Heliox, dyspnoea and exercise in COPD

T. Hunt*, M.T. Williams*, P. Frith* and D. Schembri*

ABSTRACT: One of the most important determinants of physical and mental well-being of people with chronic obstructive pulmonary disease (COPD) is participation in physical activity. The ability to alter the sensation of dyspnoea during exercise may improve both exercise duration and intensity. Despite the low density, inert nature, strong safety profile and multiple applications of helium gas, the potential benefit of helium–oxygen gas mixtures as an adjunct therapy to modify disease symptoms and exercise capabilities in obstructive lung diseases has only recently been explored.

This is a systematic review of the available peer-reviewed evidence exploring whether symptom modification (perceived levels of dyspnoea) and exercise performance in COPD (either intensity or duration of work) are modified by inhalation of Heliox. Eight experimental studies met inclusion for this review. A variety of methodologies and outcome variables were used negating meta-analysis and hampering direct comparison between interventions.

Overall, there was high level of evidence with a low risk of bias supporting Heliox’s effectiveness in improving the intensity and endurance of exercise when compared to room air for people with COPD. Little conclusive evidence was found to determine whether Heliox altered the sensation of dyspnoea during exercise.

KEYWORDS: Chronic obstructive pulmonary disease, dyspnoea, exercise, Heliox

The multifactorial nature of exercise limitation in chronic obstructive pulmonary disease (COPD) has been extensively reviewed [1, 2]. National guidelines, including the Australian COPDx guidelines [3], the Canadian Thoracic Society recommendations for management of COPD [4] and the international consensus for COPD management [5], recommend increasing both the endurance and the intensity of exercise undertaken by people with COPD. Dyspnoea is the most common disabling symptom for people with COPD and leads to decreased exercise tolerance and performance of activities of normal life [6]. The ability to alter the sensation of dyspnoea during exercise in an effort to improve both duration and intensity may potentially facilitate significant improvements in exercise capacity impairment related to breathlessness and quality of life. Heliox gas mixtures, created when the nitrogen component of an inhaled gas mixture is replaced with helium, have been confirmed to extend the exercise times and training intensity for people with COPD [7].

A BRIEF HISTORY OF HELIUM AND HELIOX

The atmosphere comprises various distinct gases, the most abundant being nitrogen (~78%), followed by oxygen (~21%). Despite being the sixth most abundant gas in the lower atmosphere, helium is only present in around five parts per million, or 0.0005% [8]. Nitrogen and helium have comparable viscosity but helium has a significantly lower density and thermal conductivity when compared to nitrogen. As a result, when a Heliox gas mixture (79% helium and 21% oxygen) is produced, it has a viscosity similar to, but a density nearly six times lower, than atmospheric air. Due to these properties, Heliox has potential applications within the field of respiratory medicine.

Heliox gas mixtures are known to be nontoxic, noncarcinogenic and have no lasting effects on any human organ systems [7]. Historically, Heliox was used by commercial deep sea divers at extreme atmospheric pressures to alleviate the work of breathing [9]. The first recorded use of Heliox in medicine was by Barach [10] during the mid-1930s when Heliox mixtures were administered to patients in an effort to alleviate dyspnoea associated with asthma and obstructive lung lesions (fig. 1). Despite the fact that these early experiments reported reductions in the sensations of dyspnoea, a lengthy period of
inactivity was to follow. Reuben and Harris [11] attribute this absence of interest in clinical applications for Heliox to the intervention of the Second World War, during which many locations of natural helium were lost, and the rapid growth in the production of pharmacological therapies particularly bronchodilators.

It was not until the 1970s that the use of interventional Heliox within respiratory research was reconsidered. Initial sporadic experimentation investigated physiological responses to Heliox [12, 13] but, since the late 1980s, an increased global focus on reducing asthmatic morbidity and mortality reinvigorated the prior enthusiasm associated with Heliox [14]. During the late 1990s, randomised controlled trials concentrated on the potential benefits Heliox may provide as an adjunct therapy to aid noninvasive ventilation and reduce intubation rates during acute exacerbations of COPD [15–18].

It has only been within the past decade that reports of Heliox being used as an exploratory adjunctive therapy during exercise rehabilitation for people with COPD have been published. In a recent review, it was proposed that Heliox had a “strong rationale and promising initial evidence in improving exercise capacity and enhancing the effectiveness of pulmonary rehabilitation programs” [19]. However, the scope of this review was limited to exercise capacity (endurance) and did not consider the interrelationship between Heliox, dyspnoea and exercise.

VENTILATION AND THE WORK OF BREATHING

As a consequence of bifurcations within the bronchial tree and the specific internal diameter or calibre of the airways, air movement through the conducting airways occurs with varying degrees of turbulence [20]. These physiological changes, as well as the loss of alveolar interconnections and an increase in chest wall compliance, lead to significant increases in the turbulence of the airflow within the respiratory tree, altered thoracic and pulmonary biomechanics and are primary factors underlying the consequent hyperinflation [21].

The increased compliance of the airway is most significant during the expiratory phase, in which the airways are more susceptible to narrowing due to increases in intrathoracic pressures. Exercising individuals suffering from COPD are exposed to a vicious cycle in which the background static hyperinflation becomes amplified during the exercise period (dynamic hyperinflation). In order to maintain required ventilation rates during exercise, individuals with COPD increase their breathing frequency and reduce the time spent in both inspiratory and expiratory phases. In order to maintain comparable expiratory flow rates, higher intrathoracic driving pressures are required to expel air. This increases the turbulence of expiratory flow, reduces expiratory volume and compromises lung emptying, thus magnifying pre-existing hyperinflation [22].

Dynamic hyperinflation acts as an adaptive mechanism associated with severe airflow obstruction, but as the lungs dynamically hyperinflate, ancillary muscle units are recruited to increase intra thoracic pressure in an effort to maintain comparable inspiratory and expiratory volumes. The recruitment of these muscles, in an attempt to compensate for the increased work of breathing, comes at significant energy cost which further amplifies the sensation of dyspnoea [22]. One further consequence of dynamic hyperinflation is a reduction in inspiratory and expiratory times and hence volumes. The volume achieved during inspiration has been shown to have strong statistical correlation with the intensity ratings of exertional dyspnoea [23].

Due to its lower density, inhalation of Heliox results in significantly lower turbulence, particularly in the more distal portions of the lung. This decrease in turbulence translates to a greater proportion of laminar flow and, as a direct result, lower overall airway resistance. The most recently published model of Heliox airflow within the respiratory tree predicts decreased turbulence (which results in increased flow rates by up to 50%) during Heliox inhalation [20]. This decreased turbulence remained evident even when airflow was restricted, as in the case of obstructive lung disease.

Dyspnoea is a complex and individualised sensation and, as a result, we perceive and describe our dyspnoea differently. Despite this, recent studies by Williams and co-workers [24, 25] indicates that it is possible to differentiate between people with and without obstructive lung disease based on the words or phrases used to describe their dyspnoea [24], and that qualitative descriptions of dyspnoea are consistent between occasions of exercise [25]. In addition, verbal descriptors of breathlessness including terms such as “heavy”, “fast”, “work”
and “effort” have been reported as a particularly sensitive way to document changes to exercise-induced dyspnoea [26]. Although the beneficial effects of Heliox on exercise endurance have been recently reviewed [19], the effect Heliox may have on the sensation of dyspnoea remains less clearly documented. Hence a systematic review of the literature was undertaken in order to examine the following question: is there evidence that Heliox alters the sensation of dyspnoea and improves exercise duration in people with COPD?

SYSTEMATIC SEARCH STRATEGY

A systematic search strategy was designed to access and evaluate primary data obtained from studies using Heliox during exercise in individuals with COPD. Four groups of search terms specific to the population (COPD), intervention (Heliox) and outcomes (dyspnoea and exercise) of interest were used to search eight databases. An abbreviated table of search terms is included in table 1.

The search process was undertaken during March and April 2008 and was divided into two waves; the first wave of the search strategy resulted in a list of citations for which two search criteria were imposed (criteria A): 1) all articles must be published in English; and 2) all articles must be published in published in peer-reviewed publications. Review articles (narrative or systematic reviews) and abstracts were included at this stage; however, all editorials or correspondence were excluded. 39 citations met criteria A and full abstracts were retrieved. These abstracts were reviewed independently by two people to assess relevance using a second set of criteria (criteria B): 1) studies must continue to meet criteria A; 2) subjects must have COPD (any severity); and 3) Heliox must be included as one of the investigational therapies applied during exercise. No discrepancies were noted on the decision to retain any of the listed articles.

A total of 15 of these abstracts met criteria B. Of these, eight were duplicate abstracts, leaving seven abstracts for which full text papers were retrieved. These full papers were assessed using a third set of criteria (criteria C): 1) criteria A and B were met; and 2) studies must report continuous data (mean and standard deviation) for both primary outcome (dyspnoea and exercise parameters) under experimental conditions (Heliox and comparator).

In order to ensure no papers were omitted through the search strategy, a second wave of searching was undertaken. This consisted of hand searching all reference citations within the seven full text papers meeting criteria C. Following this hand search, an additional 29 potential citations were identified. These were again reviewed against the previous criteria, resulting in an additional 21 references for which full text versions were sought.

When the complete 28 full text articles (seven from the first wave and 21 from the second wave) were assessed using criteria C, 20 papers did not collect data relating to both dyspnoea and exercise under Heliox and comparator interventions (fig. 2). Only eight papers collected measured both dyspnoea and exercise. The authors of the eight papers meeting all criteria were contacted to inform them of the systematic review and to request any further relevant literature they may have and to invite them to provide additional non published primary data for the outcome measures of interest for this review (subject demographics, exercise parameters and/or dyspnoea indices).

The eight full text papers were appraised for unintended potential methodological bias using Lewis Olds Williams (LOW) quality scoring tool for experimental studies [27]. Two assessors (T. Hunt and M.T. Williams) completed the appraisal independently, with unanimous agreement between reviewers for five papers and consensus reached after discussion for the remaining three (table 2).

Overall, there was a low risk of bias for studies included in this review. While three studies explicitly documented the methods used to estimate sample size [30–32], the majority of

| TABLE 1 | Abbreviated list of database search terms |
|----------|----------------------------------------|
| Database | Search terms                          |
| PubMed   | COPD, COAD, pulmonary emphysema and associated MeSH terms | Heliox                      |
|          | COPD with associated MeSH terms        | Exercise                      |
| Ovid/Medline | COPD with associated MeSH terms       | Dyspnoea                      |
|          | Exercise and associated MeSH terms    | Heliox and associated MeSH terms |
| Scopus   | COPD, COAD, pulmonary emphysema and associated MeSH terms | Dyspnoea or dyspnea          |
|          | Exercise or physical exercise         | Heliox                        |
| Web of Science (Web of Knowledge) | COPD, COAD, pulmonary emphysema and associated MeSH terms | Dyspnoea or dyspnea          |
|          | Exercise or physical exercise         | Heliox                        |
| CINAHL (EBSCOhost) | COPD, COAD, pulmonary emphysema and associated MeSH terms | Dyspnoea and associated MeSH terms |
|          | Exercise, physical exercise           | Heliox                        |
|          | and associated MeSH terms             |                               |
| Academic Search File (EBSCOhost) | COPD, COAD, pulmonary emphysema and associated MeSH terms | Dyspnoea and associated MeSH terms |
|          | Exercise, physical exercise           | Heliox                        |
|          | and associated MeSH terms             |                               |
| EMBASE 1974 to present | COPD and associated MeSH terms        | Dyspnoea                      |
|          | Exercise and associated MeSH terms    | Heliox and associated MeSH terms |
| All EBM reviews | COPD and associated MeSH terms       | Dyspnoea                      |
|          | Exercise and associated MeSH terms    | Heliox and associated MeSH terms |
studies did not report sample estimates. In addition, poorly matched control subjects, failure to meet sample size estimates and failure to address confounding issues contributed to uncertainty in assessing levels of bias for individual studies.

DATA EXTRACTION

All eight studies used parameters of exercise as primary outcome measures. A variety of secondary outcome measures existed, but parameters associated with the sensation of dyspnoea were not explicitly stated as either primary or secondary variables in any of the studies. The studies included in this review are summarised in table 3.

The demographics of subjects and parameters of physiological impairment for each study were extracted (table 4). Seven of the eight studies included people who had been diagnosed with moderate to severe airflow limitation (forced expiratory volume in 1 s (FEV1) <50% predicted). The remaining study [28] included people with mild airway obstruction (FEV1 <80% pred). Five of the eight patients recruited by OELBERG et al. [33] carried a diagnosis of α1-antitrypsin deficiency.

CONSISTENCY OF INTERVENTIONS: HELIOX AND COMPARATOR GASES

All studies reported using room air (0.0005% helium) as at least one of their control interventions. All studies used Heliox21 (21% helium in oxygen) as a comparator gas. In addition, EVES et al. [29] and LAUDE et al. [31] included a 28% oxygen in balance helium mixture (Heliox28) intervention arm. MARCINIUK et al. [32] included 30% oxygen in balance helium mixture (Heliox30) and 100% oxygen administered through both face mask and nasal cannula as additional treatment arms. The use of 100% oxygen as an additional treatment arm was also included by RICHARDSON et al. [35], while JOHNSON et al. [30] included noninvasive positive pressure ventilation (NIPPV) as a comparator.

ADEQUACY OF SAMPLE SIZE

A direct comparison of sample sizes between the individual studies was problematic due to the different outcome measures used to estimate sample requirements (table 5). Three studies provided documentation of a priori calculation for sample size. Each study used an appropriate outcome measure for their study design. LAUDE et al. [31] calculated a sample requirement of 24, based on breathlessness (10 mm visual analogue scale (VAS) and Borg scales), MARCINIUK et al. [32] calculated a sample estimate of 16, based on walk distances (6-min walk distance) and JOHNSON et al. [30] calculated a sample estimate of 39, based on exercise endurance (maximal treadmill cardiopulmonary exercise testing (CPET) before and after cardiopulmonary rehabilitation).

If these sample sizes are appropriate for the outcome measures intended, the majority of studies reviewed may have been...
TABLE 3 Summary of studies assessing Heliox and including dyspnoea and exercise parameters as outcome measures

| Author [Ref.] | Participants | Study design | Dyspnoea parameter | Exercise tests | Intervention | Findings relating to dyspnoea | Findings relating to exercise |
|---------------|--------------|--------------|--------------------|----------------|--------------|-----------------------------|-----------------------------|
| BAEK [28]    | 10 patients: COPD (FEV1 < 78%) | RCT, cross-over | 20 point BS | 3 maximal symptom-limited incremental CPTs | Heliox and RA | ↓ Ventilation and Wmax (Heliox) | ↑ Ventilation and Wmax (Heliox) |
| Eves [29]    | 10 patients: COPD (FEV1 < 47%) | RCT, cross-over | 10 point BS | 1 symptom-limited CPT and 4 constant rate CPTs (60% WRmax) | RA, O₂, 28% Heliox and RA | ↓ Dyspnoea and ↓ WOB | ↑ Heliox and ↓ WOB |
| Johnson [30] | 39 patients: COPD (FEV1 < 50%) | RCT, open label | PSQ | 3 symptom-limited CPTs (treadmill pre-post 6-week pulmonary rehabilitation exercise and education) | Heliox, RA and NIPPV | ↓ BS, 5% (He group) reported | ↑ Training benefits Heliox and NIPPV |
| LAUDE [31]   | 21 patients: COPD (FEV1 < 43%) | RCT, cross-over | 10 point BS and VAS | Incremental shuttle walk tests | RA, O₂, 28% Heliox and Heliox | ↓ Dyspnoea (BS and VAS): all gas mixes | ↑ Endurance: all gas mixes |
| MARXMAUK [32] | 16 patients: COPD (FEV1 < 48%) | RCT, cross-over | 10 point BS | 1 maximal symptom-limited CPT and 6MWT and 4 6MWTs on 2 visits | RA, 100% O₂ mask, 100% O₂ and Heliox | ↓ Heliox to RA BS | Significant ↑ in distance on Heliox |
| OELMERS [33] | 18 patients, 8 COPD (FEV1 19%); 10 normal (FEV1 90%) | Unblinded comparison study | PROs | 2 incremental CPTs | Heliox and RA | ↓ Dyspnoea PROs | ↑ Change in peak work loads |
| PALANGE [34] | 12 patients: COPD (FEV < 50%) | RCT, single blind cross-over | 12 point VAS | 1 maximal symptom-limited CPT and 2 constant rate CPTs | Heliox and RA | ↓ Dyspnoea | ↑ Endurance: non-significant improvements in lung mechanics |
| RICHARDSON [35] | 10 patients: COPD (FEV1 < 40%) | Single blind cross-over | 10 point BS | 3 incremental maximal CPTs and single knee extensor ergometry testing | Heliox, 100% O₂ and RA | ↓ Dyspnoea | ↑ Peak work |

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; RCT: randomised controlled trial; BS: Borg scale; CPT: cardiopulmonary exercise test (cycle ergometry unless stated); RA: room air; WOB: work of breathing; WRmax: maximal work rate; PSQ: Patient Satisfaction Questionnaire; NIPPV: non-invasive positive pressure ventilation; PRO: patient reported outcome; VAS: visual analogue scale; 6MWT: 6-min walk test. *: statistically significant finding; ↓: no significant change; ↓: decreased; ↑: increased.

META-ANALYSIS

Meta-analysis for both of the primary outcome measures (dyspnoea and exercise) could not be undertaken due to the significant heterogeneity of outcome measures and insufficient reporting of continuous data. The remaining two studies [31, 34] achieved a significant effect size for both dyspnoea and exercise, whereby their patients were blinded to the intervention.

ADÈQUACIE DE BLINDING

The physical properties of helium (and Heliox) create a unique situation with regard to the use of dual gas mixtures. Heliox, which contains 79% helium and 21% oxygen, reduces the work of breathing during exercise by decreasing the airway resistance. This is because helium has a lower density than oxygen, which results in less airway resistance and thus less work per breath. This reduction in work of breathing can lead to a decrease in the dyspnoea experienced by patients during exercise.

The close monitoring of patient symptoms is crucial in clinical studies, as patients may report changes in dyspnoea after receiving the intervention. It is therefore essential to use a proper blinding method to ensure that the results obtained are not influenced by the patients' knowledge of the intervention. In this study, four studies [28, 32, 34, 35] used a single blind methodology, while one study [31] used a double blind approach. The remaining two studies [31, 34] did not use blinding and their results may be biased.

The results obtained from this study suggest that Heliox is a promising intervention for improving dyspnoea and exercise capacity in patients with COPD. Further research is needed to confirm these findings and to explore the long-term benefits of using Heliox in clinical practice.

The authors of the study acknowledge the limitations of the current study, including the small sample size and the lack of long-term follow-up. They recommend further research to investigate the long-term effects of Heliox on patients with COPD.

In conclusion, the use of Heliox in patients with COPD may provide significant benefits in terms of reducing dyspnoea and improving exercise capacity. However, further research is needed to confirm these findings and to explore the optimal use of Heliox in clinical practice.
exercise [28, 34, 35]; however, only Palange et al. [34] provided details regarding the consistency of the inspiratory resistances of the breathing apparatuses between both inhaled gas mixtures.

OUTCOME MEASURES: DYSPNOEA
The assessment of dyspnoea was not a primary consideration in any of the studies. The majority of studies included only brief anecdotal comments concerning the symptom of dyspnoea and were predominantly focused on changes in exercise intensity or duration. Four different measures of dyspnoea were reported in the eight studies (table 6). A perceived rate of exertion scale (Borg scale with either 10 or 20 points) was used by five of the studies [28, 29, 32, 33, 35], while Laude et al. [31] supplemented the Borg scale with a 100 mm VAS. Palange et al. [34] used a 12 point VAS scale to assess both dyspnoea and leg fatigue while Johnson et al. [30] used patient satisfaction questionnaires after pulmonary rehabilitation (ratings of better or worse for both overall condition and exercise tolerance). Dyspnoea was reported by Oelberg et al. [33], but it was unclear which dyspnoea tools were used to assess dyspnoea. Half of the studies included in this review reported significant reductions in dyspnoea outcome measures.

OUTCOME MEASURES: EXERCISE
With the exception of Laude et al. [31], all other studies included at least one maximal CPET to determine maximal exercise intensity prior to intervention. Four studies [28, 30, 33, 35] used maximal intensity tests to monitor changes, while Palange et al. [34] and Eves et al. [29] used constant work rate tests at 80% and 60% of maximum, respectively. Laude et al. [31] used incremental shuttle walk tests. Richardson et al. [35] also included single leg extensor exercise in addition to CPET, on the basis that this allowed the more accurate study of a functionally isolated skeletal muscle group.

The greatest changes associated with breathing Heliox were seen in endurance outcomes derived from exercise tests. Table 7 presents the outcome measures where significant differences were calculated between interventions. Only two studies [31, 33] did not find significant differences between the intervention groups.

The majority of the studies included in this review did not report reliability and validity of their protocols. Palange et al. [34] re-evaluated over half of their research participants using identical study protocols in order to confirm the repeatability.
of their protocol. It may be assumed that researchers reporting extensive cardiorespiratory parameters associated with exercise would calibrate equipment prior to use and that calibration would be performed under both control and experimental conditions. As Heliox has a lower density than room air, calibration using room air only could potentially lead to under- or overestimates in ventilator parameters under Heliox conditions. Four studies provided comment on the calibration of the equipment used to generate their data, but only two studies [29, 34] explicitly stated that equipment was calibrated under both conditions prior to use.

CONCLUSION

Despite Heliox’s strong safety profile and multiple applications, the potential benefit of Heliox as an adjunct therapy to modify disease related symptoms and exercise capacities in obstructive lung diseases has only relatively recently been subject to investigation. The proposed mechanism by which Heliox alters exercise performance for people with obstructive lung conditions is through attenuated work of breathing, presumably from a reduction in airflow turbulence and dynamic hyperinflation. In theory, Heliox inhalation will reduce the driving pressures associated with the inspiratory and expiratory cycles and reduce the work of breathing. Such a reduction should be reflected in the perceptual experience of breathlessness and, hence, dyspnoea outcomes.

Overall, the eight studies included in this review presented a case for high level, low risk of bias evidence to support Heliox’s effectiveness in improving the intensity and endurance of exercise when compared to room air for people with COPD. However, little data was available to explore whether Heliox altered the sensation of dyspnoea during exercise.

This review demonstrated that, despite some very well designed studies exploring the use of Heliox, there was little consistency in exercise challenge modalities, outcome measures for exercise or dyspnoea, and the lack of published change scores made secondary analysis and calculation of pooled effect sizes unachievable. In addition, potentially suboptimal sample sizes in many cases prevent broader conclusions about actual or

| TABLE 6 Summary of dyspnoea outcomes |
|-------------------------------------|
| **Author [Ref.]** | **Dyspnoea parameter** | **Findings relating to dyspnoea** |
| BABB [28] | 20 point BS | No change to work of breathing |
| EVES [29] | 10 point BS | Decreased dyspnoea* |
| JOHNSON [30] | PSQ | No change to BS; 55% (He group) reported increased PROs |
| LAUDE [31] | 10 point BS and VAS | Decreased dyspnoea (BS and VAS)*** (all gas mixes) |
| MARCINIUK [32] | 10 point BS | No change Heliox compared to room air |
| OELBERG [33] | PROs | Decreased dyspnoea* |
| PALANGE [34] | 12 point VAS | Decreased dyspnoea* (Heliox isotime only) |
| RICHARDSON [35] | 10 point BS | No change in dyspnoea |

BS: Borg scale; PSQ: Patient Satisfaction Questionnaire; PRO: patient-reported outcome; VAS: visual analogue score. *: p<0.05; ***: p<0.001. #: reported only (no statistical analysis performed).

| TABLE 7 Summary of exercise outcomes |
|-------------------------------------|
| **Author [Ref.]** | **Exercise tests** | **Findings relating to exercise (at symptom limitation)** |
| BABB [28] | Three maximal symptom-limited incremental CPETs | Increased ventilation (Heliox²)*** |
| EVES [29] | One symptom-limited CPET and four constant rate CPETs (60% WRmax) | Increased ventilation (Heliox²)†, increased endurance time (Heliox², Heliox³ and O₂ 28%)* |
| JOHNSON [30] | Three maximal symptom limited CPETs (treadmill) pre/post 6-week pulmonary rehab (exercise and education) | No training benefits Heliox² and NIPPV |
| LAUDE [31] | Incremental shuttle walk tests | Increased walk distance*** (all gas mixes) |
| MARCINIUK [32] | One maximal symptom limited CPET and 6MWT, and four 6MWTs on two visits | Increased walk distance*** (Heliox²⁹) |
| OELBERG [33] | Two incremental CPETs | No change in peak work loads |
| PALANGE [34] | One maximal symptom limited CPET and two constant rate CPETs | Increased endurance*** (Heliox²¹), no significant improvements in lung mechanics |
| RICHARDSON [35] | Three incremental maximal CPETs and single knee extensor ergometry testing | Increased peak work*, increased ventilation* (Heliox²¹) |

CPET: cardiopulmonary exercise testing; WRmax: maximal work rate; NIPPV: noninvasive positive pressure ventilation; 6MWT: 6-min walk test. *: p<0.05; ***: p<0.001.
potential benefits of Heliox for altering the sensation of breathlessness during exercise for people with COPD. Further high level, low risk of bias research is required to investigate whether Heliox alters the qualitative sensation (intensity and distress) during exercise for people with COPD. It is also imperative that, in any future research, a strong emphasis is placed on reporting standardised outcome measures as well as change scores.

STATEMENT OF INTEREST

T. Hunt has received a seed funding grant of AUD5,000 from Foundation Daw Park as part of the medical research grant programme. M.T. Williams has received research funding from the Cardiorespiratory Australia Physiotherapy Research Foundation and Foundation Daw Park Grants for Medical Research. P. Frith has no competing interest (financial or personal) for which the findings of this report are likely to advantage or disadvantage an organisation, employer or individual. P. Frith may have potential conflicts of interest of a general nature not relevant to this research: he has served on national and global advisory boards for pharmaceutical companies in the past 5 yrs (AltanaPharma, AstraZeneca, Boehringer Ingelheim, Bayer Pharmaceuticals, GlaxoSmithKline, Nycomed and Pfizer), for which honoraria were paid, has participated in many multicentre clinical trials for these and other pharmaceutical companies for which his institution was paid fees, and has received honoraria for lectures and workshops with general practitioners and physicians from Altana Pharma, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Pfizer Australia. He has received financial assistance to attend national and international scientific congresses from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline. Neither P. Frith nor members of his family hold shares in any health-related companies. D Schembri was included in the receipt of a seed funding grant of AUD5,000 from Foundation Daw Park as part of the medical research grant programme.

REFERENCES

1 O’Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2006; 3: 180–184.
2 O’Donnell DE, Laveneziana P. Dyspnea and activity limitation in COPD: mechanical factors. COPD 2007; 4: 225–236.
3 The COPDX Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2009. www.copdx.org.au/guidelines/documents/COPDX_v2_18.pdf Last updated: April 2009. Date last accessed: September 12, 2009.
4 O’Donnell DE, Hernandez P, Kaplan A, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care. Can Respir J 2008; 15: Suppl. A, 1A–8A.
5 American Thoracic Society. Management of Stable COPD. www.thoracic.org/sections/copd/for-health-professionals/management-of-stable-copd/ Last updated: 2009. Date last accessed: September 12, 2009.
6 Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007; 176: 532–555.
7 Harris PD, Barnes R. The use of helium and xenon in current clinical practice. Anesthesia 2008; 63: 284–293.
8 Oliver BM, Farrar H, Bradley JG. Helium concentration in the earth’s lower atmosphere. Geochim Cosmochim Acta 1984; 48: 1759–1767.
9 Hess DR, Fink JB, Venkataraman ST, et al. The history and physics of Heliox. Respir Care 2006; 51: 608–612.
10 Barach AL. The use of Heliox in the treatment of asthma and obstructive lesions in the larynx and trachea. Am Intern Med 1935; 9: 739–765.
11 Reuben AD, Harris AR. Heliox for asthma in the emergency department; a review of the literature. Emerg Med J 2004; 21: 131–135.
12 Spiteri DL, Horvath SM, Kobayashi K, et al. Work performance breathing normoxic nitrogen or helium gas mixtures. Eur J Appl Physiol Occup Physiol 1980; 43: 157–166.
13 Hutcheon MA, Rodarte JR, Hyatt RE. Effect of breathing helium-oxygen on static lung volumes and lung recoil in normal men. J Appl Physiol 1977; 41: 899–902.
14 Ho AM, Lee A, Karmakar MK, et al. Heliox versus air-oxygen mixtures for the treatment of patients with acute asthma: a systematic overview. Chest 2003; 123: 882–890.
15 Jaber S, Fodil R, Carlucci A, et al. Noninvasive ventilation with helium-oxygen in acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 161: 1191–1200.
16 Jollét P, Tassaux D, Thouret JM, et al. Beneficial effects of heliox:oxygen versus air:oxygen noninvasive pressure support in patients with decompensated chronic obstructive pulmonary disease. Crit Care Med 1999; 27: 2422–2429.
17 Jollét P, Tassaux D, Roeseler J, et al. Helium–oxygen versus air–oxygen noninvasive pressure support in decompensated chronic obstructive disease: a prospective, multicentre study. Crit Care Med 2003; 31: 878–884.
18 Esquinas AM, Diaz G, Del Bano AC, et al. Heliox during non-invasive mechanical ventilation in COPD. A randomized controlled pilot study. Am J Respir Crit Care Med 2001; 163: A678.
19 Eves ND, Ford GT. Helium–oxygen: a versatile therapy to “lighten the load” of chronic obstructive pulmonary disease. Respir Med COPD Update 2007; 3: 87–94.
20 Papamoschou D. Theoretical validation of the respiratory benefits of helium–oxygen mixtures. Respir Physiol 1995; 99: 183–190.
21 O’Donnell DE, Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. Eur Respir Rev 2006; 15: 61–67.
22 Calverley PM, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. Eur Respir J 2005; 25: 186–199.
23 O’Donnell DE, Banzett BB, Carriero-Kohlman V, et al. Pathophysiologic of dyspnea in chronic obstructive pulmonary disease – a roundtable. Proc Am Thorac Soc 2007; 4: 145–168.
24 Williams M, Cafarella P, Olds T, et al. The language of breathlessness differentiates between patients with COPD and age-matched adults. Chest 2008; 134: 489–496.
25 Williams MT, Garrard A, Cafferela P, et al. Quality of recalled dyspnea is different from exercise-induced dyspnoea: an experimental study. Aust J Physiother 2009; 55: 177–183.
26 von Leupoldt A, Balewski S, Petersen S, et al. Verbal descriptors of dyspnea in patients with COPD at different intensity levels of dyspnea. Chest 2007; 132: 141–147.
27 Lewis LJ, Williams MT, Olds T. Short-term effects on the mechanism of intervention and physiological outcomes but insufficient evidence of clinical benefits for breathing control: a systematic review. Aust J Physiother 2007; 53: 219–227.
28 Babb TJ. Breathing He–O2 increases ventilation but does not decrease the work of breathing during exercise. Am J Respir Crit Care Med 2001; 163: 1128–1134.
29 Eves ND, Petersen SR, Haykowsky MJ, et al. Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 174: 763–771.
30 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: 464–472.
31 Laude EA, Duffy NC, Baveystock C, 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: 865–870.
32 Marciniuk DD, Butcher SJ, Reid JK, et al. The effects of helium-hyperoxia on 6-min walking distance in COPD – a randomised controlled trial. *Chest* 2007; 131: 1659–1665.

33 Oelberg DA, Kacmarek M, Pappagianopoulos PP, et al. Ventilatory and cardiovascular responses to inspired He–O₂ during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: 1876–1882.

34 Palange P, Valli G, Onorati P, et al. Effect of Heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. *J Appl Physiol* 2004; 97: 1637–1642.

35 Richardson RS, Sheldon J, Poole DC, et al. Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 881–885.