Alleviating mechanical constraints to ventilation with heliox improves exercise endurance in adult survivors of very preterm birth

Joseph W Duke,[1] Amy M Zidron,[2] Igor M Gladstone,[3] Andrew T Lovering[4]

[1]Department of Biological Sciences, Northern Arizona University, Flagstaff, Arizona, USA
[2]Department of Pediatrics, Ohio University Heritage College of Osteopathic Medicine, Athens, Ohio, USA
[3]Department of Pediatrics, Oregon Health & Science University, Portland, Oregon, USA
[4]Department of Human Physiology, University of Oregon, Eugene, Oregon, USA

Correspondence to
Dr Joseph W Duke, Department of Biological Sciences, Northern Arizona University, Flagstaff AZ 86011, USA; JJ.Duke@nau.edu

Received 14 July 2018
Revised 17 August 2018
Accepted 27 August 2018

To cite: Duke JW, Zidron AM, Gladstone IM, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2018-212346

ABSTRACT

Adult survivors of very preterm birth (PRET) have significantly lower aerobic exercise capacities than their counterparts born at term (CONT), but the underlying cause is unknown. To test whether expiratory flow limitation (EFL) during exercise negatively affects exercise endurance in PRET, we had PRET and CONT exercise to exhaustion breathing air and again breathing heliox. In PRET, EFL decreased and time-to-exhaustion increased significantly while breathing heliox. Heliox had a minimal effect on EFL and had no effect on time-to-exhaustion in CONT. We conclude that aerobic exercise endurance in PRET is limited, in part, by mechanical ventilatory constraints, specifically EFL.

INTRODUCTION

Adult survivors of preterm birth (PRET) have impaired pulmonary function[1–6] and a lower aerobic exercise capacity than their counterparts born at term (CONT).[1–5] The precise cause of the lower aerobic exercise capacity in PRET is unknown, but based on the characteristics of their respiratory system, could be impaired pulmonary gas exchange efficiency, mechanical ventilatory constraints and/or dyspnoea.

Impaired pulmonary gas exchange efficiency has not been detected in PRET relative to CONT[1 2 7] even when PRET with a clinically mild reduction in diffusion capacity for carbon monoxide (DL_{CO}) exercised while breathing hypoxic gas.[2] Our work demonstrates that PRET have significant mechanical ventilatory constraints, specifically expiratory flow limitation (EFL), during exercise.[3 4] PRET may have smaller airways than CONT,[3] which would predispose them to having EFL. Breathing heliox (79% helium, 21% O_2) during exercise lessens airflow resistance and EFL and, thus, allows previously constrained ventilation to increase.[8] Indeed, heliox has been shown to alleviate EFL and increase exercise endurance in patients with COPD.[9]

Therefore, the purpose of this study was to determine if breathing heliox during exercise decreases EFL and increases exercise endurance in PRET.

METHODS

Subjects

Thirty-three participants provided written informed consent prior to participation. Subjects included in the PRET group were born ≥8 weeks premature whether or not they had bronchopulmonary dysplasia (BPD). Diagnosis and classification of preterm birth and BPD, as well as matching of CONT subjects was done, as before.[1–5]

Visits 1–2

Baseline pulmonary function and DL_{CO} and aerobic exercise capacity (VO_{2peak}) and peak power output were determined on visits 1 and 2, respectively, as before.[1–5]

Visits 3–5

Subjects performed three constant load cycling time-to-exhaustion (TTE) trials at 80% of peak power output, as before.[9] The protocol was identical between trials. Metabolic and ventilatory data throughout each trial and flow-volume loops (FVLs) were collected, as before.[3 4 10] The extent of EFL (%EFL) was determined based on the percentage of the tidal volume that met or exceeded the maximal FVL, as before.[3 4 10] Visit 3, performed while breathing air, served as a familiarisation trial. During the remaining TTEs, subjects were provided identical verbal feedback including standardised statements regarding the maintenance of cycling cadence. The gas composition (air or heliox) of the remaining TTEs was blinded to the subjects and they were not allowed to speak for the duration of the trials due to the effects of helium on the vocal chords. The hypothesised effect of heliox was not described to the subjects. We had subjects perform the air TTE first (visit 4) so we could identify the time of exercise termination and collect FVLs at 'iso-time' during the heliox TTE since we expected the PRET would exercise for longer with heliox. External resistance was matched between trials.[8] TTEs were terminated when cycling cadence decreased by 10%–15%, and subjects failed to increase it with encouragement.

Data analysis

All statistical analyses were performed using GraphPad Prism statistical software (V.7.0a), and alpha was set a priori to p=0.05. Tests described in table/figure legends.

RESULTS

Descriptive information

PRET were born at 27.9±1.9 weeks gestation and weighed 1.15±0.41 kg. In general, PRET had worse pulmonary function than CONT and had a significantly lower VO_{2peak} and peak power output (table 1).

Time-to-exhaustion

There was no difference in TTE between groups in either trial, however, they exercised at significantly different workloads so this was expected (figure 1).

Table 1 Anthropometric, VO_{2peak}, resting pulmonary function and diffusion capacity data

	CONT, n=16 (9 women)		PRET, n=17 (9 women)	
Age, year	22±2		21±2	
Height, cm	170±12		169±13	
Weight, kg	70±13		67±14	
VO_{2peak}, mL/kg/min	41.0±7.2	(97±9)	36.9±6.6*	(86±13)*
Peak power output, W	255±74	(127±19)	215±64	(110±28)*
FVC, L	4.7±1.2	(100±6)	4.3±1.2	(94±11)*
SVC, L	4.9±1.4	(106±16)	4.5±1.1	(96±12)*
FEV_1, L	4.0±1.0	(100±7)	3.4±1.0*	(86±17)*
FEV_1/FVC, %	86±5	(99±5)	78±11*	(90±12)*
FEF_{25-75}, L s	4.4±1.4	(101±25)	3.1±1.3*	(71±26)*
FRC pleth, L	3.2±0.9	(108±27)	3.2±0.9	(107±17)
IC, L	3.1±0.8	(112±16)	2.9±1.1	(98±22)*
ERV, L	1.7±0.8	(101±36)	1.6±0.6	(92±25)
RV, L	1.3±0.5	(100±40)	1.6±0.4	(123±31)*
TLC, L	6.3±1.4	(106±15)	6.1±1.7	(101±14)
DL_{CO}, mL/min/mm Hg	33.3±9.4	(122±16)	30.5±7.2	(115±11)

All values are mean ±SD. Values in parentheses are mean ±SD% of predicted.
*P<0.05 compared with CONT using independent samples t-tests.
DL_{CO}, diffusion capacity for carbon monoxide; ERV, expiratory reserve volume; FEF_{25-75}, forced mid-expiratory flow; FRC pleth, functional residual capacity determined by whole body plethysmography; IC, inspiratory capacity; RV, residual volume; SVC, slow vital capacity; TLC, total lung capacity; VO_{2peak}, peak oxygen consumption.

PRET had a significant (p<0.05) increase in TTE from air to heliox while CONT had no change (figure 1).

Expiratory flow limitation

PRET had a significantly greater %EFL than CONT in both trials (p<0.05) and had a significant reduction in %EFL in heliox (p<0.001; figure 2).

DISCUSSION

Breathing heliox significantly reduced EFL and resulted in an increase in TTE and minute ventilation (V_E) in PRET, but had no effect on TTE in CONT presumably because they had minimal EFL. These data suggest that mechanical constraints to ventilation are a contributing factor limiting aerobic exercise performance in PRET.

Mechanical ventilatory constraints include several inter-related aspects of the ventilatory response to exercise such as EFL, a significant reduction in inspiratory reserve volume (IRV), dyspnoea and/or dynamic hyperinflation. We found that TTE increased significantly when EFL was decreased. Heliox reduces airflow resistance,[8] thereby increasing the maximal attainable expiratory airflow rate and expanding the maximum FVL, and consequently increasing maximal ventilatory capacity. Because CONT had minimal EFL while breathing air, there was minimal effect on TTE breathing heliox. These data support our hypothesis that EFL contributes to a lower aerobic exercise performance in PRET.

A reduction in IRV to <1.0 L has been shown to correspond to a mismatch in respiratory effort and tidal volume response resulting in intolerable dyspnoea and exercise termination in patients with COPD.[11 12] Our previous[4] and current work demonstrate PRET had a decline in IRV to <1.0 L at end exercise while breathing air and heliox. However, in the heliox trial, PRET were able to exercise for longer, perhaps because the respiratory effort was lessened with heliox, which is supported by a significant reduction in dyspnoea rating (median; 9 vs 6). In CONT, there was a similar reduction in IRV, but they did not exercise for longer nor did their dyspnoea rating at iso-time differ between trials (8 vs 8). These data suggest that a reduction in IRV may play a role in exercise termination via its effect on dyspnoea.

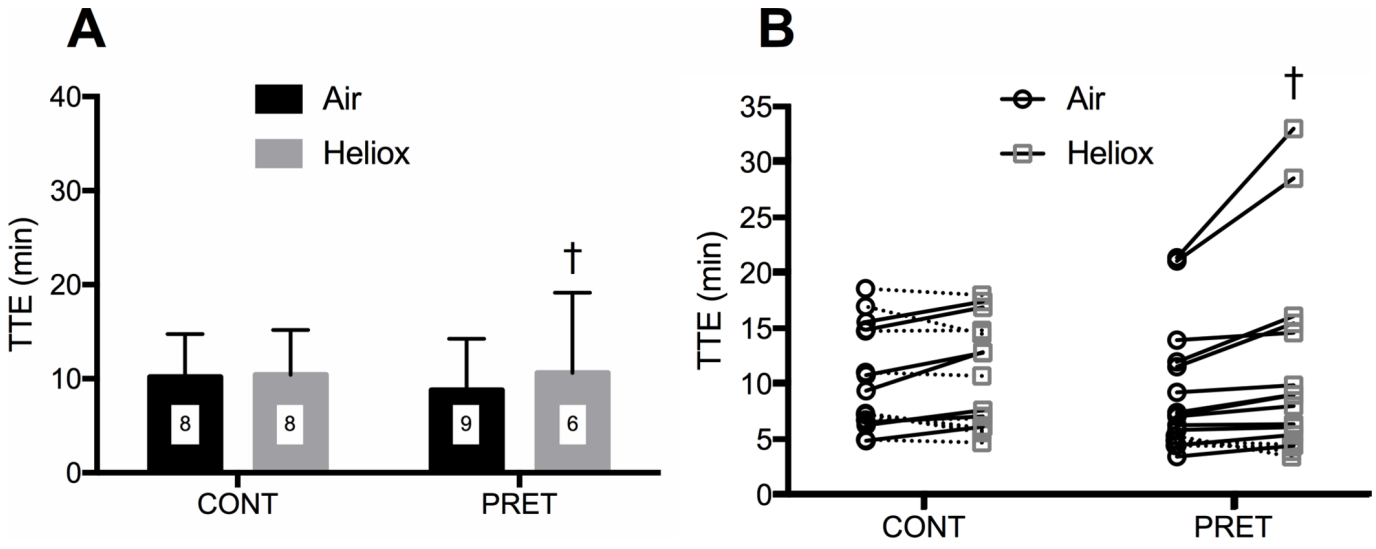

Figure 1 (A) Mean±SD time-to-exhaustion (TTE) in min in counterparts born at term (CONT) and preterm birth (PRET) groups during exercise breathing air (black) and heliox (grey). There was no difference in TTE between CONT and PRET while breathing either gas. PRET had a significant increase in TTE while breathing heliox compared with while breathing air (†). CONT had no change in TTE while breathing heliox compared with while breathing air. Numbers inside of the bars are the median dyspnoea rating acquired at iso-time. PRET had a significant reduction in dyspnoea with heliox computed with a Wilcoxon matched pairs signed rank test. (B) Individual data in CONT and PRET. Solid lines represent subjects that increased TTE and dashed lines represent subjects that had no change or a decrease in TTE. Two-way analysis of variance (ANOVA) with Tukey honestly significant difference (HSD) post hoc test was computed to identify group and gas differences on TTE.

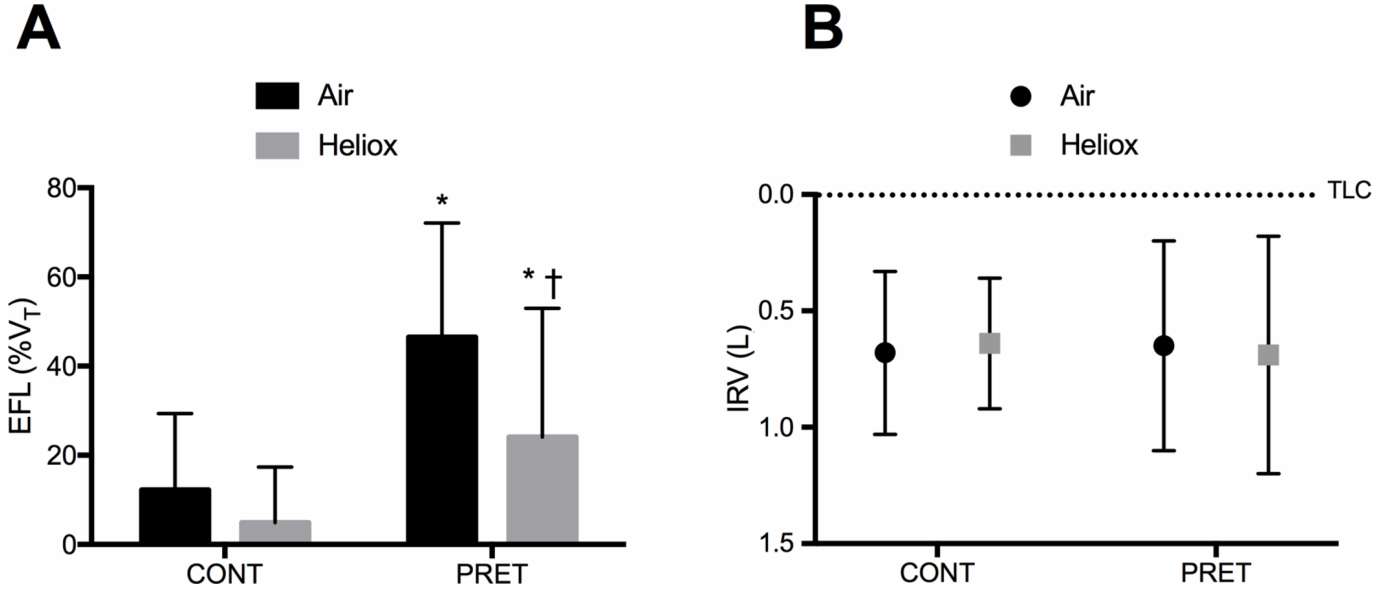

Figure 2 (A) Mean ±SD of the extent of expiratory flow limitation (EFL) as a % of tidal volume (V_T) in counterparts born at term (CONT) and preterm birth (PRET) at iso-time of exercise while breathing air (black) and heliox (grey). PRET had significantly greater EFL during air and heliox trials compared with CONT (*). Breathing heliox during exercise significantly reduced the extent of EFL in PRET (†). We did not correct %EFL for the effect of thoracic gas compression and/or exercise-induced bronchodilation so the magnitude of EFL is an overestimation. However, and importantly, the repeated measures design means that this overestimation was systematic and equal across trials since the compressibility of nitrogen and helium are not different. Two-way analysis of variance (ANOVA) with Tukey honestly significant difference (HSD) post hoc test was computed to identify group and gas differences on %EFL. (B) Mean ±SD of inspiratory reserve volume (IRV) at iso-time in CONT and PRET while breathing air (black circle) and heliox (grey square). There was no difference between groups or trials as determined with a two-way ANOVA. TLC, total lung capacity.

Limitations

Subjects performed the air TTE first and the heliox TTE second. Thus, the increase in exercise endurance while breathing heliox could be due to a 'practice effect' rather than a physiologic effect. However, there was no difference in TTE between the practice and air trials so we believe our findings represent a positive physiologic effect from heliox. Additionally, subjects were blinded to the gas they breathed and were not told what the proposed effects of helium were.

In conclusion, our data support the hypothesis that exercise endurance in PRET is primarily limited by excessive mechanical ventilatory constraints, principally EFL. When these constraints are reduced, then dyspnoea decreases and endurance time increases.

Correction notice This article has been corrected since it was published Online First. The city for affiliation 4 was incorrect.

Acknowledgements The authors thank the subjects for their participation. We also thank Tyler Mangum, Jon Elliott, Jim Davis, Dillan Firestone, Elizabeth Vulgamore, Annarose Schneider, and Kelsey Ball for assistance with data collection and analysis.

Contributors JWD, IMG, ATL: conception and design of experiments. JWD, ATL: financial support. JWD, AMZ, IMG, ATL: collection and assembly of data; data analysis and interpretation; manuscript writing and final approval of manuscript.

Funding This research was supported by an American Heart Association Scientist Development Grant #2280238 (ATL); American Physiological Society's Giles F Filley Memorial Award for Excellence in Respiratory Physiology and Medicine (ATL); Medical Research Foundation of Oregon Early Clinical Investigator Award (JWD) and Ohio University Research Committee award (JWD).

Competing interests None declared.

Patient consent Not required.

Ethics approval University of Oregon's Office of Responsible Conduct of Research and Ohio University Office of Research Compliance.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Lovering AT, Laurie SS, Elliott JE, *et al*. Normal pulmonary gas exchange efficiency and absence of exercise-induced arterial hypoxemia in adults with bronchopulmonary dysplasia. *J Appl Physiol* 2013;115:1050–6.
2 Duke JW, Elliott JE, Laurie SS, *et al*. Pulmonary gas exchange efficiency during exercise breathing normoxic and hypoxic gas in adults born very preterm with low diffusion capacity. *J Appl Physiol* 2014;117:473–81.
3 Duke JW, Gladstone IM, Sheel AW, *et al*. Premature birth affects the degree of airway dysanapsis and mechanical ventilatory constraints. *Exp Physiol* 2018;103:261–75.
4 Lovering AT, Elliott JE, Laurie SS, *et al*. Ventilatory and sensory responses in adult survivors of preterm birth and bronchopulmonary dysplasia with reduced exercise capacity. *Ann Am Thorac Soc* 2014;11:1528–37.
5 Laurie SS, Elliott JE, Beasley KM, *et al*. Exaggerated increase in pulmonary artery pressure during exercise in adults born preterm. *Am J Respir Crit Care Med* 2018;197:821–3.
6 Halvorsen T, Skadberg BT, Eide GE, *et al*. Pulmonary outcome in adolescents of extreme preterm birth: a regional cohort study. *Acta Paediatr* 2004;93:1294–300.
7 Farrell ET, Bates ML, Pegelow DF, *et al*. Pulmonary gas exchange and exercise capacity in adults born preterm. *Ann Am Thorac Soc* 2015;12:150608162646009–7.
8 Babb TG. Breathing He-O_2 increases ventilation but does not decrease the work of breathing during exercise. *Am J Respir Crit Care Med* 2001;163:1128–34.
9 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;97:1637–42.
10 Duke JW, Stickford JL, Weavil JC, *et al*. Operating lung volumes are affected by exercise mode but not trunk and hip angle during maximal exercise. *Eur J Appl Physiol* 2014;114:2387–97.
11 O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. *J Appl Physiol* 2006;101:1025–35.
12 Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? *Eur Respir J* 2012;40:322–9.