Feasibility Study of Noninvasive Ventilation With Helium-Oxygen Gas Flow for Chronic Obstructive Pulmonary Disease During Exercise

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BACKGROUND: Individually, noninvasive ventilation (NIV) and helium-oxygen gas mixtures (heliox) diminish ventilatory workload and improve exercise tolerance in patients with chronic obstructive pulmonary disease (COPD). NIV in combination with heliox may have additive effects on exercise tolerance in severe COPD. METHODS: We assessed the safety, tolerability, and efficacy of heliox and NIV during exercise in patients with severe COPD. SETTING: Pulmonary rehabilitation facility in an academic tertiary-care medical center. PROTOCOL: Twelve patients with severe COPD were enrolled. Using a sequential randomized placebo-controlled crossover study design, the patients performed 4 separate constant-work stationary bicycle cardiopulmonary exercise studies at 80% of maximal workload during application of sham NIV, NIV, 60:40 heliox with sham NIV, and 60:40 heliox with NIV. Tolerability, safety, and exercise duration as determined by constant-work cardiopulmonary exercise test were the primary outcome measures. Secondary outcome measures at peak exercise and iso-time included rate of perceived exertion, dyspnea, leg pain, heart rate, respiratory rate, systolic and diastolic blood pressure, tympanic temperature, and oxyhemoglobin saturation. RESULTS: No adverse effects occurred during or after application of NIV, heliox, or NIV with heliox. Exercise duration using heliox with NIV was significantly longer than both heliox ($P = .01$) and NIV ($P = .007$), but not placebo ($P = .09$). Relative to placebo, all treatment arms permitted lower respiratory rates at peak exercise. Heliox, with or without NIV, was associated with significant improvements in oxyhemoglobin saturation at peak exercise, relative to placebo or NIV alone. CONCLUSIONS: The adjunctive use of NIV with heliox during exercise proved both safe and tolerable in patients with severe COPD. The lack of demonstrable efficacy to any of the treatment arms relative to placebo ($P = .09$) may be the result of the small sample size (ie, type 2 error)—a conclusion emphasized by the large standard deviations and differences in treatment group variances in exercise duration alone. *Key words: chronic obstructive pulmonary disease, helium, oxygen, noninvasive positive pressure ventilation, exercise capacity.* [Respir Care 2009;54(9):1175–1182. © 2009 Daedalus Enterprises]

Introduction

In chronic obstructive pulmonary disease (COPD) expiratory airflow limitation from dynamic airway collapse causes a dysfunctional ventilatory response during exercise.[1,2] Airflow resistance combined with decreased pulmonary elastance lengthens the time necessary for complete exhalation toward functional residual capacity, pre-

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disposing COPD patients to elevations in end-expiratory lung volume (ie, air trapping) and corresponding reductions in inspiratory capacity.[3,4] Due in part to the diminished inspiratory capacity, an exercising COPD patient must enhance minute ventilation by disproportionately increasing respiratory rate relative to tidal volume. However, tachypnea is both compensatory and counterproductive, as ever higher frequencies shorten exhalation time and aggravate lung hyperinflation, placing both the thoracic and diaphragmatic musculature at a mechanical disadvantage.[5-7] Eventually this physiologic cascade leads to dyspnea and exhaustion at relatively low physical workloads. Despite these limitations, repetitive exposure to aerobic exercise regimens may lead to sustained improvements in exercise tolerance and quality of life.[8,9] This realization has spawned efforts to improve the exercise tolerance of COPD patients by introducing courses of exercise therapy under the supervision of an established pulmonary rehabilitation program. Moreover, innovative approaches to facilitate ventilation during exercise have led to additive effects on the benefits provided by pulmonary rehabilitation alone.[8,10-12]

Novel approaches to enhance the exercise capacity of COPD patients include the use of helium-based, hyperoxic (fraction of inspired oxygen [F_{IO_2}] > 0.21), combined hyperoxic helium-enriched (heliox) gas, and noninvasive ventilation (NIV).[13-16] Oxygen supplementation may reduce compensatory minute ventilation, and in turn prolong exercise duration. Helium is an inert low-density gas that imparts laminar gas flow properties, reducing airflow turbulence, airway resistance, air trapping, and the patient's work of breathing. Combined heliox, relative to both lone hyperoxic or helium mixtures, has led to significant improvements in shuttle-walking distance, constant-work-rate exercise duration, and exertional dyspnea.[13-18] NIV has also shown promise in boosting exercise outcomes in COPD by partially alleviating inspiratory workload and increasing per-breath tidal volume, permitting a compensatory reduction in respiratory rate.[18-22]

Despite the incremental benefit with each adjunctive device or gas flow, there have been conflicting reports as to their efficacy.[10-12,22] These discrepancies are probably multifactorial, but may be attributable to the fact that individual interventions (NIV or heliox) provide only a marginal advantage. NIV used in conjunction with heliox may amplify exercise tolerance relative to their individual use. Given the aforementioned benefits of heliox and NIV to patients with severe COPD, we sought to explore the safety, tolerability, and efficacy of these adjuncts when used in combination.

Methods

Patient Enrollment

The protocol was reviewed and approved by a joint institutional investigational review board (Brooke Army Medical Center and Wilford Hall Medical Center). The study was conducted at the pulmonary rehabilitation clinic of Wilford Hall Medical Center, an academic tertiary-care referral center. Patients referred for dedicated pulmonary rehabilitation were consecutively screened for study enrollment. All of the participants took part in the study after completing a 6-week out-patient-based pulmonary rehabilitation program. The rehabilitation program included at least thrice-weekly technician-supervised cardiovascular exercise sessions using either treadmill or resistance-loaded stationary bicycling, upper-extremity exercises, psychosocial counseling, nutrition guidance, and disease-specific education. All participants completed written informed consent documentation prior to protocol participation. Inclusion criteria were as follows: age > 35 years, forced expiratory volume in the first second (FEV_1) $< 50\%$ of predicted associated with a $< 12\%$ improvement in FEV_1 after actuation of 2 puffs of an albuterol multi-dose inhaler with a spacer (GlaxoSmithKline, Research Triangle Park, North Carolina), an FEV_1 to forced vital capacity ratio of < 0.7, and a > 20-pack-year history of tobacco use. Patients were excluded if they were oxygen-dependent at rest or with exertion before or after the study, had computed-tomography-evident interstitial lung disease (ie, subpleural honeycombing, prominent intralobular and interlobular septal thickening), or had a history of COPD exacerbation within 3 months of study enrollment. A COPD exacerbation was defined by any 2 of 3 symptoms, consisting of acute increase in chronic shortness of breath, an increase in cough with sputum production, or sputum purulence that necessitated the use of antibiotics and/or oral corticosteroids (or, alternatively, an increase in the dose or frequency of inhaled corticosteroids). Patients were also excluded if they had an absolute contraindication to exercise, as set forth by Zeballos et al.[23]

Spirometry and Cardiopulmonary Exercise Testing Methodology

Prior to enrollment, spirometry with body-box plethysmography (Vmax Encore, SensorMedics, Yorba Linda, California) was performed per American Thoracic Society guidelines.[24] Exercise tolerance while breathing room air

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was initially assessed with an incremental resistance cycle ergometry exercise test. Each patient completed one minute of unloaded pedaling, followed by a 10 Watt/min electronically braked incremental-load stationary bicycle test (Ergoselect 100P, Ergoline, Bitz, Germany) until exhaustion. The 10-Watt ramp is our institution's arbitrary default for incremental resistance setting, which is used for all of our patients in order to permit cardiopulmonary exercise test standardization and facilitate intra-individual and inter-individual comparisons. Registered cardiopulmonary technicians encouraged patients to maximize their exercise capacity. Heart rate, single-lead electrocardiogram, and fingertip oxyhemoglobin saturation were monitored with continuous telemetry and finger-probe oximetry (N595, Nellcor/Tyco Healthcare, Pleasanton, California). Appropriately fitted manual sphygmomanometry was performed to collect systolic and diastolic blood pressure at one-min intervals. The workload achieved during the last minute of the incremental test was recorded as the maximum tolerable workload.

Subsequent constant-work cardiopulmonary exercise tests consisted of one minute of unloaded pedaling, after which the ergometer resistance was manually programmed to apply 80% of the maximal tolerable workload attained during the incremental test over a 15-second ramp. During both the incremental and the constant-work exercise test each patient's heart rate, respiratory rate, oxyhemoglobin saturation, tympanic temperature, modified Borg scale score[25] evaluating degree of dyspnea, leg discomfort or pain, and perceived exertion were recorded in the final 15 seconds of each one-minute interval or at patient exhaustion. The modified Borg scale scores were mounted on a screen in front of the patient allowing him or her to rate the perceived effort on each factor from a scale of 1 (no dyspnea) to 10 (severe dyspnea) by pointing to a numerical value on the scale. Patient temperature was measured via a tympanic temperature probe (Thermoscan Pro 4000, Braun, South Boston, Massachusetts) to assess for possible heliox-associated hypothermia. All data points were collected in the last 15 seconds of each interval; more specifically, at rest, after one minute of unloaded pedaling, during each minute of the resistance loading period, and again at one minute post-exercise (recovery). Only one exercise session was performed each day of protocol participation, but no more than 2 days were allowed to intervene between sequential constant-work exercise test studies. To mitigate first-time cardiopulmonary exercise test effects or any individual experiential advantages, each patient performed at least 2 constant-work exercise tests after the initial incremental test and prior to utilizing the investigational devices. Each patient had his or her constant-work exercise test conducted at the same time period each day to minimize the confounding effects of diurnal variability in exercise capacity. Patients were instructed not to use their albuterol/levalbuterol inhaler within the 12 hours preceding each exercise test, but were permitted to continue using their clinician-prescribed maintenance inhalers. Notably, all of the patients were taking dry-powder-inhaler-based tiotropium bromide (Pfizer, New York, New York) and combination inhaler-based salmeterol xinofoate and fluticasone propionate (GlaxoSmithKline, Research Triangle Park, North Carolina). Each patient also completed a Medical Research Council dyspnea questionnaire[26,27] prior to each exercise test, to assess for subjective or self-perceived variability in dyspnea or daily exercise tolerance as a possible contributor to differences in cardiopulmonary exercise test performances.

Gas Mixture and Noninvasive Ventilation Instrumentation

Compressed air (ie, placebo or sham), 60:40 heliox, and NIV were all administered via a tightly-fitted gel-sealed oronasal face mask (Respironics, Murrysville, Pennsylvania). When using heliox alone or in combination with NIV, a dedicated heliox-compatible positive-pressure device was employed (Aptaer, GE HealthCare Worldwide). Compressed air inclusive tests, with or without NIV, were implemented using a heliox-incompatible device (Servo-i, Siemens Medical, Danvers, Massachusetts). Due to the different corrugated tubing circuitry required for each ventilator device, masking of the machine and/or circuitry could not be done. Patients were not told of the implemented pressure or gas mixture throughout the study, or of the different gas mixture/positive-pressure capacities of an individual device. For the NIV portions of the protocol, sham NIV was set using a default inspiratory pressure support of 3 cm H_2O. In selecting the NIV setting, each patient breathed through an oronasal face mask (connected via each device's respective corrugated tubing) at an initial pressure-support setting of 3 cm H_2O. Each patient underwent 2 pressure-support trials where the programmed pressure support was increased from 3 cm H_2O in increments of 1 cm H_2O/min until the patient reported discomfort or intolerance to the pressure setting. The pressure was reduced 1 cm H_2O from the maximal tolerable level attained during the 3 trials, and the latter pressure setting was implemented throughout the remainder of the protocol for that individual. During gas mixture administration and for the 5 minutes after completing exercise, patients were instructed not to speak so as not to disclose, by change in vocal quality, the potential application of helium gas. Based on prior studies the single 60:40 heliox gas mixture was chosen as the optimal content, as hyperoxic heliox ($F_{IO_2} > 0.21$ or 60:40 to 70:30 helium-oxygen ratio) had shown demonstrable benefit over normoxic heliox gas mixtures ($F_{IO_2} = 0.21$).[16,18] As the heliox-dedicated ventilator was unable to provide positive end-expiratory pressure, none

of the treatments included the adjunctive use of this pressure setting.

Study Protocol

After completing their baseline room-air incremental-load test and acclimating constant-work exercise tests, each patient completed a constant-work exercise test with the following gas mixture/NIV combinations in a coin-flip-determined randomized sequence: compressed air with sham NIV (placebo arm); compressed air with NIV; 60:40 heliox with sham NIV; 60:40 heliox with NIV.

Statistical Analysis

In this study the independent variables were treatment (placebo, heliox, NIV, heliox plus NIV) and exercise (rest, warm-up, iso-time, maximal exercise, and recovery). The dependent variables were total exercise time, heart rate, systolic pressure, diastolic pressure, respiratory rate, oxyhemoglobin saturation, tympanic temperature, perceived exertion rating, perceived dyspnea, leg pain, and Medical Research Council dyspnea score. The null hypothesis was that there would be no difference in the independent variables between treatment and exercise combinations. The alternative hypothesis was that there would be a difference in the independent variables between treatment and exercise combinations. The appropriate test for such an analysis was a 2-factor analysis of variance (treatment, exercise) with repeated measures on both factors, followed by post-hoc 2-tailed *t* tests corrected for multiple comparisons.

We used SPSS Sample Power 2.0 (SPSS, Chicago, Illinois) to obtain an estimate of the sample size needed. The sample size was determined from previous studies of COPD-related exercise tolerance, which utilized the constant-work exercise duration as their primary outcome measure. The mean baseline constant-work exercise test duration for patients with severe COPD was anticipated to be 4 ± 2 min, with an expected improvement to 9.0 ± 4.5 min with the use of either 60:40 heliox or NIV.[15] Assuming outcome data followed the anticipated response, the pooled standard deviation would be 3.25 min for exercise endurance time. A sample size of 12 subjects provided 80% power to detect a large effect size (approximately 1.54 standard deviations) difference between means when testing with a paired *t* test at the alpha level of .01, applying a Bonferroni correction for multiple comparisons. This would equate to a difference of approximately 5.5 min. Comparisons of rest versus maximum and of warm-up versus maximum for all outcome measures were made using repeated-measures analysis of variance to examine the effects of the 4 different treatment groups. Because of the lack of literature investigating the particular effect of NIV or heliox on initial exercise ability, rest and warm-up phases were included in the analysis to examine for any change in physiologic variables with no exertion (patient at rest) and non-resistant exertion (unloaded pedaling), where treatment may significantly alleviate initial ventilatory effort and thus perceived dyspnea and effort. Total time was compared using a single-factor analysis of variance as well as a nonparametric Kruskal-Wallis analysis of variance on ranks.

The primary outcome measure of total duration of exercise was recorded from the point of workloading of the bicycle, and did not include the one-minute unloaded pedaling period. Secondary outcome measures included evaluating the difference from the last 15 seconds of the resting baseline and warm-up periods to peak exercise between the different NIV/gas-mixture arms in terms of heart rate, respiratory rate, oxyhemoglobin saturation, tympanic temperature, and modified Borg scale scores evaluating degree of dyspnea, leg discomfort, and overall exertion. We also assessed dyspnea, exertion, and leg pain scores at "iso-time" to note for possible reductions in perceived effort for the treatment arms relative to placebo. Iso-time was determined by the total exercise duration or time achieved during the placebo trial. The subjective outcome measures for the 3 treatment arms were then referenced at the same time point (iso-time) to see if the treatments affected subjective outcome measures prior to exhaustion. As an intention-to-treat analysis, for those patients whose placebo-based exercise duration exceeded the treatment arms ($n = 3$; $n = 1$ for NIV, $n = 1$ for NIV with heliox, $n = 1$ for heliox), the lowest duration among the treatment arms was utilized as the iso-time equivalent. Post-hoc Bonferroni-corrected paired *t* tests were done to examine for inter-group differences in the outcome measures.

Results

We screened 122 consecutive referrals for pulmonary rehabilitation from either of 2 tertiary-care medical centers (Brooke Army Medical Center, Fort Sam, Houston, Texas, and Wilford Hall Medical Center, Lackland Air Force Base, Texas) over the course of a single 12-month period. Twenty-eight met inclusion criteria; 16 patients were intermittently or chronically oxygen-dependent and were thus excluded from study participation. The remainder of the screened patients had either had mild to moderate COPD ($FEV_1 > 50\%$ predicted, $n = 82$) or had been diagnosed with an underlying interstitial lung disease ($n = 14$) (Fig. 1). None of the patients deviated from protocol stipulations throughout the course of the study. Tables 1 and 2 show the patient demographics, baseline spirometry, and plethysmography measurements, and incremental-load-test results. There was no difference in the attained pressure-support level between the NIV with compressed gas or

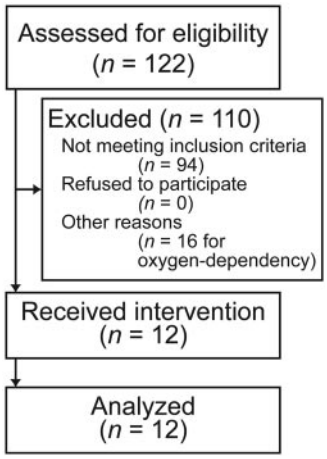

Fig. 1. Patient assessment and allocation diagram.

Table 1. Patient* Demographics and Pulmonary Function Test Results

Variable	Mean ± SD
Age (y)	70 ± 3
Height (in)	70 ± 3
Weight (kg)	72.7 ± 23.1
FEV_1 (L)	1.3 ± 0.4
FEV_1 (% predicted)	42 ± 10
FVC (L)	3.2 ± 0.7
FVC (% predicted)	74 ± 12
FEV_1/FVC	41 ± 7
TLC (% predicted)	109 ± 21
RV (% predicted)	157 ± 46
Inspiratory capacity (L)	2.3 ± 0.5
D_{LCO} (% predicted)	58 ± 8
D_{LCO}/V_A (% predicted)	68 ± 11

* 12 participants, 1 female
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
TLC = total lung capacity
RV = residual volume
D_{LCO} = diffusing capacity of the lung for carbon monoxide
V_A = alveolar volume

NIV plus heliox. (mean pressure support ± 1 standard deviation for the cohort was 16.1 ± 3.9 cm H_2O and 16.1 ± 3.6 cm H_2O, respectively (data not shown).

No adverse effects or patient intolerability to NIV, heliox, or NIV with heliox were noted during protocol participation or at one-week and 3-month follow-up in our clinic. No arrhythmias were noted during the course of the study. Table 3 shows the baseline, warm-up period, and peak exercise period mean measurements for total exercise duration, heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, oxyhemoglobin saturation, tympanic temperature, and rating of perceived dyspnea, exertion, and leg pain and Medical Research Council score in each study arm. There was a statistically significant difference in total exercise time by treatment assignment ($P = .02$). On the post-hoc Bonferroni-corrected t tests, heliox with NIV was significantly greater than both heliox ($P = .01$) and NIV ($P = .007$), but not placebo ($P = .09$) as assessed by the primary outcome measure of total exercise duration (Fig. 2).

Table 2. Incremental Cardiopulmonary Exercise Test Results at Baseline

Variable	Mean ± SD
$\dot{V}_{O_2}$ (mL/kg/min)	12.9 ± 3.5
$\dot{V}_{O_2}$ (L/min)	1.1 ± 0.3
$\dot{V}_{O_2}$ (% predicted)	57 ± 16
$\dot{V}_{CO_2}$ (mL/kg/min)	1.0 ± 0.3
Work (W)	58.3 ± 17.2
Heart rate (beats/min)	102 ± 24
Heart rate (% predicted)	66 ± 16
O_2 pulse (mL/beat)	10.9 ± 3.5
O_2 pulse (% predicted)	63 ± 40
Systolic blood pressure (mm Hg)	143 ± 13
Diastolic blood pressure (mm Hg)	73 ± 18
Maximum $\dot{V}_E$ (L/min)	42.6 ± 11.1
Respiratory rate (breaths/min)	30.8 ± 7.3
V_T (L)	1.3 ± 0.3
V_T (% predicted)	94 ± 25
Inspiratory capacity at peak exercise (% inspiratory capacity at rest)	81 ± 22
Inspiratory capacity at peak exercise (L)	1.8 ± 0.5
V_D/V_T at rest (%)	11 ± 38
V_D/V_T at peak (%)	11 ± 38
Respiratory quotient ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) (peak)	0.97 ± 0.09
S_{pO_2} (peak)	98 ± 10

$\dot{V}_{O_2}$ = oxygen consumption
$\dot{V}_{CO_2}$ = carbon dioxide production
$\dot{V}_E$ = minute volume
V_T = tidal volume
V_D = dead-space volume
S_{pO_2} = oxygen saturation measured via pulse oximetry

While there were significant changes over time (going from rest to warm-up to peak exercise for many of the outcome variables [see Table 3]), a statistically significant inter-treatment group effect occurred in only three of the secondary outcome variables. There was a statistically significant difference in heart rate by treatment ($P = .008$). On the post-hoc Bonferroni-corrected paired t tests the mean heart rate for heliox was significantly higher than during heliox with NIV ($P = .046$) and lone NIV ($P = .045$). There was a statistically significant difference in oxygen saturation by treatment ($P \leq .001$). Mean oxygen saturation during heliox was significantly higher than NIV ($P = .01$) and placebo or "sham" treatment ($P < .001$). Similarly, oxyhemoglobin saturation during heliox plus NIV was significantly higher than both NIV ($P < .001$) and placebo ($P < .001$). Lastly, the mean respiratory rate

Table 3. Secondary Outcome Measures in the Treatment and Placebo Arms*

	Placebo	Heliox	NIV	Heliox + NIV	*P* (rest vs warm-up)	*P* (warm-up vs maximum)
Total time	05:57 ± 05:50	10:10 ± 10:04	09:46 ± 10:14	13:53 ± 11:57	*	*
Heart rate (beats/min)						
Rest	70 ± 14	75 ± 13	72 ± 14	68 ± 10	< .001	< .001
Warm-up	80 ± 17	80 ± 16	82 ± 15	76 ± 14		
Maximum	99 ± 18	104 ± 20	93 ± 21	103 ± 22		
Systolic blood pressure (mm Hg)						
Rest	133 ± 10	135 ± 9	134 ± 8	133 ± 11	.007	.02
Warm-up	138 ± 9	139 ± 9	137 ± 9	134 ± 11		
Maximum	160 ± 20	163 ± 24	166 ± 26	164 ± 29		
Diastolic blood pressure (mm Hg)						
Rest	73 ± 9	74 ± 8	75 ± 10	78 ± 13	.001	< .001
Warm-up	76 ± 11	76 ± 9	78 ± 6	74 ± 13		
Maximum	84 ± 6	89 ± 11	87 ± 9	92 ± 11		
Respiratory rate (breaths/min)						
Rest	16 ± 4	16 ± 4	16 ± 2	14 ± 2	< .001	< .001
Warm-up	21 ± 6	17 ± 4	20 ± 6	18 ± 6		
Maximum	31 ± 5	28 ± 4	30 ± 5	28 ± 4		
O_2 saturation (%)						
Rest	95 ± 2	95 ± 2	95 ± 2	96 ± 2	.04	> .05
Warm-up	95 ± 1	98 ± 1	96 ± 2	98 ± 2		
Maximum	93 ± 2	99 ± 1	94 ± 3	99 ± 1		
Temperature (°F)						
Rest	97.5 ± 0.6	97.7 ± 0.3	97.6 ± 0.8	97.5 ± 0.5	> .05	> .05
Warm-up	97.6 ± 0.4	97.5 ± 0.5	97.7 ± 0.7	97.4 ± 0.5		
Maximum	97.4 ± 0.4	97.7 ± 0.7	97.4 ± 1.0	97.4 ± 0.8		
Perceived exertion rating (1–10 scale)						
Rest	0.8 ± 1.1	0.6 ± 0.8	0.5 ± 0.9	0.5 ± 0.7	< .001	< .001
Warm-up	0.4 ± 0.7	0.2 ± 0.6	0.3 ± 0.5	0.2 ± 0.6		
Maximum	2.9 ± 1.3	3.4 ± 1.9	3.7 ± 2.3	4.3 ± 2.7		
Perceived dyspnea rating (1–10 scale)						
Rest	0.6 ± 1.1	0.3 ± 0.7	0.4 ± 0.9	0.3 ± 0.6	< .001	< .001
Warm-up	0.3 ± 0.7	0.2 ± 0.6	0.2 ± 0.4	0.3 ± 0.6		
Maximum	3.1 ± 1.1	3.4 ± 1.4	3.8 ± 2.4	4.0 ± 2.8		
Perceived leg pain (1–10 scale)						
Rest	0.3 ± 0.5	0.3 ± 0.5	0.1 ± 0.3	0.4 ± 1.0	.005	.005
Warm-up	0.3 ± 0.7	0.2 ± 0.4	0.2 ± 0.4	0.3 ± 0.7		
Maximum	2.8 ± 2.7	4.0 ± 2.7	4.8 ± 2.9	4.3 ± 2.8		
MRC dyspnea score	1.1	0.9	1.1	0.9	> .05	> .05

* Values are mean ± SD unless otherwise indicated.
MRC = Medical Research Council. The subjects took the MRC dyspnea questionnaire prior to testing.

for placebo was significantly higher than all of the treatment arms at peak exercise.

There were statistically significant differences between rest phase or warm-up and peak or maximal exercise for all secondary variables except for oxyhemoglobin saturation (going from warm-up to maximal exercise) and temperature, which remained unchanged throughout (see Table 3). Pre-constant-work-exercise-test Medical Research Council scores also did not demonstrate an inter-treatment group difference. Iso-time analysis did not disclose a statistically significant difference between the 4 study arms of the trial in terms of any of the secondary outcome measures. Post-hoc analysis for possible pressure-support-level-dependent changes in any of the outcome measures

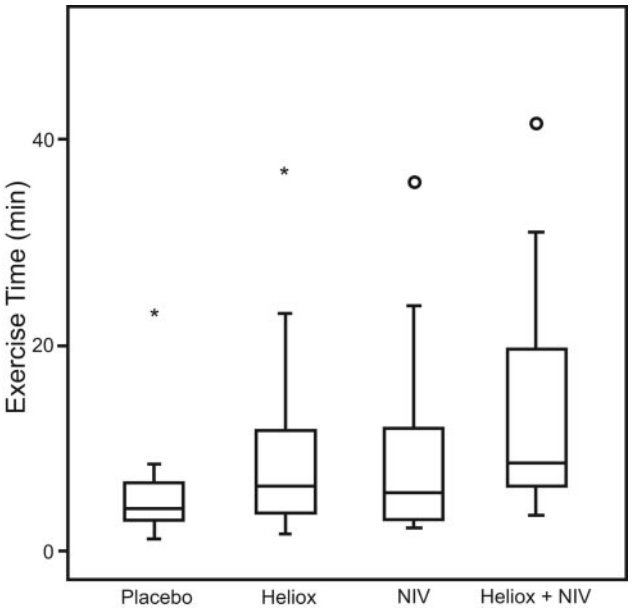

Fig. 2. Distribution of exercise time by treatment. In the box plots, the median is the dark line within the box. The box is defined by the 25th and 75th percentiles, so 50% of the cases have values within the box. The error flags (whiskers) represent the largest and smallest observed values that are not outliers. Outliers (designated by asterisks) are values more than 1.5 box-lengths from the quartile. Extremes (designated by open circles) are values more than 3 box-lengths from the quartiles.

failed to disclose a significant relationship at any of the constant-work-exercise-test intervals.

Discussion

This is the first effort to examine heliox and NIV in combination as ventilatory assist approaches to enhance the exercise capacity of patients with severe COPD. Our assessment showed that the individual or combined use of these ventilatory adjuncts was both safe and tolerable. None of the participants experienced substantial hypothermia or adverse cardiopulmonary effects. Furthermore, the implementation of the NIV/heliox was associated with a statistically significant increase in exercise duration over both the NIV and the heliox arms, but not the placebo arm. With the exception of significant improvements in oxyhemoglobin saturation (during the administration of heliox and heliox plus NIV) and respiratory rate at peak exercise (heliox, heliox with NIV, and NIV), none of the secondary outcome measures showed significant differences between treatment and placebo. Although there was a statistically significant elevation in heart rate during the administration of heliox, the difference in the magnitude (only 2–5 beats per minute between groups) is of uncertain clinical relevance.

Palange et al[15] used a similar exercise regimen to evaluate the efficacy of 80:20 heliox versus compressed air and demonstrated a significant improvement in constant-work-exercise-test duration during heliox administration relative to control. Using the latter trial as a backdrop, we predicted that heliox with or without NIV would increase performance relative to placebo.[16,18] Contrary to expectations, statistically significant improvements in oxyhemoglobin saturation and respiratory rate during both heliox and heliox-NIV relative to placebo did not translate into significant improvements in total exercise duration.

Gas flow and ventilatory adjunct efficacy studies have often shown inconsistent results on exercise outcomes in COPD.[10-12,22] Contradictory findings arise from an amalgamation of both patient and methodological variables. For instance, observational studies have pinpointed the existence of heterogeneity in the extent of dynamic hyperinflation and the importance of its contribution to dyspnea and exercise intolerance.[28] Therefore, measures intended to alleviate hyperinflation (eg, heliox) may be less effective in certain physiologically defined COPD subsets. Peripheral muscle wasting or dysfunction, impaired cardiac function, or altered cardiopulmonary interactions may also variably impact upon the exercise capacity of patients with COPD and compound difficulties at studying a well-defined COPD cohort.[8] Additional methodological variance could be traced to clinician inexperience with the use of the device, patient-ventilator asynchrony, inadequate inspiratory flow or flow-cycling times, unappreciated imposed work of breathing due to exhalation valve delays or resistance, or poor mask fit. The lack of demonstrable efficacy to any of the treatment arms in our protocol relative to placebo ($P = .09$) may also reflect the small sample size (ie, type 2 error): a conclusion emphasized by the large standard deviations and differences in treatment group variances in exercise duration alone. Despite the a priori sample-size selection, our enrollment goal failed to account for the eventual marked disparity in observed patient responses. Based on our results, a similar study would require 38 participants to demonstrate significant differences in constant-work exercise duration.

This feasibility study is limited in terms of physiologic insight. Without the assistance of concurrent esophageal manometry and helium-oxygen calibrated airway pneumotachometry, conclusions cannot be drawn as to the whether there were unappreciated physiologic benefits in intrinsic end-expiratory pressure, inspiratory or expiratory work load, or pressure-time products throughout the course of exercise. Detailed examination of these factors may clarify which patients would be most likely to benefit from the studied gas flow and NIV mixtures. However, the primary question for the study was answered: it is feasible, safe, and tolerable to combine heliox and NIV. Additional protocols enrolling larger sample sizes are needed to test the

presence and extent of clinical efficacy and ease of clinical application.

Conclusions

Hyperoxic helium gas mixtures used in tandem with NIV proved safe, tolerable, and feasible in a clinical setting. However, the efficacy of such adjunctive measures remains inconsistent and thus awaits studies enrolling larger sample sizes.

REFERENCES

1. Dodd D, Brancatisano T, Engel L. Chest wall mechanics during exercise in patients with severe chronic airflow obstruction. Am Rev Respir Dis 1984;129(1):33-38.
2. O'Donnell D, Revell S, Webb K. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164(5):770-777.
3. O'Donnell D, Lam M, Webb K. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;158(5 Pt 1): 1557-1565.
4. O'Donnell D, Webb K. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. Am Rev Respir Dis 1993;148(5):1351-1357.
5. Yan S, Kaminski D, Sliwinski P. Inspiratory muscle mechanics of patients with chronic obstructive pulmonary disease during incremental exercise. Am J Respir Crit Care Med 1997;156(3 Pt 1):807-813.
6. Montes de Oca M, Rassulo J, Celli BR. Respiratory muscle and cardiopulmonary function during exercise in very severe COPD. Am J Respir Crit Care Med 1996;154(5):1284-1289.
7. Vogiatzis I, Georgiadou O, Golemati S, Roussos C. Patterns of dynamic hyperinflation during exercise and recovery in patients with severe chronic obstructive pulmonary disease. Thorax 2005;60(9): 723-729.
8. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest 2007;131(Suppl 5):4S-42S.
9. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis 1991;143(1):9-18.
10. Costes F, Agresti A, Court-Fortune I, Roche F, Vergnon JM, Barthélémy JC. Noninvasive ventilation during exercise training improves exercise tolerance in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2003;23(4):307-313.
11. Hoo GW. Nonpharmacologic adjuncts to training during pulmonary rehabilitation: the role of supplemental oxygen and noninvasive ventilation. J Rehab Respir Dev 2003;40(Suppl 2):81-97.
12. Ambrosino N, Strambi S. New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. Eur Respir J 2004; 24(2):313-22.
13. Emtner M, Porszasz J, Lee S, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;168(9):1034-1042.
14. O'Donnell D, D'Arsigny C, Webb K. Effects of hyperoxia on ventilatory limitation during exercise during exercise in advanced chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 163(4):892-898.
15. Palange P, Valli G, Onorati P, Antonucci R, Paoletti P, Rosato A, et al. Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. J Appl Physiol 2004; 97(5):1637-1642.
16. Laude EA, Duffy NC, Baveystock C, Dougill B, Campbell MJ, Lawson R, et al. The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease: a randomized crossover trial. Am J Respir Crit Care Med 2006;173(8):865-870.
17. Petersen SR, Haykowsky MJ, Wong EY, Jones RL. Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;174(7):763-771.
18. van't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Training with inspiratory pressure support in patients with severe COPD. Eur Respir J 2006;27(1):65-72.
19. Garrod R, Mikelsons C, Paul E, Wedzicha J. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162(4 Pt 1):1335-1341.
20. Maltais F, Reissmann H, Gottfried SB. Pressure support reduces inspiratory effort and dyspnea during exercise in chronic airflow obstruction. Am J Respir Crit Care Med 1995;151(4):1027-1033.
21. Kyroussis D, Polkey MI, Hamnegård CH, Mills GH, Green M, Moxham J. Respiratory muscle activity in patients with COPD walking to exhaustion with and without pressure support. Eur Respir J 2000; 15(4):649-655.
22. Johnson JE, Gavin DJ. Adams-Dramiga S. Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. Chest 2002;122(2):464-472.
23. Zeballos RJ, Weisman I. Behind the scenes of cardiopulmonary exercise testing. Clin Chest Med 1994;15(2):193-213.
24. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152(3):1107-1136.
25. Borg GA. Psychophysical basis of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-387.
26. Altose MD. Assessment and management of breathlessness. Chest 1985;88(2 Suppl):775-835.
27. Sweer L, Zwillich CW. Dyspnea in the patient with chronic obstructive pulmonary disease. Clin Chest Med 1990;11(3):417-44.
28. Aliverti A, Stevenson N, Dellaca RL, Lo Mauro A, Pedotti A, Calverley PM. Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. Thorax 2004;59(3):210-216.