and heliox(<em>{40}) ↔ Peak dyspnea or leg fatigue ↓ Desaturation with heliox(</em>{50}) and oxygen(_{100}) (mask)</td>
</tr>
<tr>
<td>Eves et al.(^{6})</td>
<td>10 COPD</td>
<td>Randomized crossover</td>
<td>Four constant load cycling trials (at 60% WL max) to symptom limitation</td>
<td>Oxygen(<em>{21}), oxygen(</em>{40}), heliox(<em>{40}) and heliox(</em>{40})</td>
<td>Heliox(<em>{40}) ↑ Exercise time more than oxygen(</em>{40}) or heliox(_{40}) At isotime — ↓ dyspnea with all gases but ↓ DH and ↑ V(_t) only with helium gases</td>
<td></td>
</tr>
<tr>
<td>Marcinuk et al.(^{54})</td>
<td>16 COPD</td>
<td>Randomized crossover</td>
<td>Four 6-min walk tests (mask)</td>
<td>Oxygen(<em>{21}) (mask) oxygen(</em>{100}) (mask) oxygen(<em>{100}) (nasal prongs) heliox(</em>{21}) (mask)</td>
<td>Heliox(<em>{28}) ↑ walking distance more than Oxygen(</em>{100}) delivered by mask or nasal prongs</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** for gas interventions: ”oxygen” gases are nitrogen based (unless 100%) and the subscript indicates O\(_2\) concentration; FEV\(_1\), forced expired volume in 1 s; VO\(_{2\text{peak}}\), peak O\(_2\) uptake; WL, workload; P\(_a\)CO\(_2\), partial pressure of arterial CO\(_2\); S\(_O_2\), arterial O\(_2\) saturation; DH, dynamic hyperinflation; V\(_t\), tidal volume; WOB, work of breathing; PEEPi, intrinsic positive end-expiratory pressure.
number of methodological issues could have affected their results. For example, Raimondi et al. performed three exercise tests to symptom limitation on the same day, separated by only 30 min rest and as a result fatigue may have influenced their findings.

It was not until the late 1990s that two groups revisited the hypothesis that helium–oxygen may have significant benefits for exercising patients with COPD. Oelberg et al. administered 79:21 helium–oxygen to 10 very severe COPD patients (mean FEV1 = 0.56 L) during incremental cycle exercise to symptom limitation and demonstrated a 16% increase in VO2peak, which coincided with a 31% increase in ventilation and an increase in arterial saturation from 85% with air to 88%. The authors also reported a significant reduction in pulmonary vascular resistance with helium–oxygen but there was no increase in cardiac output likely demonstrating that a ventilatory constraint was still limiting exercise with the helium–oxygen gas. Richardson et al. also recruited 10 patients with COPD following a pulmonary rehabilitation program and demonstrated that helium–oxygen increased VO2peak (17.9%) and peak power output (15.5%), without any improvement in arterial saturation. The authors reasoned that the enhanced VO2peak with helium–oxygen came from greater peripheral O2 availability and improved perfusion of the locomotory muscles due to a decreased work of breathing and a reduction in the O2 demand of the respiratory musculature. Although this mechanism was probably partly responsible for the improved VO2peak seen with this gas, it is also possible that a reduction in the work of breathing reduced dyspnea, allowing the patient to reach a higher workload before a ventilatory limitation occurred.

Palange et al. was the first to investigate the effects of helium–oxygen on lung volumes and dyspnea during exercise in 12 patients with COPD. Using a double-blind randomized crossover design, patients performed two constant load cycling exercise tests to symptom limitation and demonstrated that 79:21 helium–oxygen increased endurance capacity at 80% of workload maximum from 4.2 ± 2.0 to 9.0 ± 4.5 min. At symptom limitation, helium–oxygen also increased ventilation, inspiratory capacity and tidal volume, while decreasing PaCO2. At an isotime during exercise, there were significant reductions in dyspnea and dynamic hyperinflation as demonstrated by an increase in inspiratory capacity and inspiratory reserve volume. This isotime change in dyspnea was inversely related to the change in inspiratory capacity (r = −0.75, p < 0.01), which in turn was positively correlated with the change in endurance time observed with the helium–oxygen gas (r = 0.70, p < 0.05). These findings demonstrated that helium–oxygen breathing during exercise reduced dynamic hyperinflation and dyspnea and improved exercise endurance capacity in moderate to severe COPD patients.

### Helium–hyperoxia for reducing exercise limitation in patients with COPD

The use of an increased oxygen content (hyperoxia) for reducing dynamic hyperinflation and dyspnea in COPD patients with and without hypoxemia is now well accepted. Hyperoxia reduces ventilatory demand and increases expiratory time, which decreases dynamic hyperinflation and leads to reduced dyspnea and improved exercise tolerance. As helium can improve expiratory flow rates and also reduces dynamic hyperinflation and dyspnea, it raises the question of whether a gas that combines hyperoxia and helium will have an additive effect on dynamic hyperinflation, PEEPi, exertional dyspnea and exercise tolerance than either gas mixture alone.

Table 2 summarizes the three recent studies that have addressed this question. Using a double-blind randomized crossover design, Laude et al. was the first to report that 72:28 helium-oxygen mixture improved endurance shuttle walking distance more than 72:28 nitrogen-oxygen or 79:21 helium-oxygen. The authors calculated that changing FIO2 from 21% to 28% improved walking distance by 30%, whereas replacing nitrogen with helium improved walking distance by 29%, combining the two led to a 64% increase. This finding demonstrated the additive effect of combining the two gases and as dyspnea was unchanged at the end of the walking tests established that a greater exercise capacity can be achieved without worsening symptoms.

Similar findings were also reported by Eves et al. who recruited 10 patients with moderate to severe COPD who performed four constant load cycling trials at 60% of a predetermined maximal workload. The primary finding of the study was that a 60:40 helium–oxygen mixture significantly improved exercise time (26.3 ± 10.6 min) to symptom limitation, compared to 79:21 nitrogen–oxygen (9.4 ± 5.2 min), 60:40 nitrogen–oxygen gas (17.8 ± 5.8 min) and 79:21 helium–oxygen (16.7 ± 9.1 min). In contrast to Laude et al., this study also investigated the mechanisms associated with the improvements in exercise capacity and demonstrated greater reductions in end-expiratory lung volume, resistive and total work of breathing, the work to overcome PEEPi and dyspnea during exercise compared to the other gases. There was also a reduction in respiratory rate with the oxygen-based gases and an increase in tidal volume with the helium-based mixtures. These findings clearly demonstrate the additional benefits of helium–hyperoxia for reducing dynamic hyperinflation and improving lung mechanics in patients with COPD, leading to improved dyspnea and exercise tolerance.

In the latest study in this area, Marciniuk et al. reported similar findings with 16 patients who performed four 6-min walk tests with either compressed air delivered through a mask, 100% O2 delivered through a mask or nasal prongs (8 L/min) and a 70:30 helium-oxygen mixture delivered through a mask. The masks used were commercial breathing masks (Pulmonex® Hi-Ox®, Viasys Medsystems, Wheeling, IL), which delivered each gas at a flow rate of 15 L/min such that some entrainment of room air occurred in all conditions. They also found that helium–hyperoxia increased walking distance (564 m) compared to compressed air (497 m, p < 0.001), mask O2 (520 m, p < 0.001) or nasal O2 (528 m, p < 0.01) without increasing exertional symptoms. Evidence from all three of these studies demonstrates that combining helium and hyperoxia significantly improves exercise capacity more than either hyperoxia or 79:21 helium–oxygen. It waits to be seen whether these large acute increases in exercise capacity can significantly increase the volume and/or
intensity of exercise performed in the exercise component of a pulmonary rehabilitation program and whether this increased volume of exercise translates into improved patient outcomes.

Conclusion

There is a strong rationale and some promising initial evidence for utilizing helium–oxygen gas mixtures for treating acute exacerbations of COPD and for improving exercise capacity of these patients to enhance the effectiveness of pulmonary rehabilitation. However, there is a definite lack of high-level evidence to support the use of helium–oxygen gases in the clinical setting. There is now real need for large, properly powered, randomized controlled trials to address whether helium is a cost-effective and beneficial therapy for improving patient outcome and for reducing health care cost and utilization in the clinical setting.

References


