Eur Respir Rev 2010; 19: 115, 30–38
DOI: 10.1183/09059180.00006009

REVIEW

Heliox, dyspnoea and exercise in COPD

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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**

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Received:
Oct 14 2009
Accepted after revision:
Nov 24 2009

PROVENANCE
Submitted article, peer reviewed.

European Respiratory Review
Print ISSN 0905-9180
Online ISSN 1600-0617

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 mixes, created when the nitrogen component of an inhaled gas mixtures 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’’

FIGURE 1. Evolution of the use of Heliox in medicine.

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	Exercise	Dyspnoea
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 and associated MeSH terms	Heliox
Academic Search File (EBSCOhost)	COPD, COAD, pulmonary emphysema and associated MeSH terms	Dyspnoea and associated MeSH terms	Exercise, physical exercise and associated MeSH terms	Heliox
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

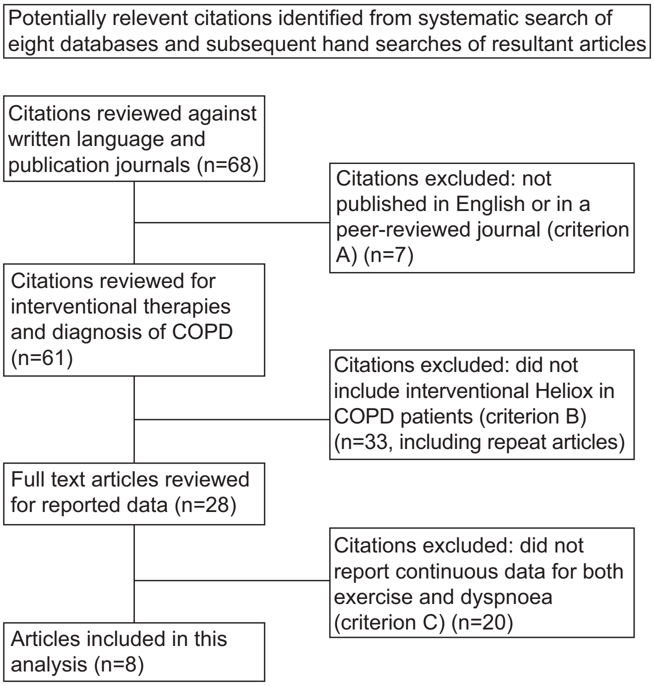

FIGURE 2. Graphical representation of the outcomes of the search strategy. COPD: chronic obstructive pulmonary disease.

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 α_1-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 Heliox^{21} (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 (Heliox^{28}) intervention arm. Marciniuk *et al.* [32] included 30% oxygen in balance helium mixture (Heliox^{30}) 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 2 Lewis Olds Williams scaling results for unintended methodological bias

	Babb [28]	Eves [29]	Johnson [30]	Laude [31]	Marciniuk [32]	Oelberg [33]	Palange [34]	Richardson [35]
Clear focus?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Acceptable recruitment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size justified?	No	No	Yes	Yes	Yes	No	No	No
Separate control groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Well-matched control groups?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Baseline measures or self-controls?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Bias minimisation for outcomes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Accounts for confounding issues?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Results allow for self-determination of sample size	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Plausible results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Score	**8**	**8**	**9**	**9**	**8**	**6**	**8**	**7**

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
Babb [28]	10 patients: COPD (FEV_1 ~78%)	RCT, cross-over	20 point BS	3 maximal symptom-limited incremental CPETs	Heliox[21] and RA	↔ WOB	↑ Ventilation and WR_{max} (Heliox[21]), ↑ Heliox[21#]
Eves [29]	10 patients: COPD (FEV_1 ~47%)	RCT, cross-over	10 point BS	1 symptom-limited CPET and 4 constant rate CPETs (60% WR_{max})	RA, O_2 28%, Heliox[21] and Heliox[28]	↓ Dyspnoea[#] and ↓ WOB	↑ ↑ Heliox[28], ↑ Heliox[21] and O_2 28%, ↑ Ventilation Heliox[21#]
Johnson [30]	39 patients: COPD (FEV_1 ~50%)	RCT, open label	PSQ	3 maximal symptom-limited CPETs (treadmill) pre/post 6-week pulmonary rehabilitation (exercise and education)	Heliox[21], RA and NIPPV	↔ BS, 55% (He group) reported ↑ PROs	↔ Training benefits Heliox[21] and NIPPV
Laude [31]	21 patients: COPD (FEV_1 ~43%)	RCT, cross-over	10 point BS and VAS	Incremental shuttle walk tests	RA, O_2 28%, Heliox[21] and Heliox[28]	↓ Dyspnoea (BS and VAS): all gas mixes[#]	↑ Endurance: all gas mixes[#]
Marciniuk [32]	16 patients: COPD (FEV_1 ~48%)	RCT, cross-over	10 point BS	1 maximal symptom-limited CPET and 6MWT, and 4 6MWTs on 2 visits	RA, 100% O_2 (mask), 100% O_2 (nasal cannula) and Heliox[30]	↔ Heliox to RA BS	Significant ↑ in distance on Heliox[30#]
Oelberg [33]	18 patients: 8 COPD (FEV_1 19%); 10 normal (FEV_1 93%)	Unblinded comparison study	PROs	2 incremental CPETs	Heliox[21] and RA	↓ Dyspnoea PROs[#]	↔ Change in peak work loads
Palange [34]	12 patients: COPD (FEV_1 <50%)	RCT, single blind cross-over	12 point VAS	1 maximal symptom-limited CPET and 2 constant rate CPETs	Heliox[21] and RA	↓ Dyspnoea[#]	↑ Endurance, non-significant improvements in lung mechanics[#]
Richardson [35]	10 patients: COPD (FEV_1 <40%)	Single blinded cross-over	10 point BS	3 incremental maximal CPETs and single knee extensor ergometry testing	Heliox[21], 100% O_2 and RA	↔ Dyspnoea	↑ Peak work, ↑ Ventilation[#]

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; RCT: randomised controlled trial; BS: Borg scale; CPET: cardiopulmonary exercise test (cycle ergometry unless stated); RA: room air; WOB: work of breathing; WR_{max}: maximal work rate; PSQ: Patient Satisfaction Questionnaire; NIPPV: noninvasive positive pressure ventilation; PRO: patient reported outcome; VAS: visual analogue scale; 6MWT: 6-min walk test. [#]: statistically significant finding; ↔: no significant change; ↓ decreased; ↑ increased.

underpowered and as a result, confidence in accepting that no significant differences ($p<0.05$) exist between interventions cannot be assured. Four studies concluded that there were no significant differences between Heliox and the control (room air) for at least one primary outcome measure. One study Johnson *et al.* [30] was unable to analyse complete datasets, due to withdrawals from the pulmonary rehabilitation programme, and failed to provide comment regarding how this incomplete data set impacted upon power estimates. The absence of power determination in the other studies [28, 33] may have led to under-recruitment of patient samples.

ADEQUACY OF BLINDING

The physical properties of helium (and Heliox) create a challenge for blinding subjects and investigators to the intervention. Helium (Heliox) results in noticeable changes in phonics during and immediately after inhalation. Six studies reported using a randomised blinded methodology. Four of these studies [28, 32, 34, 35] used a single blind approach, whereby their patients were blinded to the intervention. Richardson *et al.* [35] and Marciniuk *et al.* [32] commented that they ensured patients did not vocalise throughout each intervention and for a period of 2 and 1 min, respectively, after exercise to ensure the blind was maintained. Babb [28] and Palange *et al.* [34] commented only that their studies were blinded and failed to elaborate further on how this was achieved. The remaining two studies, carried out by Laude *et al.* [31] and Eves *et al.* [29], used a double blind approach and patients were asked not to vocalise throughout each of the tests. Laude *et al.* [31] further asked their participants to refrain from talking for a period of 2 min after exercise. Eves *et al.* [29] asked their participants to refrain from talking for an undisclosed ''short period of time'' after exercise.

Helium gas mixtures are significantly cooler than room air and it is plausible that subjects, during periods of exercise with rapid inhalation would note the difference in inhaled gas temperature. Babb [28] and Eves *et al.* [29] recognised this as a significant confounding issue and attempted to offset it by using humidified air from a reservoir bag. The size of the reservoir bag was not reported by Eves *et al.* [29], while Babb [28] reported using a 2,300 L, heat and tape sealed, 4 mm thick polyethylene reservoir bag. No other studies made reference to helium's thermal conductivity in relation to study blinding.

META-ANALYSIS

Meta-analysis for both of the primary outcome measures (dyspnoea and exercise) could not be undertaken due to heterogeneity of outcome measures, variations in exercise test modalities and insufficient reporting of continuous data (baseline and isotime).

Heliox is known to reduce inspiratory airway resistance, yet comparative studies rarely report procedures for ensuring the inspiratory resistance at different levels of ventilation between experimental conditions is similar. Five studies included commentary concerning issues of matching inspiratory resistance between conditions. One study provided commentary concerning the confounding effect of inspiratory resistance [31], another reported baseline (pre-exercise challenge) airway resistance only [29]. Three studies attempted to measure airways resistance during control and Heliox-modified

TABLE 4 Demographic and lung function information for each individual study

Author [Ref.]	Subjects (M/F)	Age yrs	FEV$_1$ % pred	FVC % pred	FEV$_1$/FVC	TLC % pred	RV % pred	FRC % pred
Babb [**28**]	10 (6/4)	70±3	78±7	98±11	0.61±0.04	106±12		
Eves [**29**]	10 (10/0)	65±11	47±17	83±21	0.56±0.10	136±29	192±63	157±44
Johnson [**30**] (Heliox)	10 (4/6)	62±9	34.1±12.8	57.3±16		108±23	291±66	
Johnson [**30**] (NIPPV)	11 (8/3)	69±9	31.6±9.3	56.9±14.5		111±17	203±63	
Laude [**31**]	82 (57/25)	69.7	42.6±15.5					
Marciniuk [**32**]	16 (7/9)	67±8	55±13	89±12	0.48±0.08	130±15	175±37	
Oelberg [**33**] (Control)	10 (9/1)	60.3±3.2	93±3			105±4		
Oelberg [**33**] (COPD)	8 (2/6)	47±2.3	19±1			132±7		
Palange [**34**]	12 (12/0)	68±8	38±10	76±14				
Richardson [**35**]	10 (4/6)	64.7±7.62	40±11.9					

Data are presented as n or mean±SD, when SD available. M/F: male/female; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; NIPPV: noninvasive positive pressure ventilation; COPD: chronic obstructive pulmonary disease.

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, 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

TABLE 5 Comparison of predetermined sample sizes per outcome measure

Study (exercise method)	Sample size n	Breathlessness (n=24)	Walk distance (n=16)	Endurance (n=39)
Babb [**28**] (CPET)	10	×	NA	×
Eves [**29**] (CPET)	10	×	NA	×
Johnson [**30**] (CPET)	39	✓	✓	✓
Laude [**31**] (ISW)	21	×	✓	×
Marciniuk [**32**] (6MWT)	16	×	✓	×
Oelberg [**33**] (CPET)	18	×	NA	×
Palange [**34**] (CPET)	12	×	NA	×
Richardson [**35**] (CPET)	10	×	NA	×

CPET: cardiopulmonary exercise testing; ISW: incremental shuttle walking; 6MWT: 6-min walk test; ×: insufficient sample size to determine statistical significance; ✓: sufficient sample size to determine statistical significance; NA: not applicable.

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).

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 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 (Heliox^{21})***
Eves [**29**]	One symptom-limited CPET and four constant rate CPETs (60% WRmax)	Increased ventilation (Heliox^{21})*, increased endurance time (Heliox^{28}, Heliox^{21} and O$_2$ 28%)*
Johnson [**30**]	Three maximal symptom limited CPETs (treadmill) pre/post 6-week pulmonary rehab (exercise and education)	No training benefits Heliox^{21} 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*** (Heliox^{30})
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*** (Heliox^{21}), no significant improvements in lung mechanics
Richardson [**35**]	Three incremental maximal CPETs and single knee extensor ergometry testing	Increased peak work*, increased ventilation* (Heliox^{21})

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 AltanaPharma, 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.

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