Contrasting pressure-support ventilation and helium–oxygen during exercise in severe COPD

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Summary
Helium–oxygen mixtures and pressure-support ventilation have been used to unload the respiratory muscles and increase exercise tolerance in COPD. Considering the different characteristics of these techniques, we hypothesized that helium–oxygen would be more effective in reducing exercise-induced dynamic hyperinflation than pressure-support. We also hypothesized that patients would experience greater increases in respiratory rate and minute ventilation with helium–oxygen than with pressure-support. The hypotheses were tested in ten patients with severe COPD (FEV1 = 28 ± 3% predicted [mean ± SE]) during constant-load cycling (80% maximal workrate) while breathing 30% oxygen-alone, helium–oxygen, and pressure-support in randomized order. As hypothesized, helium–oxygen had greater impact on dynamic hyperinflation than did pressure-support (end-exercise; p < 0.03). For the most part of exercise, respiratory rate and minute ventilation were greater with helium–oxygen than with pressure-support (p < 0.008). During the initial phases of exercise, helium–oxygen caused less rib-cage muscle recruitment than did pressure-support (p < 0.03), and after the start of exercise it caused greater reduction in inspiratory reserve volume (p < 0.02). Despite these different responses, helium–oxygen and pressure-support caused similar increases in exercise duration (oxygen-alone: 6.9 ± 0.8 min; helium–oxygen: 10.7 ± 1.4 min; pressure-support: 11.2 ± 1.6 min; p = 0.003) and similar decreases in inspiratory effort (esophageal pressure-time product), respiratory drive, pulmonary resistance, dyspnea and leg effort (p < 0.03). In conclusion, helium–oxygen reduced exercise-induced dynamic hyperinflation by improving the relationship between hyperinflation and minute ventilation. In contrast, pressure-support reduced hyperinflation solely as a result of lowering ventilation. Helium–oxygen was more effective in reducing...
Introduction

Exercise tolerance is decreased in patients with chronic obstructive pulmonary disease (COPD). Decreased exercise tolerance causes significant disability, which, in turn, profoundly affects quality of life. Mechanisms responsible for decreased exercise tolerance include inability to increase oxygen delivery to the peripheral muscles, variable peripheral-muscle dysfunction, pulmonary gas-exchange abnormalities, pulmonary hypertension, and, possibly, psychological factors. In many patients, however, abnormal lung mechanics and functional respiratory muscle weakness secondary to dynamic hyperinflation predominate.

Helium–oxygen mixtures and pressure-support ventilation have been used to unload the respiratory muscles and, thus, decrease inspiratory effort and increase exercise tolerance in COPD. Considering the different technical characteristics of these techniques, we expect the unloading with helium–oxygen and pressure-support to be achieved by different mechanisms. Unique to helium–oxygen is the improvement in airflow that results from a lower density of helium in relation to air. By improving airflow, helium–oxygen can limit exercise-induced dynamic hyperinflation in COPD.

Unique to pressure-support is a slowing of respiratory frequency. This slowing possibly results from vagally-mediated increases in the duration of neural exhalation. In addition, pressure-support increases tidal volume (VT) while unloading the respiratory muscles and it may also hinder expiratory flow. We speculate that all these effects of pressure-support could have contrasting consequences on exercise-induced dynamic hyperinflation. A lower frequency might decrease exercise-induced dynamic hyperinflation. Alternatively the combination of a higher VT in the presence of flow-limitation — almost invariable with severe COPD — and an impediment to expiratory flow could worsen dynamic hyperinflation. We, therefore, expect that in severe COPD helium–oxygen and pressure-support will have different effects on exercise-induced dynamic hyperinflation. Specifically, we hypothesize that exercise-induced dynamic hyperinflation will be less with helium–oxygen than with pressure-support. In addition, considering possible vagally-mediated increases in neural exhalation with pressure-support, we also hypothesize that during constant workrate exercise, patients with severe COPD will experience more modest increases in respiratory frequency and minute ventilation with pressure-support than with helium–oxygen.

The primary purpose to perform such a head-to-head comparison of helium–oxygen versus pressure-support is to gain insights into the mechanisms of action that are unique to each modality. Without doing a head-to-head comparison it would be impossible to determine which changes are quantitatively unique for a given modality. Confirmation of our primary and secondary hypothesis will shed new light into the mechanisms of action that are distinctive to helium–oxygen or pressure-support.

Methods

Further methodological details are available in the online supplement.

Patients

Thirteen sedentary patients (modified Baecke score <9) with severe COPD (FEV₁/FVC < 0.7, FEV₁ < 50% predicted) were enrolled in the study. Exclusion criteria were significant cardiovascular, neuromuscular, or orthopedic impairments that could have interfered with exercise testing. Appropriate institutional review boards approved the study and written consent was obtained. After randomization, three patients withdrew or were withdrawn. One withdrew because of newly diagnosed prostate cancer requiring radiation therapy. The second patient withdrew because of newly diagnosed peripheral vascular disease, and the third because of knee pain secondary to degenerative joint disease that required surgery. Characteristics of patients who did not complete the study were similar to those who did.

Experimental setup

Flow and pressure measurements

Inspiratory flow was measured with a heated, large-diameter pneumotachometer connected to a differential pressure transducer. Calibration of the pneumotachometer was confirmed with the experimental gas mixture immediately before each exercise trial. Volumes were obtained by electronic integration of the flow signal. The pneumotachometer was attached in series to a low-resistance one-way valve and mouthpiece (Fig. 1).

Esophageal (Pes) and gastric (Pga) pressures were separately measured with two thin-walled, 10 cm long latex balloon-tipped catheters coupled to pressure transducers. A balloon containing 1.0 mL of air was positioned in the midesophagus; a gastric balloon containing 2.0 mL of air was advanced 70 cm from the nares. Proper positioning of the esophageal balloon was ensured with the occlusion technique. Airway pressure was measured at the mouthpiece using a third pressure transducer.

Protocol

Based on symptom-limited, incremental cycle-ergometry testing, three submaximal constant-load exercise tests, equal to 80% of the highest workrate (Watts) achieved, were selected (Fig. 1). During the three submaximal tests, patients breathed 30% oxygen-alone, 30% oxygen plus 70%
helium, and 30% oxygen with pressure-support in random order (See online supplement for further details).

For the constant-load test on pressure-support (Puritan Bennett 7200) the starting level of support was determined by patient’s comfort before exercise. Every 2 min during exercise, after each inspiratory capacity maneuver, patients were asked whether they desired an increase or decrease in the level of support to optimize comfort. When requested, pressure-support was increased or decreased by 2-to-4 cm H2O according to patient’s comfort — i.e., average (SE) pressure-support at the start of exercise was 9 ± 2 cm H2O and end-exercise it was 19 ± 2 cm H2O. Positive end-expiratory pressure was always zero cm H2O. Ventilator inspiratory and expiratory breathing circuits were separated, which prevented the possibility of rebreathing.

Every 2 min during exercise and at end-exercise, patients indicated level of breathlessness and leg effort (Borg-scale), and performed an inspiratory capacity (IC) maneuver. Respiratory muscle recruitment was continuously monitored (See online supplement for further details).

Physiologic measurements

IC and operational lung volumes

Operational lung volumes (end-inspiratory and end-expiratory lung volumes, inspiratory reserve volume) were derived from measured total lung capacity and from recordings of IC and VT during exercise. Changes in IC accurately reflect changes in end-expiratory lung volume during exercise as total lung capacity remains unaltered. Thus, development of exercise-induced dynamic hyperinflation was operationally defined as a progressive reduction in IC during exercise. Using this operational definition, significant dynamic hyperinflation (~ 0.5 L) has been reported in symptomatic patients with early COPD.

Respiratory mechanics and effort

Inspiratory resistance of the lung was computed according to standard formulae. Pressure-time product of inspiratory muscles (PTPes) and diaphragm (PTPdi) were calculated as previously described. The relative contribution of the respiratory muscles to tidal breathing was assessed as the ratio of tidal-change in Pga to tidal-change in Pes (ΔPga/ΔPes). Respiratory drive was estimated by measuring the maximum rate of change in Pes during inhalation (ΔPes max/dt).

Data analysis

Physiologic data were continuously recorded and digitized at 2000 Hz using a 12-bit analog-to-digital converter connected to a computer using Windaq software (Dataq Instruments, Akron, OH). Physiologic data were analyzed at four points in time: the first minute of exercise, the last minute, isotime, and half-isotime. Isotime (100% isotime) was the shortest length of time that a patient tolerated constant-load exercise. Half-isotime was 50% of that duration. Nine patients exercised for a shorter time with oxygen-alone and one with pressure-support. Data at different time periods were compared by one-way analysis of variance and protected Fisher’s LDS post-hoc multiple comparison testing. Pearson’s correlation coefficient was used to detect correlation among variables.

Results

Patients’ characteristics

Patients’ characteristics are summarized in Table 1. All had severe COPD, considerable hyperinflation and gas trapping, and all were sedentary.

Dynamic hyperinflation, operational lung volumes

During exercise, IC (measurement used to monitor changes in dynamic hyperinflation) decreased in all patients (Fig. 2). After the first minute of exercise, the decrease in IC was always less with helium—oxygen or pressure-support than with oxygen-alone (p < 0.03). At end-exercise, the decrease in IC with pressure-support and oxygen-alone were equivalent, and, in both instances, the decrease in IC was greater than with helium—oxygen (p = 0.03; Fig. 2).

The operational lung volumes during exercise are shown in Fig. 3. Differences in VT with helium—oxygen and pressure-support did not reach statistical significance. VT was always greater with pressure-support than with oxygen-alone (p < 0.04). The combined responses of VT and IC (Fig. 2) were responsible for a larger inspiratory reserve volume (IRV) with helium—oxygen than with pressure-support from half-isotime to end-exercise (p ≤ 0.02) (Fig. 3).
Respiratory adjuncts and exercise in COPD

Respiratory frequency, minute ventilation and breath components

During exercise, respiratory frequency and minute ventilation increased for all three conditions (Fig. 2). At isotime, frequency and minute ventilation were less with pressure-support than with helium–oxygen or with oxygen-alone (p < 0.003). Isotime frequency and minute ventilation with helium–oxygen and with oxygen-alone were equivalent. At end-exercise, minute ventilation continued to be less with pressure-support than with helium–oxygen (p = 0.008) and frequency tended to be less with pressure-support than with helium–oxygen (p = 0.06; Fig. 2).

The relationship of IC to minute ventilation during the three conditions is shown in Fig. 4. Compared to oxygen, helium–oxygen caused less decrease in IC despite a greater increase in minute ventilation; with pressure-support, the relationship IC to minute ventilation was similar to that with oxygen-alone.

Table 1  Patients’ characteristics at rest and responses to symptom-limited incremental testing (n = 10).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>% Predicted</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>65 ± 3</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30 ± 2</td>
<td></td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.9 ± 0.1</td>
<td>28 ± 3</td>
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<tr>
<td>FVC, L</td>
<td>2.3 ± 0.3</td>
<td>59 ± 6</td>
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<tr>
<td>FEV₁/FVC, %</td>
<td>39 ± 4</td>
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<tr>
<td>Total lung capacity, L</td>
<td>7.7 ± 0.8</td>
<td>123 ± 10</td>
</tr>
<tr>
<td>Residual volume, L</td>
<td>5.0 ± 0.8</td>
<td>223 ± 34</td>
</tr>
<tr>
<td>DL/VA, ml/min/mm Hg/L</td>
<td>2.6 ± 0.5</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.01</td>
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</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>45 ± 2</td>
<td></td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>69 ± 2</td>
<td></td>
</tr>
<tr>
<td>Modified Baecke score</td>
<td>3 ± 1</td>
<td></td>
</tr>
</tbody>
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Incremental Exercise (*)

<table>
<thead>
<tr>
<th>(end-exercise values)</th>
<th></th>
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<tbody>
<tr>
<td>Power, Watts</td>
<td>55 ± 9</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>40 ± 3</td>
<td>59 ± 5</td>
</tr>
<tr>
<td>Minute ventilation/MVV, %</td>
<td>113 ± 11</td>
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</tr>
<tr>
<td>Tidal volume, L</td>
<td>1.25 ± 0.14</td>
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<tr>
<td>Respiratory frequency, breaths/min</td>
<td>34 ± 3</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>118 ± 7</td>
<td>76 ± 5</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>96 ± 1</td>
<td></td>
</tr>
<tr>
<td>Borg dyspnea score</td>
<td>7 (6–9)</td>
<td></td>
</tr>
<tr>
<td>Borg leg effort score</td>
<td>7 (5–9)</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: BMI = body mass index, FEV₁ = forced expired volume in 1 s, FVC = forced vital capacity, DL/VA = specific diffusing capacity, PaCO₂ = partial pressure of arterial carbon dioxide, PaO₂ = partial pressure of arterial oxygen, MVV = maximal voluntary ventilation, SpO₂ = oxygen saturation by pulse oximetry. Values are means ± SE with the exception of symptoms (median and range). (To convert standard error values to standard deviation multiply the standard error by 3.2). (*) Predicted values from: ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167 (2):211–277.

Exercise-induced increases in respiratory frequency were associated with decreases in inspiratory time (TI) and expiratory time (TE) for all three conditions (Fig. 2). At isotime, TI and TE were longer with pressure-support than with helium–oxygen or with oxygen-alone (p ≤ 0.007). At end-exercise, TI continued to be longer with pressure-support than with helium–oxygen (p = 0.001) while TE became equivalent (Fig. 2). During exercise, decreases in TI and TE with helium–oxygen were not different than those with oxygen-alone.

Dyspnea and perceived leg fatigue

At isotime, median (IQR) dyspnea score decreased from 9 (4.5–10.0) with oxygen-alone to 4 (2.5–5.0) with helium–oxygen and to 3 (2.5–5.0) with pressure-support (p = 0.002). At isotime, median perceived leg effort also decreased from 6.5 (3.8–10) with oxygen-alone to 4.5 (3.0–5.5) with helium–oxygen and to 4.0 (2.5–5.0) with pressure-support (p = 0.01). Five minutes after exercise, patients were asked “what was the primary reason that forced you to stop exercising”. Dyspnea was the primary reason in 80% of patients on oxygen-alone, 30% during helium–oxygen and 40% during pressure-support.

Inspiratory effort, respiratory drive

During exercise PTPes/min, PTPdi/min and ΔPmax/dt, increased for all three conditions (Fig. 5). The rise in ΔPmax/dt was closely associated with the rise in PTPes/min (data normalized to corresponding rises with oxygen-alone) both with helium–oxygen (r = 0.72, p = 0.019) and with pressure-support (r = 0.79, p = 0.006). At isotime, PTPes/min, PTPdi/min and ΔPmax/dt were less with helium–oxygen or with pressure-support than with oxygen-alone (p ≤ 0.02). At end-exercise, all three variables with helium–oxygen were equivalent to the corresponding values with pressure-support (Fig. 5). In contrast, at end-exercise, inspiratory effort per breath (PTPes/br) and inspiratory effort per liter (PTPes/L) were less with helium–oxygen than with pressure-support (p ≤ 0.03) (Fig. 2E-repository).

Pattern of respiratory muscle recruitment

At start of exercise and half-isotime, ΔPGA/ΔPes was greater with pressure-support than helium–oxygen or oxygen-alone (p < 0.03) (Fig. 5). As exercise progressed, ΔPGA/ΔPes increased with helium–oxygen and oxygen-alone, and did not change with pressure-support. At end-exercise, ΔPGA/ΔPes with helium–oxygen was equivalent to the corresponding value with pressure-support (Fig. 5).

Airflow and inspiratory pulmonary resistance

After the first minute of exercise, inspiratory flows were always less with pressure-support than with helium–oxygen or with oxygen-alone (p ≤ 0.03; Fig. 5). At half-isotime and isotime, expiratory flows were less with pressure-support than helium–oxygen or oxygen-alone (p ≤ 0.01; Fig. E3-repository).
During exercise, rises in inspiratory pulmonary resistance did not reach statistical significance in any of the three conditions (Fig. 5). At isotime, inspiratory pulmonary resistance with helium-oxygen or pressure-support were less than with oxygen-alone ($p < 0.003$). At isotime, $T_i$ and $T_e$ were longer with pressure-support than with helium-oxygen or oxygen-alone ($p \leq 0.007$); the opposite occurred with $f_R$ and minute ventilation ($p \leq 0.003$). At isotime, IC was greater with helium-oxygen or pressure-support than with oxygen-alone ($p = 0.003$). At end-exercise, minute ventilation and IC were greater with helium-oxygen than with pressure-support ($p \leq 0.03$), and the opposite occurred with $T_i$ ($p < 0.001$). No time-effect for $V_T$ was recorded in all three conditions. Differences in $V_T$ with pressure-support and helium-oxygen did not reach statistical significance ($V_T$ with pressure-support was always greater than with oxygen-alone; $p \leq 0.04$) (See text for details). Data presented as mean ± SE and analyzed by ANOVA.

**Figure 2** Inspiratory time ($T_i$) (A), expiratory time ($T_e$) (B), respiratory frequency ($f_R$) (C), tidal volume ($V_T$) (D), minute ventilation (E), and inspiratory capacity (IC) (F) with oxygen-alone (squares), helium-oxygen mixture (circles) and pressure-support (triangles) during the first minute of constant-load exercise (Start), half-isotime ($1/2$ Isot), isotime (Isot), and end-exercise (End). From the first minute to the end of exercise, $T_i$, $T_e$ and IC decreased while $f_R$ and minute ventilation increased for all three conditions ($p < 0.02$). At isotime, $T_i$ and $T_e$ were longer with pressure-support than with helium-oxygen or oxygen-alone ($p \leq 0.007$); the opposite occurred with $f_R$ and minute ventilation ($p \leq 0.003$). At isotime, IC was greater with helium-oxygen or pressure-support than with oxygen-alone ($p = 0.003$). At end-exercise, minute ventilation and IC were greater with helium-oxygen than with pressure-support ($p \leq 0.03$), and the opposite occurred with $T_i$ ($p < 0.001$). No time-effect for $V_T$ was recorded in all three conditions. Differences in $V_T$ with pressure-support and helium-oxygen did not reach statistical significance ($V_T$ with pressure-support was always greater than with oxygen-alone; $p \leq 0.04$) (See text for details). Data presented as mean ± SE and analyzed by ANOVA.

**Exercise performance**

Despite the different responses to exercise particularly in terms of hyperinflation, minute ventilation, respiratory rate with helium-oxygen and pressure-support, both strategies caused similar increases in exercise duration (Fig. 6). The effect size on exercise duration was large for both helium-oxygen (Cohen’s $d = 1.42$) and pressure-support (Cohen’s $d = 1.13$).³¹

Heart rate at end-exercise was $122 ± 7$ beats per minute ($78 ± 4$ maximum percent predicted) with oxygen-alone, and it was higher with helium-oxygen ($137 ± 7$ beats per minute) and with pressure-support ($139 ± 7$ beats per minute; $p = 0.013$).

**Discussion**

This is the first study to directly explore the relative functional effects of helium-oxygen and pressure-support — with both being compared against a control state of breathing 30% oxygen — during constant-load exercise in patients with severe COPD. As hypothesized, helium-oxygen was more effective in reducing exercise-induced dynamic hyperinflation than pressure-support. For the most part of exercise, respiratory rate and minute ventilation were greater with helium-oxygen than with pressure-support. The study contains four additional novel findings. First, compared to oxygen-alone, helium-oxygen reduced exercise-induced dynamic hyperinflation by improving the relationship between hyperinflation and minute ventilation. In contrast, pressure-support reduced hyperinflation solely as a result of lowering ventilation. Second, helium-oxygen was associated with greater inspiratory reserve volumes and with less inspiratory effort per breath and per liter than with pressure-support. Third, inspiratory effort per minute was decreased...
to a similar amount by the two modalities. Finally, before peak-exercise, helium–oxygen produced a different pattern of respiratory muscle recruitment than did pressure-support.

**Dynamic hyperinflation and operational lung volumes**

At isotime, IC was greater with helium–oxygen or pressure-support than with oxygen-alone (p = 0.005) and, at end-exercise, it was greater with helium–oxygen than with pressure-support (p = 0.03) (Fig. 2). These findings support our primary hypothesis that helium–oxygen has a greater quantitative effect on exercise-induced dynamic hyperinflation than has pressure-support, despite both having a similar qualitative effect on hyperinflation.

The mechanisms for the greater IC with helium–oxygen than with pressure-support at end-exercise — i.e., less exercise-induced dynamic hyperinflation (Fig. 2 panel F) — despite greater minute ventilation with helium–oxygen than with pressure-support remain unclear. One possibility is an improvement in expiratory flow and, thus, lung emptying. This, however, is not supported by our data (Fig. 3E-repository). Less exercise-induced dynamic hyperinflation with helium–oxygen than with pressure-support at end-exercise was also not due to longer TE (Fig. 2). Mechanisms that could contribute to a greater reduction in dynamic hyperinflation with helium–oxygen include helium-associated increases in the resting maximal flow-volume envelope and increases in the resting maximal ventilatory capacity. As patients with COPD exercise, end-expiratory and end-inspiratory lung volumes increase. These increases prevent dynamic airway closure during exhalation. A greater maximal exhalation flow for a given lung volume will allow patients to sustain the same ventilation before and after administration of helium–oxygen but with a lower end-expiratory lung volume under the latter condition. The capacity to maintain the same ventilation with a lower end-expiratory lung volume with helium–oxygen can take place as long as expiratory flow-limitation is located in the central airways.

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**Figure 3** Operational lung volumes with oxygen-alone (light blue) and pressure-support (green) (A), with oxygen-alone and helium–oxygen (pink) (B), and with all three conditions (C) during the first minute of constant-load exercise (Start), half-isotime (1/2 Isot), isotime (Isot), and end-exercise (End). (The darkest area in panel C represents the overlapping values recorded with helium–oxygen and pressure-support). (Panel A) During the first minute of exercise, the end-expiratory lung volume (EELV) recorded with pressure-support was not different from the corresponding value with oxygen-alone (EELV was calculated by subtracting IC from total lung capacity). Because of the larger tidal volume (VT) with pressure-support during the first minute of exercise (p = 0.003), the end-inspiratory lung volume (EILV) was greater and, thus, inspiratory reserve volume (IRV) was smaller than with oxygen-alone (p = 0.01). As exercised progressed, VT with oxygen-alone continued to be smaller than with pressure-support (p ≤ 0.04); yet, as a result of the exercise-induced increase in EELV with oxygen, the IRV recorded with the two modalities became equivalent. (Panel B) During the first minute of exercise, EELV, EILV and IRV recorded with helium–oxygen were not different from the corresponding values with oxygen-alone. As exercised progressed, EELV increased more with oxygen-alone than with helium–oxygen while VT was not significantly different with the two techniques. Accordingly, IRV at half-isotime and isotime were less with oxygen-alone than with helium–oxygen (p ≤ 0.04). (Panel C) During the first minute of exercise, IRV tended to be less with pressure-support than with helium–oxygen (p = 0.07) and, thereafter IRV was significantly less with pressure-support than with helium–oxygen (p ≤ 0.02). Only at end-exercise, EELV with pressure-support was significantly greater than with helium–oxygen (p = 0.03). TLC = total lung capacity (See text for details). Data presented as mean ± SE and analyzed by ANOVA.
Brusasco and Pellegrino’s group⁴ have reported that airway collapse proximal to a flow-limiting segment during exhalation triggers dyspnea during exercise. To avoid dyspnea, the respiratory centers tend to stop exhalation prematurely with resulting rise in end-expiratory lung volume.⁴ When these investigators imposed a small expiratory threshold load, $T_E$ increased sufficiently to decrease end-expiratory volume despite reducing mean expiratory flow.⁴ We cannot exclude that the added expiratory resistance of the ventilator’s circuit during pressure-support caused responses similar to those reported by Brusasco and Pellegrino’s group.³ This possibility is supported by the longer $T_E$ and slower expiratory flow with pressure-support than with helium—oxygen at half-isotime and isotime (Fig. 2 and E3-repository). Responses to the ventilator’s expiratory resistance could contribute to the equivalent decreases in IC with pressure-support and helium—oxygen at half-isotime and isotime (Fig. 2, E3-repository).

In addition to airflow collapse,³⁴ dyspnea is mechanistically linked also to exercise-induced reductions of IRV.⁵ In accordance with the findings of O'Donnell et al,⁵ when breathing oxygen-alone our patients experienced an abrupt rise in dyspnea when IRV decreased to $<0.4$ L ($0.39 ± 0.05$ L; Fig. 7). A novel finding of the current investigation, however, is that even with helium—oxygen and with pressure-support there was an abrupt rise in dyspnea when IRV decreased to $<0.4$ L (Fig. 7).

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**Figure 4** Relationship of inspiratory capacity to minute ventilation with oxygen-alone (squares), helium—oxygen (circles) and pressure-support (triangles) during (from left-to-right) the first minute of constant-load exercise, half-isotime, isotime, and end-exercise. From the first minute of exercise to end-exercise the increase in minute ventilation was associated with a decrease in inspiratory capacity for all three conditions. During exercise with pressure-support the relationship between inspiratory capacity and minute ventilation was equivalent to the inspiratory capacity to minute ventilation relationship with oxygen-alone (See text for details). Data presented as mean ± SE.

**Figure 5** Pressure output of the respiratory muscles (esophageal pressure-time product per minute, PTPes/min) (A) and of the diaphragm muscle (transdiaphragmatic pressure-time product per minute, PTPdi/min) (B), ratio of tidal-change in gastric pressure to tidal-change in esophageal pressure, an index of rib-cage and expiratory muscle contribution to respiratory effort ($\Delta P_{ga}/\Delta P_{es}$) (C), maximum rate of change in esophageal pressure, an index of drive ($\Delta P_{es} \text{ max}/\text{dt}$) (D), inspiratory airflow (E), and inspiratory pulmonary resistance (F) with oxygen-alone (squares), helium—oxygen mixture (circles) and pressure-support (triangles) during the first minute of constant-load exercise (Start), half-isotime ($1/2$ Isot), isotime (Isot), and end-exercise (End). From the first minute of exercise to the end of exercise, PTPes/min, PTPdi/min, $\Delta P_{es}$ max/dt and inspiratory flow increased for all three conditions ($p < 0.0005$). At isotime, PTPes/min, PTPdi/min, $\Delta P_{es}$ max/dt and inspiratory pulmonary resistance were greater with oxygen-alone than with helium—oxygen or pressure-support ($p < 0.007$), while inspiratory flow was less with pressure-support than with helium—oxygen or oxygen-alone ($p < 0.0005$). During the first minute of exercise and at half-isotime, the $\Delta P_{ga}/\Delta P_{es}$ ratio was greater with pressure-support than with oxygen-alone or helium—oxygen ($p < 0.03$). As exercise progressed, $\Delta P_{ga}/\Delta P_{es}$ increased while patients received helium—oxygen or oxygen-alone ($p < 0.04$), and did not change while patients received pressure-support. At end-exercise (End), the values all physiologic variables with helium—oxygen were not different from the corresponding values with pressure-support with the exception of inspiratory flow that was greater with helium—oxygen ($p < 0.0005$). (See text for details). Data presented as mean ± SE and analyzed by ANOVA.
Although V<sub>T</sub> was equivalent with the two techniques, the ratio of mechanical T<sub>1</sub> beyond neural T<sub>1</sub> was greater with than with oxygen-alone (6.9 ± 0.8 min; p = 0.003). Horizontal lines represent mean values. Data analyzed by ANOVA.

With pressure-support or oxygen-alone, the critical IRV was reached at half-isotime; yet patients continued to exercise for another 7.7 ± 1.3 min with pressure-support as compared to 3.5 ± 0.4 min with oxygen-alone (p = 0.006). This finding is likely the result of direct respiratory muscle unloading by pressure-support, which allowed patients to maintain greater V<sub>T</sub> with less effort (Figs. 2 and 5). Notwithstanding the smaller IRV with pressure-support than helium–oxygen (p < 0.02), dyspnea scores at isotime and end-exercise with the two modes were equivalent (Figs. 3 and 7): despite more unfavorable operating volumes, unloading by pressure-support limits dyspnea.

**Minute ventilation, respiratory rate and breath components**

The differences in minute ventilation and respiratory frequency recorded with pressure-support and helium–oxygen support our secondary hypothesis that patients with severe COPD would experience more modest increases in respiratory frequency and minute ventilation with pressure-support than with helium–oxygen (Fig. 2). Prolongation of mechanical T<sub>1</sub> beyond neural T<sub>1</sub> is a likely mechanism for the lower respiratory frequency with pressure-support than with helium–oxygen. Such prolongation maintains lung inflation during neural T<sub>E</sub>. Inflation during neural T<sub>E</sub> may result in vagally-mediated increases in the duration of neural T<sub>E</sub>. The reduction in frequency with pressure-support is likely together with the non-significant smaller V<sub>T</sub> — caused minute ventilation to be less than with helium–oxygen (Fig. 2).

The combination of equivalent PTPes/min with helium–oxygen and pressure-support and greater minute ventilation with the former caused end-exercise inspiratory-pressure output per liter (PTPes/L) to be less with helium–oxygen than with pressure-support. In addition, although V<sub>T</sub> was equivalent with the two techniques, inspiratory-pressure output per breath (PTPes/br) was less with helium–oxygen (Fig. E2-repository). Decreased PTPes/L and PTPes/br imply more favorable mechanics. Indeed, despite greater inspiratory flow (isotime and end-exercise) and less dynamic hyperinflation (end-exercise) with helium–oxygen than pressure-support (Fig. 2) — factors that should have caused resistance to be greater with helium–oxygen — inspiratory pulmonary resistance was not dissimilar with the two modalities.

Similar to the findings of other investigators, isoventilation (Table 2), the pattern of physiologic responses to oxygen-alone versus helium–oxygen was equivalent minute ventilations with the three modalities were recorded. During oxygen-alone, isoventilation occurred in five patients at isotime and in five at half-isotime. The corresponding epochs during helium–oxygen occurred in five patients during half-isotime and in five during isotime. During pressure-support, isoventilation occurred in five patients at end-exercise and in five at isotime.

During isoventilation (Table 2), the pattern of physiologic responses to oxygen-alone versus helium–oxygen was equivalent to the pattern recorded at isotime. This result indicates that the differences in the physiologic responses recorded at isotime were not driven by minute ventilation but by the indirect muscle unloading achieved with helium–oxygen. This result is not surprising considering that...
Table 2  Physiological variables at isoventilation during constant-load exercise on oxygen-alone, helium—oxygen and on pressure-support (n = 10).

<table>
<thead>
<tr>
<th></th>
<th>Oxygen</th>
<th>Helium-oxygen</th>
<th>Pressure-support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minute ventilation, L/min</td>
<td>37 ± 2</td>
<td>37 ± 2</td>
<td>37 ± 3</td>
</tr>
<tr>
<td>Inspiratory capacity, L ($^\lambda$)</td>
<td>1.6 ± 0.1</td>
<td>1.9 ± 0.2</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td>Inspiratory reserve volume, L ($^\lambda$)</td>
<td>0.34 ± 0.05</td>
<td>0.52 ± 0.08</td>
<td>0.23 ± 0.05</td>
</tr>
<tr>
<td>PTPes/min, cm H$_2$O · sec/min ($^\Delta$,$^\ast$)</td>
<td>772 ± 76</td>
<td>556 ± 53</td>
<td>853 ± 128</td>
</tr>
<tr>
<td>PTPes/L, cm H$_2$O·sec/L ($^\lambda$)</td>
<td>22 (17-26)</td>
<td>15 (11-20)</td>
<td>19 (18-23)</td>
</tr>
<tr>
<td>PTPes/br, cm H$_2$O·sec</td>
<td>28 ± 5</td>
<td>22 ± 4</td>
<td>31 ± 5</td>
</tr>
<tr>
<td>PTPdi/min, cm H$_2$O · sec/min</td>
<td>362 ± 49</td>
<td>248 ± 35</td>
<td>232 ± 36</td>
</tr>
<tr>
<td>$\Delta$Pes max/dt, cm H$_2$O·100 ms$^{-1}$ ($^\Delta$,$^\ast$)</td>
<td>19 (15-26)</td>
<td>16 (10-18)</td>
<td>20 (15-27)</td>
</tr>
<tr>
<td>Inspiratory flow, L/sec</td>
<td>2.27 ± 0.12</td>
<td>2.36 ± 0.13</td>
<td>1.85 ± 0.12</td>
</tr>
<tr>
<td>Mean expiratory flow, L/sec ($^\Delta$,$^\ast$)</td>
<td>0.97 ± 0.08</td>
<td>0.97 ± 0.09</td>
<td>1.05 ± 0.10</td>
</tr>
<tr>
<td>Expiratory time, sec ($^\Delta$,$^\ast$)</td>
<td>1.4 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>Inspiratory pulmonary resistance, cm H$_2$O/L/sec</td>
<td>6.1 (5.1-8.4)</td>
<td>4.9 (3.9-5.4)</td>
<td>4.4 (3.2-6.2)</td>
</tr>
</tbody>
</table>

All responses at isoventilation with oxygen-alone and helium—oxygen were equivalent to the responses at isotime recorded with the two modalities. The responses marked with ($^\lambda$) indicate responses to oxygen-alone and pressure-support that at isoventilation were not equivalent to the responses recorded at isotime with the two modalities. With the exception the responses marked with ($^\ast$), all other responses at isoventilation with pressure-support and helium—oxygen were equivalent to the responses at end-exercise recorded with the two modalities (See text for details). Definition of abbreviations: PTPes/min = esophageal pressure-time product per minute, PTPes/L = PTPes per liter, PTPes/br = PTPes per breath, PTPdi/min = pressure-time product of the diaphragm per minute, $\Delta$Pes max/dt = maximum rate of change in esophageal pressure (an index of drive). Values are means ± SE with the exception of PTPes/L, $\Delta$Pes max/dt, and inspiratory airflow resistance (median and interquartile range). In all cases ANOVA was <0.05; *p < 0.05 by protected Fisher’s LDS post-hoc multiple comparison testing.
isotime minute ventilations with oxygen-alone and helium—oxygen were equivalent (Fig. 2). During isotime IC, PTPes/min, PTPes/L, PTPes/br drive, T_e and mean expiratory flow with oxygen-alone and pressure-support were equivalent (Table 2). These results suggest that the difference in the physiologic responses between oxygen-alone and pressure-support recorded at isotime (see Figs. 2 and 3) were primarily driven by the reduced minute ventilation with pressure-support than with oxygen-alone. This result is not surprising considering that during exercise the relationship between inspiratory capacity and minute ventilation with these two modalities was equivalent (Fig. 4)—i.e., pressure-support decreased dynamic hyperinflation only by its capacity to decrease ventilation while helium—oxygen decreased dynamic hyperinflation despite increasing minute ventilation.

With the exception for equivalent expiratory time and less drive, PTPes/min, and mean expiratory flow with helium—oxygen than with pressure-support (Table 2), all other responses with these two modalities of breathing assistance were equivalent with those at end-exercise (see Figs. 2 and 3). This observation suggests that (most of) the different responses to helium—oxygen and pressure-support result from different operational characteristics of the two techniques (indirect muscle unloading with helium—oxygen and direct with pressure-support) rather than the different response of minute ventilation.

**Pattern of respiratory muscle recruitment**

During the first minute of exercise, $\Delta P_{ga}/\Delta P_{es}$ was greater with pressure-support than with helium—oxygen (Fig. 5). A greater $\Delta P_{ga}/\Delta P_{es}$ ratio can occur with increased recruitment of rib-cage muscles (during inhalation) or increased recruitment of expiratory muscles (during exhalation). The latter is unlikely because expiratory rise in Pga was equivalent with pressure-support and helium—oxygen. Therefore, the higher $\Delta P_{ga}/\Delta P_{es}$ ratio with pressure-support resulted from a relatively greater recruitment of the rib-cage muscles than of the diaphragm. Increased rib-cage muscle recruitment occurs when tidal breathing requires increased diaphragmatic effort.79,37 Yet, the possibility that increased rib-cage muscle recruitment was a response to increased diaphragmatic effort when patients received pressure-support is unlikely: PTPdi/min was less with pressure-support than with helium—oxygen during the first minute of exercise and at half-isotime when $\Delta P_{ga}/\Delta P_{es}$ ratios with pressure-support were greater than with helium—oxygen (Fig. 5). We hypothesize that pressure-support per se modulates the relative contribution of rib-cage muscles and diaphragm to tidal breathing independent of ventilatory load. This is supported by the greater median $\Delta P_{ga}/\Delta P_{es}$ ratio just before starting exercise with pressure-support (0.46) than with helium—oxygen (0.17; $p = 0.01$) recorded in seven of the nine patients (in one patient, no recording of resting breathing during pressure-support was available). Whether this difference in recruitment is secondary to larger $V_T$ (1.39 ± 0.19 L with pressure-support and 0.95 ± 0.09 L with helium—oxygen; $p = 0.01$), need of triggering the ventilator during pressure-support, and added expiratory resistance of the ventilator circuit16,17 remains to be determined.

**Functional consequences of supported breathing during exercise**

As expected,6,7,10 exercise tolerance improved with helium—oxygen and with pressure-support. Despite different responses in terms of operational lung volumes and breathing pattern the improvement in exercise tolerance with the two modalities was equivalent. This improvement was achieved with similar decreases in inspiratory effort per minute (PTPes/min; Fig. 5). It is biologically plausible that the smaller PTPes/min with helium—oxygen was due to improvements in airflow,14 and the smaller PTPes/min with pressure-support was due to direct muscle unloading.16 The reduction in inspiratory effort per minute with helium—oxygen and pressure-support (as compared to oxygen-alone) needed to generate minute ventilation probably contributed to the recorded decrease in respiratory drive (Fig. 5). This is supported by the close relationship between rise in PTPes/min and rise in $\Delta P_{es}$ max/dt both with helium—oxygen ($r = 0.72$, $p = 0.019$) and with pressure-support ($r = 0.79$, $p = 0.006$).

We hypothesize that the reduction in inspiratory effort with both modalities had at least two effects. First, by decreasing respiratory limitations to exercise, assisted breathing (helium—oxygen and pressure-support) allowed for a greater cardiovascular demand. This is supported by greater end-exercise heart rate with assisted breathing than with oxygen-alone. Second, by unloading the respiratory muscles (Figs. 5, E2-repository) assisted breathing could have fostered redistribution of blood flow from respiratory to working locomotor muscles as reported by others.9 Redistribution of blood flow and greater end-exercise cardiovascular performance support the hypothesis that differences in leg perfusion improved exercise tolerance and affected the different type of symptoms experienced by our patients.

Why did dyspnea and exercise tolerance did not improve to a larger extent with helium—oxygen than with pressure-support given that operating lung volumes were more favorable with the former? We suspect that the answer rests on the observed rise in respiratory drive ($\Delta P_{es}$ max/dt) and minute ventilation. First, the $\Delta P_{es}$ max/dt recorded when patients stopped exercising on helium—oxygen and on pressure-support were comparable to each other (and to the $\Delta P_{es}$ max/dt at end-exercise with oxygen-alone) (Fig. 5). These results suggest that at end-exercise drive was equivalent in the three conditions. Second, with each constant-load exercise there was no ventilatory reserve at the end of the test: the ratio of minute ventilation-to-predicted maximal voluntary ventilation was 124 ± 11% with helium—oxygen, 107 ± 11% with pressure-support (and 117 ± 8% with oxygen-alone). These two observations raise the possibility that although limitations to exercise were possibly different in the different experimental conditions— including early hyperinflation with oxygen-alone, late hyperinflation with pressure-support and (more so) with helium—oxygen, high inspiratory effort per breath or per liter with oxygen-alone and with pressure-support, encroachment to a maximal tolerable reduction in IRV—the common final pathway was an equivalent and unsustainable rise in drive and an unsustainable rise in minute ventilation.
These are complex physiologic interactions that warrant further research. In addition, further research is needed to assess whether the combination of helium—oxygen and noninvasive ventilation could enhance the ability of each technique to reduce the patients’ effort to breathe and to enhance gas exchange—as reported in patients with acute exacerbations of COPD—remains to be determined.

Conclusion

Compared to oxygen-alone, helium—oxygen reduced exercise-induced dynamic hyperinflation by improving the relationship between hyperinflation and minute ventilation. In contrast, pressure-support reduced hyperinflation solely as a result of lowering ventilation. Helium—oxygen was more effective in reducing exercise-induced dynamic hyperinflation in severe COPD, and was associated with greater increases in respiratory rate and minute ventilation than pressure-support.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.rmed.2010.08.008.

Conflict of interest statement

No author has any financial conflicts of interest as well any other forms of conflict of interest, including personal, academic and intellectual issues that could inappropriately influence the submitted work. The study was supported, in part, by grants from the Veterans Administration Research Service. The Veterans Administration Research Service had no role in study design, data collection, analysis and interpretation. It had no role in the writing of the manuscript and in the decision to submit the manuscript for publication.

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