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ORIGINAL ARTICLE

Breathing a low-density gas reduces respiratory muscle force development and marginally improves exercise performance in master athletes

Toni Haddad[1,2,3] · Valentin Mons[1,2,6] · Olivier Meste[4] · Jerome A. Dempsey[5] · Chris R. Abbiss[3] · Jeanick Brisswalter[1,2] · Gregory M. Blain[1,2]

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Abstract

Introduction We tested the hypothesis that breathing heliox, to attenuate the mechanical constraints accompanying the decline in pulmonary function with aging, improves exercise performance.

Methods Fourteen endurance-trained older men (67.9 ± 5.9 year, $\dot{V}O_{2max}$: 50.8 ± 5.8 ml/kg/min; 151% predicted) completed two cycling 5-km time trials while breathing room air (i.e., 21% O_2–79% N_2) or heliox (i.e., 21% O_2–79% He). Maximal flow–volume curves (MFVC) were determined pre-exercise to characterize expiratory flow limitation (EFL, % tidal volume intersecting the MFVC). Respiratory muscle force development was indirectly determined as the product of the time integral of inspiratory and expiratory mouth pressure ($\int P_{mouth}$) and breathing frequency. Maximal inspiratory and expiratory pressure maneuvers were performed pre-exercise and post-exercise to estimate respiratory muscle fatigue.

Results Exercise performance time improved (527.6 ± 38 vs. 531.3 ± 36.9 s; $P = 0.017$), and respiratory muscle force development decreased during inspiration (− 22.8 ± 11.6%, $P < 0.001$) and expiration (− 10.8 ± 11.4%, $P = 0.003$) with heliox compared with room air. EFL tended to be lower with heliox (22 ± 23 vs. 30 ± 23% tidal volume; $P = 0.054$). Minute ventilation normalized to CO_2 production ($\dot{V}_E/\dot{V}CO_2$) increased with heliox (28.6 ± 2.7 vs. 25.1 ± 1.8; $P < 0.001$). A reduction in MIP and MEP was observed post-exercise vs. pre-exercise but was not different between conditions.

Conclusions Breathing heliox has a limited effect on performance during a 5-km time trial in master athletes despite a reduction in respiratory muscle force development.

Keywords Aging · Expiratory flow limitation · Pulmonary function · Heliox · Training

Abbreviations

EFL	Expiratory flow limitation
$\dot{V}O_{2max}$	Maximal oxygen consumption
ml	Milliliters
L	Liters
kg	Kilogram
sec	Second
min	Minute
h	Hour
W	Watt
rpm	Rotation per minute
PPO	Peak power output
P_{mouth}	Mouth pressure
MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure
km	Kilometer
TT	Time trial
MFVC	Maximal flow–volume curve

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✉ Toni Haddad
toni.haddad@univ-cotedazur.fr

1 LAMHESS, Sciences et Techniques des Activités Physiques et Sportives, Université Côte d'Azur, 261 Bd du Mercantour, 06200 Nice, France

2 Centre VADER, Université Côte d'Azur, Nice, France

3 Centre for Exercise and Sport Science Research, School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia

4 Lab I3S, Université Côte d'Azur, CNRS, Sophia Antipolis, Nice, France

5 John Rankin Laboratory of Pulmonary Medicine, University of Wisconsin-Madison, Madison, WI, USA

6 LJAD, Université Côte d'Azur, CNRS, Nice, France

TLC	Total lung capacity
RV	Residual volume
FVC	Forced vital capacity
FEV_1	Forced expiratory volume in 1 s
FEF	Forced expiratory flow
IC	Inspiratory capacity
EELV	End-expiratory lung volume
EILV	End-inspiratory lung volume
$\dot{V}_E$	Minute ventilation
F_B	Breathing frequency
V_T	Tidal volume
IRV	Inspiratory reserve volume
$\int Pm$	Integrated P_{mouth} signal over time
$\int Pm \times F_B$	Respiratory muscle force development
Hz	Hertz
CO_2	Carbon dioxide
P_{ET}	End-tidal partial pressure
SpO_2	Hemoglobin oxygen saturation
HR	Heart rate
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}_E/\dot{V}CO_2$	Minute ventilation normalized to CO_2 production
CI	Confidence interval
SD	Standard deviation
WOB	Work of breathing
PAV	Proportional assisted ventilation

Introduction

Aging is associated with numerous structural changes to the respiratory system such as a loss of elastic recoil of the lungs and a stiffening of the chest wall (Johnson and Dempsey 1991). These structural changes impair pulmonary function with a dynamic narrowing of the airways, a reduction in ventilatory reserve, an increase in pulmonary resistance, and an increase in respiratory muscle work to a given ventilation especially when the ventilatory demand is high such as during physical exercise (Janssens et al. 1999; Johnson et al. 1994; Johnson and Dempsey 1991; Molgat-Seon et al. 2018; Smith et al. 2018). It is, however, generally accepted that the healthy respiratory system is "overbuilt" to meet the considerable alveolar ventilation and gas transport demands imposed by exercise in young healthy individuals (Dempsey 1986; Dempsey et al. 1990) and possibly in older individuals. Indeed, even though pulmonary capacity decreases with aging, it appears to remain adequate to meet the decreased metabolic requirements of older individuals. These individuals typically lead a more deconditioned and sedentary lifestyle than their younger counterparts, characterized by factors such as an age-related decline in muscle function and maximal oxygen consumption ($\dot{V}O_{2max}$) (Hawkins and Wiswell 2003; Taylor and Johnson 2010). However, there might be exceptions where the respiratory system limits O_2 transport to exercising locomotor muscles and may therefore limit exercise performance in the elderly.

The long-term practice of endurance exercise training over the lifespan counteracts the negative effects of physical inactivity on the physiological determinants of exercise performance (Coggan et al. 1990; McKendry et al. 2020; Ogawa et al. 1992). For example, older endurance-trained individuals, often referred to as master athletes, present similar skeletal muscle capillarization to younger trained athletes (Coggan et al. 1990) which could prevent the decline in arteriovenous difference in oxygen during exercise observed in older sedentary individuals (Ogawa et al. 1992). As such, older endurance-trained individuals represent a model of successful physiological and healthy aging (Hawkins and Wiswell 2003; Tanaka and Seals 2003). (Hawkins and Wiswell 2003; Tanaka and Seals 2003). Despite the positive effect of chronic exercise on the cardiovascular and muscular systems, it is, however, unclear whether regular training can slow the decline in pulmonary function in older individuals (Degens et al. 2013; McClaran et al. 1995; O'Donovan and Hamer 2018; Pelkonen et al. 2003). It might therefore become challenging for the aging lung to yield the adequate ventilation (110–120 L/min) required to accommodate the locomotor muscle oxygen demand (> 40–45 ml/kg/min) during intense exercise in master athletes (Johnson and Dempsey 1991; Johnson et al. 1991a, b). Specifically, some degree of expiratory flow limitation (EFL) was observed in young trained adults during maximal exercise (Dominelli et al. 2017b; Johnson et al. 1992; Wilkie et al. 2015) and in older healthy individuals during both moderate (Molgat-Seon et al. 2018, 2019) and maximal exercise (Johnson et al. 1991a, b; Johnson et al. 1991a, b; Molgat-Seon et al. 2018). EFL is characterized by the inability of the respiratory system to increase expiratory flow despite the increase in transpulmonary pressure (Johnson and Dempsey 1991). EFL is associated with dynamic hyperinflation (i.e., increase in end-expiratory lung volume above resting values), lower inspiratory reserve volume, and greater respiratory muscle work and effort (Johnson and Dempsey 1991; Johnson et al. 1991a, b; Molgat-Seon et al. 2018). In older trained individuals, the oxygen cost of breathing represents approximately 15–23% of $\dot{V}O_{2max}$ at maximal exercise compared with the 5–7% for the same minute ventilation in young adults (Johnson and Dempsey 1991). Together, the respiratory constraints associated with EFL may provoke/exacerbate exercise-induced respiratory muscle fatigue (Johnson et al. 1993). This can lead to a redistribution of blood flow from locomotor to respiratory muscles (Dominelli et al. 2017a; Harms et al. 1997, 1998) and may exacerbate exercise-induced arterial hypoxemia (Dempsey et al. 2008a, b; Dominelli et al. 2013),

ultimately limiting exercise performance during prolonged high-intensity exercise (i.e., ≥ 85% $\dot{V}O_{2max}$) (Harms et al. 2000). In contrast, heliox was found to alleviate EFL, decrease the work of breathing, and/or increase ventilation in young trained (Dominelli et al. 2013; Mann et al. 2020; McClaran et al. 1998, 1999; Wilkie et al. 2015) and untrained adults (Babb 1997a; Dominelli et al. 2013), as well as in older untrained individuals (Babb 1997b; Molgat-Seon et al. 2019). Yet, the consequences of the reduction of EFL with heliox on exercise performance/tolerance during prolonged maximal exercise are currently unknown in older population and a fortiori in older trained athletes.

We thus aimed to assess the effects of heliox on mechanical ventilatory constraints, respiratory muscle force development and fatigue, and exercise performance during a 5-km cycling time trial in older trained individuals. We hypothesized that, when compared with room air, breathing heliox during strenuous exercise can (i) alleviate expiratory flow limitation, (ii) decrease respiratory muscle force development, thereby reducing exercise-induced respiratory muscle fatigue, and (iii) improve exercise performance.

Methodology

Participants

Fourteen endurance-trained older male participants (age: 67.9 ± 5.9 years, height: 174.2 ± 6.4 cm, body mass: 69.9 ± 7.2 kg, $\dot{V}O_{2max}$: 50.8 ± 5.8 ml/kg/min, representing 151% of predicted values (de Souza et al. 2018)) completed this study. Participants had reported completing running, cycling, and/or triathlon for an average of at least 8 h per week over at least 10 years and were all familiar with cycling at high intensity. Subjects were ineligible for the study if they were current smokers or had previously smoked for more than five years. None of the subjects had current symptoms of cardiovascular, metabolic, or respiratory disease, nor were they taking medication known to interfere with the ventilatory response to exercise. Prior to all visits, participants were requested to refrain from stimulants or depressants (including caffeine or alcohol) and strenuous exercise for 24 h while replicating the same dietary intake. Throughout the duration of the study, participants were asked to maintain regular training commitments.

Participants were informed about the procedures and risks associated with their participation in the study. Prior to data collection, written informed consent was obtained from the participants. All study procedures were approved by the local Human Research Ethics Committee and adhered to the Declaration of Helsinki.

Experimental overview

All participants completed four experimental sessions, each separated by at least 48 h and no more than 10 days, in a single-blind, randomized crossover design. The sessions were performed in the LAMHESS lab (Université Côte d'Azur), and all participants completed the study within 4 weeks. During the first visit, anthropometric measurements and pulmonary function were assessed at rest. Then, participants completed an incremental cycling test starting at 80 W with an increment of 40 W every 2.5 min until volitional exhaustion or a cadence ≤ 60 rpm could not be maintained. Throughout the incremental cycling test, pulmonary ventilation and gas exchange were measured using a respiratory gas analyzer (Metasys TR-M, Brainware, France). Maximal oxygen consumption ($\dot{V}O_{2max}$) was defined as the highest $\dot{V}O_2$ value recorded over a 30 s average and peak power output (PPO) was defined as the power output that elicited $\dot{V}O_{2max}$. During the second visit, participants were thoroughly familiarized with the experimental protocol. Pulmonary function and maximal static mouth pressure (P_{mouth}) during inspiration (MIP) and expiration (MEP) were assessed at rest prior to (PRE) and after (POST) a 5-km cycling time trial (TT). Participants breathed during exercise from a 200L Douglas bag filled with humidified room air. Throughout the time trials, distance was the only feedback provided. Participants were instructed to complete all time trials (i.e., visits 2, 3, and 4) in the fastest time possible. Verbal encouragement was given to the participants. Prior to each time trial, a standardized 5-min warm-up at 50% of PPO was performed. The delay between the warm-up and 5-km TT was 10 min. During visits 3 and 4 (experimental visits), participants replicated the exact same protocol as visit 2 and inhaled either humidified room air or heliox (21% oxygen, 79% helium) during the 5-km TT, in a single-blind, randomized crossover design. Cardiopulmonary indices and P_{mouth} were continuously measured during exercise. All cycling exercises were conducted under supervision on an electromagnetically braked cycle ergometer (Velotron, RacerMate, Seattle, WA) under standard laboratory conditions (20–21 °C, 40–60% relative humidity). All tests were completed at a similar time of day (± 1 h) to avoid any possible effect of the circadian rhythm.

Room air and Heliox breathing

During all experimental sessions participants wore a silicon mask (7450 V2 Mask, Hans Rudolph, KS, USA) connected to a heated pneumotachograph (3813 series, Hans Rudolph, KS, USA). The heated pneumotachograph was connected to a two-way valve (2700 series, Hans Rudolph, KS, USA). The inspiratory valve was connected to a 200 L Douglas bag (1196 series, VacuMed, Ventura, CA, USA),

filled with either normoxic room air (i.e., ~ 21% oxygen; 79% nitrogen) or heliox (i.e., 21% oxygen; 79% helium, Linde, France). The Douglas bag was connected to compressed gas tanks that delivered gas through a humidifier to standardize humidity between trials. Because helium alters the human voice, talking was not allowed throughout the experimental trials to keep the participants blind regarding the gas that they inhaled.

Maximal expiratory flow–volume curves

Participants performed a series of maximal flow–volume curves (MFVC) using the same exact equipment as per during the 5-km TT. MFVC were performed at rest, prior to exercise, seated on the bike, to replicate the position adopted during exercise and to account for the effect of posture on respiratory mechanics (Charlton et al. 2017). Participants were asked to perform a maximal and full expiration from total lung capacity (TLC) to residual volume (RV), followed by a maximal and full inspiration from RV to TLC. Encouragement was provided to ensure that participants were making maximum efforts and that expiration lasted as long as possible (Sylvester et al. 2020). Maneuvers were interspersed by at least 1 min of recovery. Measurements were repeated at least 6 times, and the values reported for the MFVC correspond to the average of the two greatest measurements for each participant. A visual inspection was performed by two operators to confirm the quality of the maneuvers (e.g., sharp increase in flow when forced expiration started, undisrupted and complete expiration) (Sylvester et al. 2020). Pulmonary function was measured from the MFVC and included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, peak expiratory flow at 25%, 50%, and 75% vital capacity (i.e., respectively, $FEF_{25,}$ $FEF_{50,}$ and FEF_{75}), and forced expired flow between 25 and 75% of FVC (FEF_{25-75}). The difference between FVC and FEV_1 between the two greatest MFVCs was less than 0.10 (Sylvester et al. 2020). The assessment of MFVC was performed using room air or heliox, depending on the gas mixture inhaled by participants during the 5-km TT.

Ventilation, operating lung volumes, and expiratory flow limitation

At rest and during exercise, inspiratory and expiratory flows were continuously collected using a 16-channel analog-to-digital data acquisition system (PowerLab/16/35, AD Instruments, Colorado Springs, CO), sampled at 2000 Hz, recorded using LabChart 7.3.7 software, and analyzed using MATLAB R2021b 9.11.0 software. Volume was obtained by numerical integration of the flow signal. The pneumotachograph was calibrated using a 3-L syringe (Hans Rudolph, Kansas, USA) with the same gas mixture (i.e., room air or heliox) used during the experimental session. A syringe was used to perform a manual calibration pre-exercise using six different volumes (0.5, 1, 1.5, 2, 2.5, and 3 L) and three different speeds (slow < 70 L/min, medium around 100-120 L/min, and fast > 150 L/min). A total of five in and out cycles were performed at each volume and each speed, respectively (i.e., 90 data points). Inspiratory capacities (IC) were performed at rest and twice during each kilometer throughout the time trial to determine operational lung volumes and to assess expiratory flow limitation (EFL). The two IC were interspersed by at least 30 s and averaged to characterize a typical pattern for each kilometer. Participants were asked to perform the IC maneuvers by inspiring maximally to TLC from end-expiratory lung volume (EELV). Participants were asked to maintain spontaneous breathing prior to IC maneuvers to ensure that expiration was not forced. A linear correction was applied to the calibrated volume signal over a 10 loops window between n-12 and n-2 (n being the IC maneuver) to account for the well-described drift in flow–volume signal (Guenette et al. 2013; Johnson et al. 1999). This linear correction was applied to the median of each tidal volume (i.e., intermediate point between end-inspiration and end-expiration lung volume) to account for the natural physiological variability of breathing, instead of applying it to each EELV based on the assumption that it remained constant over time (Johnson et al. 1999). The inspiratory capacity was calculated from the averaged values of EELV over the eight breathing cycles, therefore minimizing the risk of underestimation or overestimation of IC induced by a sudden change in end-expiratory lung volume (Guenette et al. 2013). In addition, if any of the EILV among the breaths selected was greater than IC, the maneuver was considered submaximal and therefore excluded. Following a visual inspection by two operators to remove any potential outliers (e.g., swallowing and coughing), the average of eight tidal breaths (from n-10 to n-3 with n being the IC maneuver) was calculated to characterize a representative tidal breath and assess EFL during exercise (described below). The breaths n-2 and n-1 were not considered to ensure that any potential change in breathing pattern (i.e., rate and depth) immediately prior to the IC would not affect the measurements, although participants were instructed to keep breathing naturally and perform the IC maneuver at the end of a normal breath out. The averaged tidal breath was placed within MFVC based on IC. The percent of the tidal flow–volume loop that met or exceeded the expiratory boundary of the MFVC (Johnson et al. 1991a, b; Johnson et al. 1999) was calculated for every kilometer. The severity of EFL was quantified as the percent of the tidal volume that meets or exceeds the boundary of the MFVC (Johnson et al. 1999) over the entire 5-km TT, and EFL prevalence was classified as 5% or greater (17). Minute ventilation ($\dot{V}_E$), breathing frequency (F_B), tidal volume (V_T), inspiratory reserve volume (IRV), end-expiratory lung

volume (EELV), and end-inspiratory lung volume (EILV) were determined from the calibrated and corrected signal for volume measured immediately prior every IC maneuvers as previously described (Guenette et al. 2013).

Respiratory muscle fatigue and respiratory muscle force development

Respiratory muscle fatigue was estimated indirectly by measuring MIP and MEP pre-exercise and post-exercise in a standardized sitting position, using a flanged mouthpiece, with a 1 mm leak, occluded at the distal end (American Thoracic Society/European Respiratory 2002). Participants wore a nose clip during the testing procedure. MIP and MEP were measured at residual volume (RV) and total lung capacity (TLC), respectively. Encouragement was provided to ensure that participants produced a maximal effort for at least 3 s. Maximal pressure was defined as the highest value over a 1 s window. This method and procedure show good inter-test reliability (Romer and McConnell 2004). Baseline measurements (i.e., prior the 5-km TT, PRE) were repeated at least six times in the same order (i.e., MIP before MEP) and the reported pressures correspond to the mean of the three best measurements for both inspiration and expiration, respectively. MIP and MEP measurements were also performed 1 min, 2 min, 4 min, 6 min, 10 min, and 15 min after exercise (POST), with participants seated in the same position as PRE. During exercise, mouth pressure (P_{mouth}) was continuously measured through a port in the mouthpiece (between the mask and the heated pneumotachograph) using a calibrated differential transducer (MLT844, AD Instruments, Colorado Springs, CO, USA) and sampled before every IC (similar to flow and volume). The integrated P_{mouth} signal over time ($\int$Pm) was calculated as the cumulated area under the curve for P_{mouth} divided by the number of breaths (cmH_20/breath) during each km and averaged over the 5-km TT. The product $\int Pm \times F_B$ (cmH_20/breath/min) during inspiration and expiration was also calculated for every km to estimate inspiratory and expiratory muscle force development, respectively (Sheel et al. 2001; Turner et al. 2016; Witt et al. 2007). Mouth pressure was sampled at a rate of 4000 Hz.

Gas exchange, hemoglobin oxygen saturation, heart rate, and blood lactate

Throughout all trials, pulmonary ventilation, gas exchange, and CO_2 end-tidal partial pressure ($P_{ET}CO_2$) were recorded on a breath-by-breath basis using a pneumotachograph (3813 series, Hans Rudolph, KS, USA) and respiratory gas analyzer equipped with a spectrophotometer (Metasys TR-M, Brainware, France). The gas analyzer was calibrated using a reference gas (15% O_2 and 5% CO_2) prior to each test. Oxygen could not be measured when participants inhaled heliox due to the inability of the analyzer to determine oxygen concentration in the presence of helium. Hemoglobin oxygen saturation (SpO_2) was measured using a forehead pulse oximeter (Radical-7; Massimo, Irvine, CA, USA). Heart rate (HR) was continuously measured and sampled at 1 Hz (Polar, RCX5, Polar Electro Oy, Finland). During exercise, similar to ventilation, gas exchange and SpO_2 values were averaged over a 1 km window. Blood lactate concentration (LactatePro, Arkray, Kyoto, Japan) was determined 3 min post-exercise from capillary blood sampled from the fingertip.

Perceptual responses

Participants rated the intensity of "breathing discomfort" (dyspnea) and "leg discomfort" prior to exercise (already equipped with the breathing apparatus) and during the last 15 s of each kilometer pointing a 0–100 Borg CentiMax (CR100) visual analog scale (Borg and Borg 2002). The perceptual response for the last kilometer was given immediately at the end of exercise to limit disturbances during the final effort. Dyspnea was defined as "the sensation of labored or difficult breathing," and leg discomfort was defined as the "sensation of discomfort in the legs." The end points of the scale were anchored such that 0 represented "no breathing/leg discomfort" and 100 represented "the most severe breathing/leg discomfort ever experienced or imagined."

Statistical analysis

The sample size for this study was determined through a power analysis (G*Power 3.1; Dusseldorf, Germany) using previous results for the effects of heliox in male individuals at rest (FEF_{50}; effect size = 1.978) and during exercise ($\dot{V}_E/\dot{V}CO_2$; effect size = 0.784) (Mann et al. 2020). The smallest standardized mean difference was used for the calculation (effect size = 0.784, $\alpha = 0.05$ and power = 0.8) giving a required sample size of 12 participants. To increase the robustness of the analysis and to accommodate a 15% attrition rate, our study included a minimum of 14 participants.

Spirometry data at rest (i.e., PEF, FEF_{25}, FEF_{50}, FEF_{75}, and FEF_{25-75}) were compared under room air vs. heliox using two-sided paired samples *t*-tests. Normality of the distribution was tested and confirmed using a Shapiro–Wilk test. Performance variables (i.e., time, power, cadence, SpO_2, heart rate, lactate), ventilatory indices (i.e., %EFL, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, $\dot{V}CO_2$, $P_{ET}CO_2$, F_B, V_T, IRV, EELV, EILV), mouth pressure (indicative of pressure developed by the respiratory muscles, $\int P_{mouth}$), respiratory muscle force development (i.e., $\int P_{mouth} \times F_B$), and perceptual response (i.e., breathing discomfort and leg discomfort were compared under two conditions (i.e., room air vs.

heliox) using a linear mixed model to accommodate for missing data and determine the variation attributable to participants. Condition was set as a fixed effect and participants were set as random effect. Because $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, $P_{ET}CO_2$, and F_B were different between conditions, we also set distance as a fixed effect in the linear mixed model to compare the estimated trends (i.e., slope/rate of increase) throughout the time trial ($\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, $P_{ET}CO_2$, or F_B were set as dependent variables, and participants were set as random effect). Assumptions of residuals normality and homoscedasticity were confirmed by inspecting residuals plots. Change in maximal inspiratory and expiratory pressures (i.e., MIP, MEP) pre-exercise vs. post-exercise was compared between conditions using a two-way analysis of variance (ANOVA) with repeated measures. Effect size was assessed using Cohen's d index and considered as small ($d < 0.35$), medium ($0.35 < d < 0.65$), or large ($d > 0.65$) (Cohen 1988). 95% confidence interval (CI) for effect size was presented as [lower limit, upper limit]. Statistical significance was set at $P < 0.05$. All data are presented as means ± SD. Statistical analysis was performed using JASP 0.16 software.

Table 1 Baseline pulmonary function indices ($n = 13$)

	Measured	Predicted (%)
FVC (L)	4.25 ± 0.59	106 ± 17
FEV_1 (L)	3.09 ± 0.51	106 ± 21
FEV_1/FVC	73 ± 7	99 ± 9
FEF_{25-75} (L/sec)	2.76 ± 1.03	106 ± 39
MIP (cmH_2O)	101 ± 23	116 ± 26
MEP (cmH_2O)	145 ± 32	102 ± 22

FVC—forced vital capacity; *FEV_1*—forced expiratory volume in 1 s; *FEF_{25-75}*—forced expired flow between 25 and 75% of FVC; *MIP*—maximum inspiratory pressure; and *MEP*—maximum expiratory pressure. Values are presented as mean ± SD

Results

Pulmonary function at rest

All subjects had normal pulmonary function (Table 1, $n = 13$) based on predicted values (Enright et al. 1995; Quanjer et al. 2012). PEF, FEF_{25}, FEF_{50}, and FEF_{25-75} were significantly increased when breathing heliox compared to room air (Table 2, $n = 13$). FEF_{75} was not significantly different between conditions. MFVC data were excluded for one participant because of measurement artifacts.

Performance and physiological and perceptual responses during exercise

Performance time and power output were slightly improved when breathing heliox compared to room air, while no between conditions difference was found for cadence (Fig. 1, Table 3, $n = 14$). $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, F_B, and SpO_2 were significantly greater, while $P_{ET}CO_2$ was significantly lower in heliox compared with room air (Tables 3, 4, Figs. 2, 3, $n = 13$). A significant interaction was found for condition x distance for $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$, F_B, and $P_{ET}CO_2$ (Fig. 2, $n = 13$). For each kilometer, $\dot{V}_E$ increased by an average of 7.38 L/min when inhaling heliox (95% CI = [4.21, 10.55]) ($P = 0.011$) and 4.62 L/min when inhaling room air (95% CI = [1.43, 7.81]). In contrast, no significant difference was found between conditions for heart rate, lactate, breathing discomfort, and leg discomfort.

Expiratory flow limitation and operational lung volume data could not be assessed in three participants because of artifact contamination. EFL was found in nine and ten participants when breathing heliox and room air, respectively. EFL severity (i.e., % of tidal volume that meets or exceeds the boundary of the MFVC) tended to be reduced (~Δ8% tidal volume, $P = 0.054$, Cohen's $d = 0.67$) with heliox compared to room air during the 5-km TT (Table 4,

Table 2 Baseline pulmonary function indices with inhalation of room air or Heliox ($n = 13$)

	Room air	Heliox	*P* value	Cohen's *d*
FVC (L)	4.25 ± 0.59	4.37 ± 0.52	0.339	− 0.29 [− 0.86, 0.30]
PEF (L/sec)	10.2 ± 1.2	14.3 ± 2.6	< 0.001*	− 2.23 [− 3.29, − 1.14]
FEF_{25} (L/sec)	7.3 ± 1.9	11.9 ± 2.3	< 0.001*	− 3.82 [− 5.48, − 2.14]
FEF_{50} (L/sec)	3.4 ± 1.3	5.1 ± 1.5	< 0.001*	− 1.79 [− 2.71, − 0.85]
FEF_{75} (L/sec)	1.2 ± 0.8	1.1 ± 0.4	0.488	− 0.12 [− 0.69, 0.45]
FEF_{25-75} (L/sec)	2.6 ± 1.2	3.5 ± 1.2	0.002*	-1.07 [-1.78, -0.34]
FEF_{25-75} (% predicted)	99 ± 44	133 ± 42	< 0.001*	− 1.14 [− 1.86, − 0.39]

FVC—forced vital capacity; *PEF*—peak expiratory flow; *FEF_{25}*—peak expiratory flow at 25% vital capacity; *FEF_{50}*—peak expiratory flow at 50% vital capacity; *FEF_{75}*—peak expiratory flow at 75% vital capacity; and *FEF_{25-75}*—peak expiratory flow between 25 and 75% of forced vital capacity measured in each condition. Values are presented as mean ± SD

*$P < 0.05$ main effect of condition

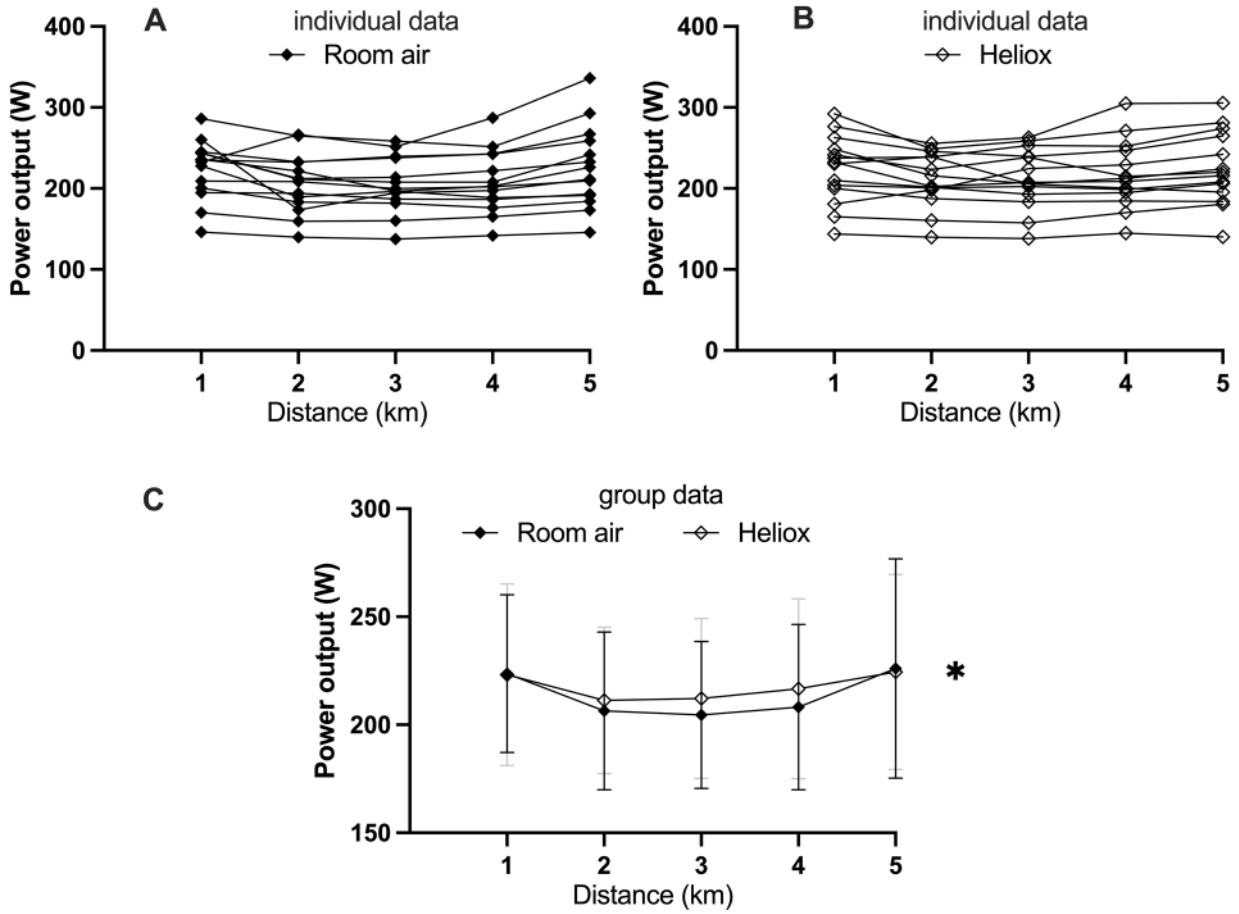

Fig. 1 Individual (**A**, **B**) and group (**C**) power output (W) during the 5-km TT with inhalation of room air or heliox ($n = 14$). Values are presented as mean ± SD. *$P < 0.05$ main effect of condition. Mean power output was 213 ± 37 W when inhaling room air and 217 ± 38 W when inhaling heliox

Table 3 Performance and perceptual response during the 5-km TT with inhalation of room air and heliox ($n = 14$)

	Room air	Heliox	*P* value	Cohen's *d*
Time (sec)	531.3 ± 36.9	527.6 ± 38	0.017*	0.73 [0.13, 1.32]
Power (W)	213 ± 37	217 ± 38	0.011*	− 0.79 [− 1.39, − 0.18]
Cadence (rpm)	92 ± 7	93 ± 6	0.547	− 0.17 [− 0.69, 0.37]
SpO_2 (%)[a]	97 ± 1	98 ± 1	0.007*	− 0.96 [− 1.64, − 0.26]
Heart rate (bpm)	148 ± 9	148 ± 8	0.375	− 0.31 [− 0.97, 0.37]
Lactate (mmol/L)	11.2 ± 2.2	12.0 ± 2.6	0.136	− 0.43 [− 0.97, 0.13]
Breathing discomfort (a.u.)	48 ± 12	46 ± 10	0.573	0.16 [− 0.38, 0.68]
Leg discomfort (a.u.)	47 ± 13	46 ± 10	0.663	0.12 [− 0.41, 0.64]

SpO_2—hemoglobin oxygen saturation ([a]$n = 13$). Values are presented as mean ± SD

*$P < 0.05$ main effect of condition

Fig. 4, $n = 11$). During exercise, ∫Pm was reduced during both inspiration (− 28.4 ± 12.9%, $P < 0.001$) and expiration (− 18.5 ± 17.8%, $P = 0.005$) with Heliox (Fig. 5A, $n = 13$). Similarly, inspiratory (− 22.8 ± 11.6%, $P < 0.001$) and expiratory (− 10.8 ± 11.4%, $P = 0.003$) muscle force development was reduced with heliox (Fig. 5B, $n = 13$). Maximal inspiratory and expiratory pressures were reduced at the end of exercise compared to pre-exercise, after inhaling both heliox (MIP − 29.1 ± 21%, MEP − 22.9 ± 13.5%, $P < 0.001$) and room air (MIP − 23.9 ± 18.1%, MEP − 20.9 ± 10.6%, $P < 0.001$), indicative of respiratory muscle fatigue. MIP remained lower from 1 to 2 min, and MEP remained lower

Table 4 Ventilatory response during the 5-km TT with inhalation of room air and heliox ($n = 13$)

	Room air	Heliox	*P* value	Cohen's *d*
EFL (% V_T)[a]	30 ± 23	22 ± 23	0.056	0.67 [− 0.03, 1.35]
$\dot{V}_E$ (L/min), STPD	94 ± 13	112 ± 22	0.011*	− 1.02 [− 1.78, − 0.23]
$\dot{V}CO_2$ (L/min), STPD	3.73 ± 0.66	3.92 ± 0.72	0.594	− 0.18 [− 0.77, 0.42]
$\dot{V}_E/\dot{V}CO_2$	25.1 ± 1.8	28.6 ± 2.7	< 0.001*	− 1.51 [− 2.37, − 0.61]
$P_{ET}CO_2$ (mmHg)	38.8 ± 4.6	34.2 ± 3.5	< 0.001*	0.84 [0.13, 1.52]
F_B (breaths/min)	47 ± 7	52 ± 11	0.030*	− 0.88 [− 1.6, − 0.12]
V_T (L), STPD	2.1 ± 0.4	2.2 ± 0.3	0.123	− 0.52 [− 1.17, 0.16]
IRV (L)	0.40 ± 0.14	0.45 ± 0.13	0.152	− 0.51 [− 1.16, 0.17]
EILV (% FVC)	90 ± 3	90 ± 3	0.167	0.46 [− 0.2, 1.11]
EELV (% FVC)	36 ± 8	33 ± 8	0.175	0.46 [− 0.2, 1.11]

EFL—expiratory flow limitation ([a]$n = 11$); $\dot{V}_E$—minute ventilation; $\dot{V}CO_2$—carbon dioxide production; $\dot{V}_E/\dot{V}CO_2$—ventilatory equivalent for CO_2; $P_{ET}CO_2$—end-tidal partial pressure for CO_2; F_B—breathing frequency; V_T—tidal volume; *IRV*—inspiratory reserve volume; *EELV*—end-expiratory lung volume; *EILV*—end-inspiratory lung volume; and *FVC*—forced vital capacity. Values are presented as mean ± SD over the 5-km time trial

*$P < 0.05$ main effect of condition

from 1 to 15 min following the end of exercise compared to pre-exercise, in both heliox and room air conditions. Exercise-induced reduction in MIP and MEP was not different between conditions (Fig. 6, $n = 13$). Due to technical issues, SpO_2, MIP, and MEP were not recorded in one participant.

Discussion

The purpose of this study was to determine the influence of breathing a low-density gas (i.e., heliox) on mechanical ventilatory constraints, respiratory muscle force development, and exercise performance during a cycling time trial in master athletes. The rationale for our study was based on findings showing that heliox could partially alleviate the age-related decline in pulmonary function such as the dynamic narrowing of airways during expiration, the associated increased pulmonary resistance, the reduction in the reserve for increasing ventilation, and the increase in respiratory muscle work during physical exercise (Janssens et al. 1999; Johnson et al. 1994; Johnson and Dempsey 1991; Molgat-Seon et al. 2018; Smith et al. 2018). The major findings were that heliox had a significant but modest effect on exercise performance in master athletes during a 5-km time trial and tended to decrease the severity of expiratory flow limitation. Moreover, heliox reduced respiratory muscle force development during exercise but did not attenuate exercise-induced respiratory muscle fatigue.

Our older trained individuals increased their power output by 1.8 ± 2.4% and improved their performance time by 0.7 ± 0.9% when breathing heliox compared with room air (Fig. 1, Table 3). Our results extend previous findings obtained in young trained athletes showing an improvement in performance when breathing heliox during a constant workload exercise performed at 85–110% maximum oxygen consumption (Aaron et al. 1985; Powers et al. 1986; Wilson and Welch 1980) and an intermittent high-intensity exercise performed at 160% maximum aerobic power output (Tong et al. 2004).

Our findings also indicate that the performance improvement observed with heliox during a 5-km time trial in master athletes is not greater than the 0.7% improvement in performance time (equivalent to 3.2 s) previously observed in younger trained male athletes (Wilkie et al. 2015). This suggests that age-related increase in pulmonary mechanical constraints does not impose additional limitations (if any) on exercise performance compared to younger adults. However, even a small improvement in performance, such as the one observed in the present study, can be relevant and significant for competitive master athletes (Hopkins et al. 2001). For example, the margin between winning gold and silver world championship medals in males between 60 and 65 years was 0.48 s in the 2000 m track cycling pursuit (2022) and 0.25 s in the 1500 m indoor track and field race (2023).

The slight performance improvement observed with heliox may be attributed to reduced internal (e.g., airways) and external (e.g., breathing apparatus) resistance to breathing, as indicated by the decreased inspiratory (~ 31%) and expiratory (~ 19%) mouth pressures, along with indices of reduced inspiratory (~ 24%) and expiratory (~ 12%) muscle force development during heliox breathing (Fig. 5). These reductions in mouth pressure and respiratory muscle force development during exercise were likely associated with a decrease in the overall work of breathing (WOB), thereby allowing blood flow to redistribute from the respiratory muscles to the locomotor muscles via a reduction in the respiratory muscle metaboreflex (Dempsey et al. 2008a, b; Harms et al. 1997, 1998, 2000; Sheel et al. 2018). Indeed,

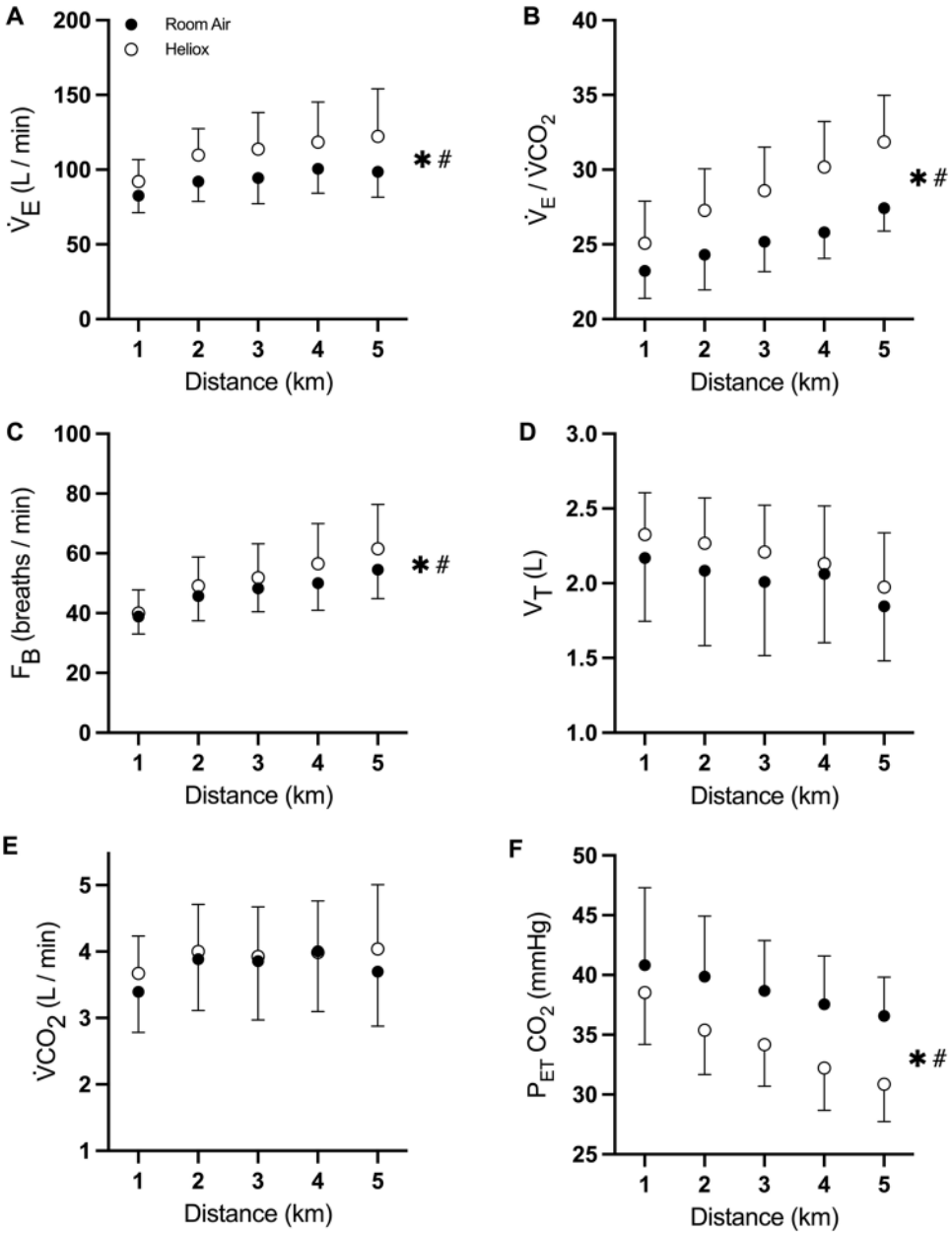

Fig. 2 Minute ventilation ($\dot{V}_E$, **A**), ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$, **B**), breathing frequency (F_B, **C**), tidal volume (V_T, **D**), carbon dioxide production ($\dot{V}CO_2$, **E**), and end-tidal partial pressure of CO_2 ($P_{ET}CO_2$, **F**) during the 5-km TT with inhalation of room air or heliox ($n = 13$). Values are presented as mean ± SD. *$P < 0.05$ main effect of condition. #$P < 0.05$ interaction between condition and distance

decreasing the WOB may have increased blood flow and improved oxygen availability to the locomotor muscles (Dominelli et al. 2017a), therefore delaying the development of locomotor muscle fatigue (Dominelli et al. 2017b; Romer et al. 2006) and improving exercise performance (Harms et al. 2000). It is important to note that our experiment did not enable us to directly measure the WOB, and the methodology used in this study did not allow us to distinguish between the effects of a reduction in airway resistance and a reduction in resistance related to the breathing apparatus on indices associated with mouth pressure measurement (Hunt et al. 2010).

Our findings showed a decrease in maximal inspiratory (MIP) and expiratory (MEP) pressures post-exercise compared to pre-exercise which indirectly suggests inspiratory and expiratory muscle fatigue. Such findings are consistent with previous results showing significant diaphragmatic fatigue, as assessed using bilateral supramaximal electrical stimulation of the phrenic nerve, following a cycling exercise of similar duration (i.e., 9.6 min) (Babcock et al. 2002). It also extends previous results showing a 13 to 17% reduction in MIP and MEP following a maximal and graded cycling exercise test in young moderately trained athletes (Coast et al. 1999; Oueslati et al. 2018; Ozkaplan et al. 2005; Volianitis et al. 2001). However, exercise-induced reductions in MIP and MEP were not different between conditions in the present study (Fig. 6), suggesting that the "unloading effect" of heliox on WOB, previously reported

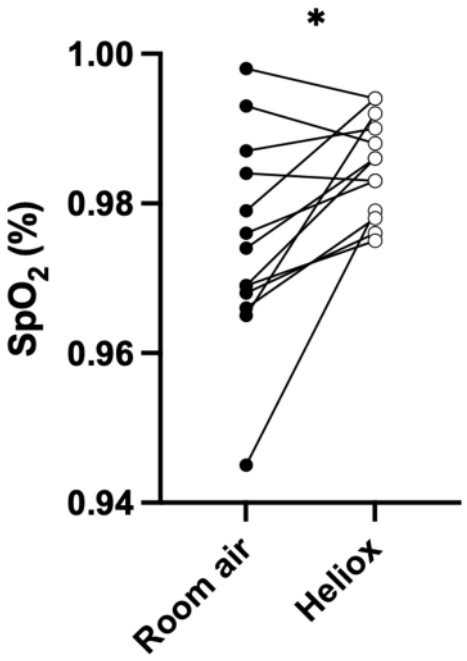

Fig. 3 Hemoglobin oxygen saturation (SpO_2) during the 5-km TT with inhalation of room air or heliox ($n = 13$). Values are presented as mean ± SD. *$P < 0.05$ main effect of condition

to be ~ 12–28% (Mann et al. 2020; Molgat-Seon et al. 2019; Wilkie et al. 2015), was insufficient to attenuate the exercise-induced failure of the respiratory muscles to develop pressure. Indeed, previous findings showed that exercise-induced diaphragmatic fatigue can be effectively prevented (Babcock et al. 2002) and exercise performance improved to a greater extent (i.e., ~ 14%) (Harms et al. 2000) when a substantially larger reduction in the work of breathing (i.e., 40–80%) is obtained using PAV. Furthermore, while aging is associated with an increase in both the resistive (e.g., increase in airway resistance) and viscoelastic (e.g., decrease in elastic recoil of the lung) components of the work of breathing (Smith et al. 2018), heliox only alleviates the resistive work of breathing (Mann et al. 2020) in contrast to PAV. This might explain, at least in part, why heliox had no influence on exercise-induced reductions in MIP and MEP. Alternatively, because the effect of heliox is flow-dependent (Dominelli et al. 2016; Mann et al. 2020), another possible explanation could be that, at a ventilation of ~ 94 L/min, the airflow in our master athletes may not have reached a sufficiently high level, and turbulence may not have been significant enough, for heliox to significantly attenuate airway resistance and the work of breathing. Indeed, heliox was found to significantly lower the work of breathing only when ventilation exceeded ~ 90 L/min in young healthy males (Mann et al. 2020). However, previous results showed that the work of breathing can be reduced by ~ 16% at minute ventilation averaging ~ 60 L/min in recreationally active older individuals during exercise (Molgat-Seon et al. 2018). Finally, the ~ 19% heliox-induced increase in ventilation might have counteracted the beneficial "unloading effect" of heliox on the work of breathing.

Ten out of eleven older trained athletes showed expiratory flow limitation (EFL) when inhaling room air in the present study. This is consistent with previous findings showing that older individuals exhibit greater expiratory flow limitation than younger individuals (Johnson et al. 1991a, b; Molgat-Seon et al. 2018; Smith et al. 2018), as substantiated by the greater frequency of EFL observed in older compared with younger individuals during maximal exercise (e.g., 82–90% vs. 55–60%, Molgat-Seon et al. 2018). Older individuals are indeed more predisposed to EFL during exercise as a consequence of their increased ventilatory response (e.g., greater minute ventilation for a same workload) and

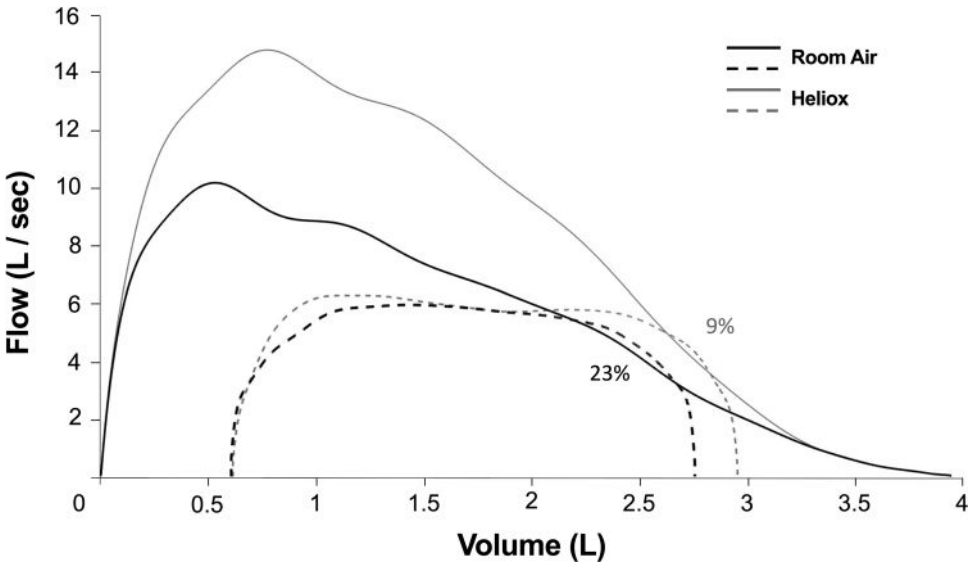

Fig. 4 Maximal flow–volume loops (solid lines) and exercise tidal flow–volume loops (dashed lines) during 5-km time trial when inhaling room air or heliox in a representative subject. Tidal flow–volume loops were obtained during the last 30 s of the time trial. The severity of expiratory flow limitation is presented in $\%V_T$

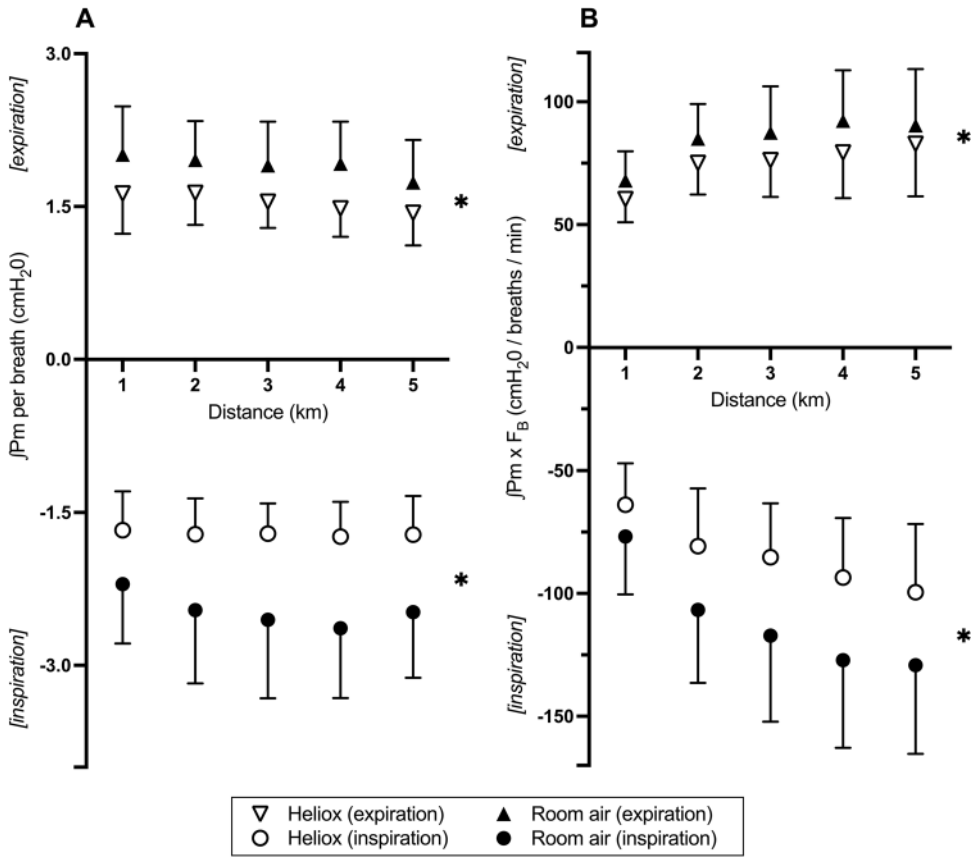

Fig. 5 Pressure developed by the respiratory muscles ("$\int$Pm per breath," **A**) and respiratory muscle force development ("$\int P_{mouth} \times F_{B,}$" **B**) in inspiration (INS) and expiration (EXP) during the 5-km TT with inhalation of room air or heliox ($n = 13$). Values are presented as mean ± SD. *$P < 0.05$ main effect of condition

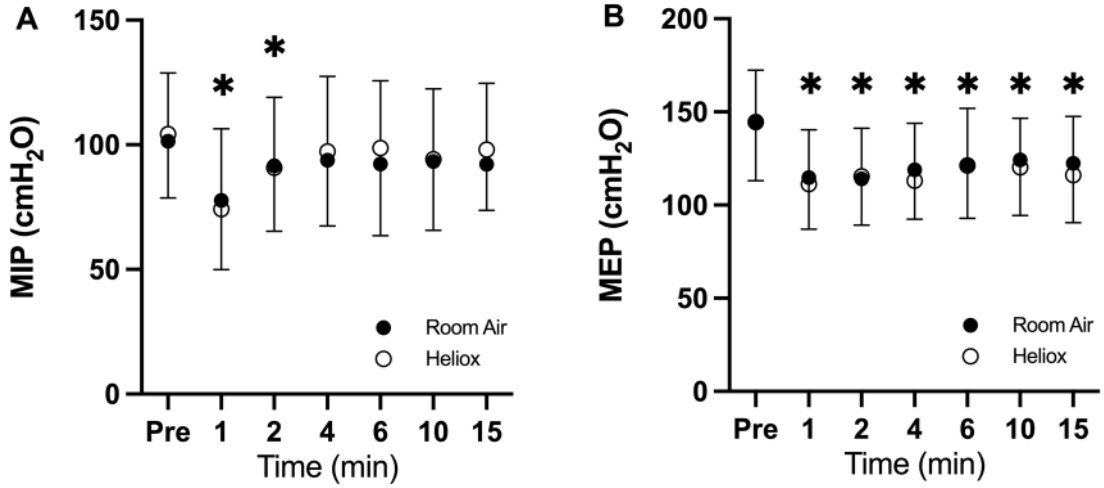

Fig. 6 Maximal inspiratory pressures (MIP, **A**) and maximal expiratory pressure (MEP, **B**) assessed PRE vs. POST 5-km TT ($n = 13$). Values are presented as mean ± SD. *$P < 0.05$ for time vs PRE. No condition x time interaction was observed for MIP ($P = 0.282$) or MEP ($P = 0.509$). No condition effect was observed for MIP ($P = 0.539$) or MEP ($P = 0.953$)

reduced ventilatory capacity (e.g., greater EELV and EILV) compared with younger individuals (DeLorey and Babb 1999; Molgat-Seon et al. 2018). Breathing heliox can, however, increase the envelope of the maximal expiratory flow–volume curve through an improvement in the capacity to generate flow (Table 2, Fig. 4), thereby increasing the available pulmonary reserve (i.e., distance between the boundaries of the tidal volume and the MFVC (Babb 1997b)). This increase in the pulmonary reserve is supported in the present study by the ~ 19% increase in ventilation in

heliox compared with room air (Fig. 2, Table 4) and the trend toward a reduction in the severity of EFL ($P = 0.054$, Cohen's $d = 0.67$). Yet, mechanical ventilatory constraints persisted despite the inhalation of heliox in the present study (i.e., EFL remained present in 9 participants), and operational lung volumes were not significantly different between room air and heliox breathing, which is in agreement with previous findings in young individuals (Mann et al. 2020; McClaran et al. 1998). For example, EILV corresponded to ~ 90% of FVC when inhaling both room air and Heliox (Table 4), suggesting that the inspiratory muscle work was likely very high in both conditions (Johnson et al. 1991a, b). Likewise, EELV was not different between room air and heliox (Table 4), which may explain the absence of further significant increase in tidal volume with heliox since an increase in EILV beyond ~ 90% FVC does not appear to be a viable option (Babb 2013; McClaran et al. 1999). This result contrasts with previous findings showing a lower EELV and a higher tidal volume with heliox (Babb 1997a, 1997b; McClaran et al. 1999). However, despite similar tidal volume between conditions in the present study (Table 4, Fig. 2), we observed a ~ 19% increase in minute ventilation when inhaling heliox, which was mainly attributable to an increase in breathing frequency. Considering the lack of arterial hypoxemia during room air exercise, as suggested by a hemoglobin oxygen saturation of 97% (Table 3, Fig. 3), alveolar ventilation was unlikely compromised in our master athletes. Therefore, the increase in minute ventilation with heliox likely did not significantly contribute to the performance improvement during the 5-km time trial. Conversely, the hyperventilation-induced hypocapnia with heliox (Fig. 3) might have resulted in a leftward shift in the oxygen–hemoglobin dissociation curve, potentially compromising muscle O_2 delivery and thus limiting the enhancement in performance (Hayashi et al. 1999).

Study limitations

While we used validated methods to characterize pulmonary mechanical function, EFL, and respiratory muscle fatigue, one of the primary limitations of our study is the absence of invasive esophageal pressure measurements. For example, we were unable to ascertain peak esophageal pressure and verify whether participants achieved maximal inspiration to total lung capacity during the volitional inspiratory capacity maneuvers performed throughout exercise. This limitation may affect the accuracy and reliability of our estimates of operating lung volumes and expiratory flow limitation (EFL). Nevertheless, participants received comprehensive training in conducting maximal effort during IC maneuver, and such maneuvers are considered to be reliable and reproducible once participants are properly familiarized (Guenette et al. 2013).

In the absence of transpulmonary pressure measurement or a negative expiratory pressure device, we estimated EFL by evaluating the percentage of the tidal volume loop that overlapped with the maximal expiratory flow–volume (MEFV) curve (Johnson et al. 1999). To minimize the risk of false detection of EFL, we assessed EFL repeatedly during the 5-km time trial, and we considered expiratory flow as limited only when the tidal volume loop overlapped with the MEFV curve by at least 5% (Chapman et al. 1998). Although our methodology did not account for the effect of thoracic gas compression (Guenette et al. 2010) or potential heliox effect on the external breathing apparatus (Hunt et al. 2010), potentially leading to EFL overestimation, it is a common approach to evaluate expiratory flow limitation (Chapman et al. 1998; Cox et al. 2020; Derchak et al. 2000; Johnson et al. 1999; Verges et al. 2005). Furthermore, our EFL results are consistent with previous findings from studies using esophageal pressure measurements and accounting for thoracic gas compression in older individuals (Johnson et al. 1991a, b; Johnson et al. 1991a, b; Molgat-Seon et al. 2018). This suggests that our chosen methodology was appropriate to assess EFL.

The lack of invasive esophageal pressure measurement also prevented a direct assessment of respiratory muscle pressure-generating capacity. Instead, we used maximal inspiratory and expiratory pressures to indirectly assess respiratory muscle fatigue. Our findings must be interpreted with caution because this method has notable limitations when compared to twitch transdiaphragmatic pressure measurment in response to supramaximal phrenic nerve stimulation. These limitations include its reliance on participant motivation and volitional effort, susceptibility to be influenced by accessory muscles, and inability to differentiate between central and peripheral components of neuromuscular fatigue. However, the assessment of maximal inspiratory and expiratory pressures (MIP and MEP) is considered a valid noninvasive method for assessing respiratory muscle fatigue, as acknowledged by the American Thoracic Society/European Respiratory guidelines Respiratory (American Thoracic Society/European Respiratory 2002) (Brown and Kilding 2011; Coast et al. 1999; Oueslati et al. 2018; Ozkaplan et al. 2005; Ross et al. 2008; Volianitis et al. 2001*).* and its frequent use in the literature to evaluate exercise-induced respiratory muscle fatigue. Finally, this study specifically involved male master athletes, and our findings may not be directly applicable to master female athletes. Existing evidence suggests that, compared with males, smaller conducting airways might increase the prevalence of EFL and the work of breathing for a given level of ventilation in young and old females (Dominelli et al. 2015; Mann et al. 2020; Molgat-Seon et al. 2018). Future studies are thus necessary to determine the effect of reducing the resistive work

of breathing with heliox on exercise performance in female master athletes.

Conclusion

Breathing a low-density gas (i.e., heliox), which reduces mechanical ventilatory resistance and increases the pulmonary reserve of master athletes, enhanced exercise performance during a 5-km time trial although this improvement was somewhat limited. The decrease in respiratory muscle force development, the greater minute ventilation, and the tendency toward a reduction in EFL with heliox indeed yield to < 2% improvement in power output and performance time. This limited impact on exercise performance might be explained by the absence of beneficial effects of breathing heliox on exercise-induced respiratory muscle fatigue and operational lung volumes. Our findings suggest that while the effect of pulmonary mechanical resistance on endurance exercise performance is somewhat limited in master athletes, it remains significant and meaningful for highly trained competitive individuals in this age group.

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Author contributions TH, VM, GB, JB, and JD contributed to the study conception and design. Material preparation, data collection, and analysis were performed by TH, VM, GB, OM, JD, and CA. The first draft of the manuscript was written by TH and GB. VM, OM, CA, JB, and JD commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest No potential conflict of interest was reported by the author(s).

References

Aaron EA, Henke KG, Pegelow DF, Dempsey JA (1985) Effects of mechanical unloading of the respiratory system on exercise and respiratory muscle endurance. Med Sci Sports Exerc 17(2):290

American Thoracic Society/European Respiratory S (2002) ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 166(4):518–624. https://doi.org/10.1164/rccm.166.4.518

Babb TG (1997a) Ventilation and respiratory mechanics during exercise in younger subjects breathing CO2 or HeO2. Respir Physiol 109(1):15–28. https://doi.org/10.1016/s0034-5687(97)84026-1

Babb TG (1997b) Ventilatory response to exercise in subjects breathing CO2 or HeO2. J Appl Physiol 82(3):746–754. https://doi.org/10.1152/jappl.1997.82.3.746

Babb TG (2013) Exercise ventilatory limitation: the role of expiratory flow limitation. Exerc Sport Sci Rev 41(1):11–18. https://doi.org/10.1097/JES.0b013e318267c0d2

Babcock MA, Pegelow DF, Harms CA, Dempsey JA (2002) Effects of respiratory muscle unloading on exercise-induced diaphragm fatigue. J Appl Physiol 93(1):201–206. https://doi.org/10.1152/japplphysiol.00612.2001

Borg E, Borg G (2002) A comparison of AME and CR100 for scaling perceived exertion. Acta Psychol (amst) 109(2):157–175. https://doi.org/10.1016/s0001-6918(01)00055-5

Brown S, Kilding AE (2011) Exercise-induced inspiratory muscle fatigue during swimming: the effect of race distance. J Strength Cond Res 25(5):1204–1209. https://doi.org/10.1519/JSC.0b013e3181d67ab8

Chapman RF, Emery M, Stager JM (1998) Extent of expiratory flow limitation influences the increase in maximal exercise ventilation in hypoxia. Respir Physiol 113(1):65–74. https://doi.org/10.1016/s0034-5687(98)00043-7

Charlton JM, Ramsook AH, Mitchell RA, Hunt MA, Puyat JH, Guenette JA (2017) Respiratory mechanical and cardiorespiratory consequences of cycling with aerobars. Med Sci Sports Exerc 49(12):2578–2584. https://doi.org/10.1249/MSS.0000000000001393

Coast JR, Haverkamp HC, Finkbone CM, Anderson KL, George SO, Herb RA (1999) Alterations in pulmonary function following exercise are not caused by the work of breathing alone. Int J Sports Med 20(7):470–475. https://doi.org/10.1055/s-1999-8828

Coggan AR, Spina RJ, Rogers MA, King DS, Brown M, Nemeth PM, Holloszy JO (1990) Histochemical and enzymatic characteristics of skeletal muscle in master athletes. J Appl Physiol 68(5):1896–1901. https://doi.org/10.1152/jappl.1990.68.5.1896

Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Routledge, Milton Park. https://doi.org/10.4324/9780203771587

Cox KR, Smith JR, Luden ND, Saunders MJ, Kurti SP (2020) The prevalence of expiratory flow limitation in youth elite male cyclists. Med Sci Sports Exerc 52(9):1933–1939. https://doi.org/10.1249/MSS.0000000000002325

de Souza ESCG, Kaminsky LA, Arena R, Christle JW, Araujo CGS, Lima RM, Ashley EA, Myers J (2018) A reference equation for maximal aerobic power for treadmill and cycle ergometer exercise testing: analysis from the FRIEND registry. Eur J Prev Cardiol 25(7):742–750. https://doi.org/10.1177/2047487318763958

Degens H, Maden-Wilkinson TM, Ireland A, Korhonen MT, Suominen H, Heinonen A, Radak Z, McPhee JS, Rittweger J (2013) Relationship between ventilatory function and age in master athletes and a sedentary reference population. Age (dordr) 35(3):1007–1015. https://doi.org/10.1007/s11357-012-9409-7

DeLorey DS, Babb TG (1999) Progressive mechanical ventilatory constraints with aging. Am J Respir Crit Care Med 160(1):169–177. https://doi.org/10.1164/ajrccm.160.1.9807045

Dempsey JA (1986) Wolffe memorial lecture. Is the lung built for exercise? Med Sci Sports Exerc 18(2):143–155

Dempsey JA, Johnson BD, Saupe KW (1990) Adaptations and limitations in the pulmonary system during exercise. Chest 97(3 Suppl):81S-87S. https://doi.org/10.1378/chest.97.3_supplement.81s-a

Dempsey JA, Amann M, Romer LM, Miller JD (2008a) Respiratory system determinants of peripheral fatigue and endurance performance. Med Sci Sports Exerc 40(3):457–461. https://doi.org/10.1249/MSS.0b013e31815f8957

Dempsey JA, McKenzie DC, Haverkamp HC, Eldridge MW (2008b) Update in the understanding of respiratory limitations to exercise performance in fit, active adults. Chest 134(3):613–622. https://doi.org/10.1378/chest.07-2730

Derchak PA, Stager JM, Tanner DA, Chapman RF (2000) Expiratory flow limitation confounds ventilatory response during exercise in athletes. Med Sci Sports Exerc 32(11):1873–1879. https://doi.org/10.1097/00005768-200011000-00009

Dominelli PB, Foster GE, Dominelli GS, Henderson WR, Koehle MS, McKenzie DC, Sheel AW (2013) Exercise-induced arterial

hypoxaemia and the mechanics of breathing in healthy young women. J Physiol 591(12):3017–3034. https://doi.org/10.1113/jphysiol.2013.252767

Dominelli PB, Molgat-Seon Y, Bingham D, Swartz PM, Road JD, Foster GE, Sheel AW (2015) Dysanapsis and the resistive work of breathing during exercise in healthy men and women. J Appl Physiol 119(10):1105–1113. https://doi.org/10.1152/japplphysiol.00409.2015

Dominelli PB, Henderson WR, Sheel AW (2016) A proportional assist ventilator to unload respiratory muscles experimentally during exercise in humans. Exp Physiol 101(6):754–767. https://doi.org/10.1113/EP085735

Dominelli PB, Archiza B, Ramsook AH, Mitchell RA, Peters CM, Molgat-Seon Y, Henderson WR, Koehle MS, Boushel R, Sheel AW (2017a) Effects of respiratory muscle work on respiratory and locomotor blood flow during exercise. Exp Physiol 102(11):1535–1547

Dominelli PB, Molgat-Seon Y, Griesdale DEG, Peters CM, Blouin JS, Sekhon M, Dominelli GS, Henderson WR, Foster GE, Romer LM, Koehle MS, Sheel AW (2017b) Exercise-induced quadriceps muscle fatigue in men and women: effects of arterial oxygen content and respiratory muscle work. J Physiol 595(15):5227–5244. https://doi.org/10.1113/JP274068

Enright PL, Adams AB, Boyle PJ, Sherrill DL (1995) Spirometry and maximal respiratory pressure references from healthy Minnesota 65- to 85-year-old women and men. Chest 108(3):663–669. https://doi.org/10.1378/chest.108.3.663

Guenette JA, Dominelli PB, Reeve SS, Durkin CM, Eves ND, Sheel AW (2010) Effect of thoracic gas compression and bronchodilation on the assessment of expiratory flow limitation during exercise in healthy humans. Respir Physiol Neurobiol 170(3):279–286. https://doi.org/10.1016/j.resp.2010.01.017

Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE (2013) Inspiratory capacity during exercise: measurement, analysis, and interpretation. Pulm Med 2013:956081. https://doi.org/10.1155/2013/956081

Harms CA, Babcock MA, McClaran SR, Pegelow DF, Nickele GA, Nelson WB, Dempsey JA (1997) Respiratory muscle work compromises leg blood flow during maximal exercise. J Appl Physiol 82(5):1573–1583. https://doi.org/10.1152/jappl.1997.82.5.1573

Harms CA, Wetter TJ, McClaran SR, Pegelow DF, Nickele GA, Nelson WB, Hanson P, Dempsey JA (1998) Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. J Appl Physiol 85(2):609–618. https://doi.org/10.1152/jappl.1998.85.2.609

Harms CA, Wetter TJ, St Croix CM, Pegelow DF, Dempsey JA (2000) Effects of respiratory muscle work on exercise performance. J Appl Physiol 89(1):131–138. https://doi.org/10.1152/jappl.2000.89.1.131

Hawkins S, Wiswell R (2003) Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training. Sports Med 33(12):877–888. https://doi.org/10.2165/00007256-200333120-00002

Hayashi N, Ishihara M, Tanaka A, Yoshida T (1999) Impeding O(2) unloading in muscle delays oxygen uptake response to exercise onset in humans. Am J Physiol 277(5):R1274-1281. https://doi.org/10.1152/ajpregu.1999.277.5.R1274

Hopkins WG, Schabort EJ, Hawley JA (2001) Reliability of power in physical performance tests. Sports Med 31(3):211–234. https://doi.org/10.2165/00007256-200131030-00005

Hunt T, Williams MT, Frith P, Schembri D (2010) Heliox, dyspnoea and exercise in COPD. Eur Respir Rev 19(115):30–38. https://doi.org/10.1183/09059180.00006009

Janssens JP, Pache JC, Nicod LP (1999) Physiological changes in respiratory function associated with ageing. Eur Respir J 13(1):197–205. https://doi.org/10.1034/j.1399-3003.1999.13a36.x

Johnson BD, Dempsey JA (1991) Demand vs. capacity in the aging pulmonary system. Exerc Sport Sci Rev 19:171–210

Johnson BD, Reddan WG, Pegelow DF, Seow KC, Dempsey JA (1991a) Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. Am Rev Respir Dis 143(5 Pt 1):960–967. https://doi.org/10.1164/ajrccm/143.5_Pt_1.960

Johnson BD, Reddan WG, Seow KC, Dempsey JA (1991b) Mechanical constraints on exercise hyperpnea in a fit aging population. Am Rev Respir Dis 143(5 Pt 1):968–977. https://doi.org/10.1164/ajrccm/143.5_Pt_1.968

Johnson BD, Saupe KW, Dempsey JA (1992) Mechanical constraints on exercise hyperpnea in endurance athletes. J Appl Physiol 73(3):874–886. https://doi.org/10.1152/jappl.1992.73.3.874

Johnson BD, Babcock MA, Suman OE, Dempsey JA (1993) Exercise-induced diaphragmatic fatigue in healthy humans. J Physiol 460:385–405. https://doi.org/10.1113/jphysiol.1993.sp019477

Johnson BD, Badr MS, Dempsey JA (1994) Impact of the aging pulmonary system on the response to exercise. Clin Chest Med 15(2):229–246

Johnson BD, Weisman IM, Zeballos RJ, Beck KC (1999) Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. Chest 116(2):488–503. https://doi.org/10.1378/chest.116.2.488

Mann LM, Granger EA, Chan JS, Yu A, Molgat-Seon Y, Dominelli PB (2020) Minimizing airflow turbulence in women lowers the work of breathing to levels similar to men. J Appl Physiol 129(2):410–418. https://doi.org/10.1152/japplphysiol.00347.2020

McClaran SR, Babcock MA, Pegelow DF, Reddan WG, Dempsey JA (1995) Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. J Appl Physiol 78(5):1957–1968. https://doi.org/10.1152/jappl.1995.78.5.1957

McClaran SR, Harms CA, Pegelow DF, Dempsey JA (1998) Smaller lungs in women affect exercise hyperpnea. J Appl Physiol 84(6):1872–1881. https://doi.org/10.1152/jappl.1998.84.6.1872

McClaran SR, Wetter TJ, Pegelow DF, Dempsey JA (1999) Role of expiratory flow limitation in determining lung volumes and ventilation during exercise. J Appl Physiol 86(4):1357–1366. https://doi.org/10.1152/jappl.1999.86.4.1357

McKendry J, Joanisse S, Baig S, Liu B, Parise G, Greig CA, Breen L (2020) Superior aerobic capacity and indices of skeletal muscle morphology in chronically trained master endurance athletes compared with untrained older adults. J Gerontol A Biol Sci Med Sci 75(6):1079–1088. https://doi.org/10.1093/gerona/glz142

Molgat-Seon Y, Dominelli PB, Ramsook AH, Schaeffer MR, Molgat Sereacki S, Foster GE, Romer LM, Road JD, Guenette JA, Sheel AW (2018) The effects of age and sex on mechanical ventilatory constraint and dyspnea during exercise in healthy humans. J Appl Physiol 124(4):1092–1106. https://doi.org/10.1152/japplphysiol.00608.2017

Molgat-Seon Y, Ramsook AH, Peters CM, Schaeffer MR, Dominelli PB, Romer LM, Road JD, Guenette JA, Sheel AW (2019) Manipulation of mechanical ventilatory constraint during moderate intensity exercise does not influence dyspnoea in healthy older men and women. J Physiol 597(5):1383–1399. https://doi.org/10.1113/JP277476

O'Donovan G, Hamer M (2018) The association between leisure-time physical activity and lung function in older adults: the English longitudinal study of ageing. Prev Med 106:145–149. https://doi.org/10.1016/j.ypmed.2017.10.030

Ogawa T, Spina RJ, Martin WH 3rd, Kohrt WM, Schechtman KB, Holloszy JO, Ehsani AA (1992) Effects of aging, sex, and physical training on cardiovascular responses to exercise. Circulation 86(2):494–503. https://doi.org/10.1161/01.cir.86.2.494

Oueslati F, Berriri A, Boone J, Ahmaidi S (2018) Respiratory muscle strength is decreased after maximal incremental exercise in

trained runners and cyclists. Respir Physiol Neurobiol 248:25–30. https://doi.org/10.1016/j.resp.2017.11.005

Ozkaplan A, Rhodes EC, Sheel AW, Taunton JE (2005) A comparison of inspiratory muscle fatigue following maximal exercise in moderately trained males and females. Eur J Appl Physiol 95(1):52–56. https://doi.org/10.1007/s00421-005-1399-z

Pelkonen M, Notkola IL, Lakka T, Tukiainen HO, Kivinen P, Nissinen A (2003) Delaying decline in pulmonary function with physical activity: a 25-year follow-up. Am J Respir Crit Care Med 168(4):494–499. https://doi.org/10.1164/rccm.200208-954OC

Powers SK, Jacques M, Richard R, Beadle RE (1986) Effects of breathing a normoxic He-O2 gas mixture on exercise tolerance and VO2 max. Int J Sports Med 7(4):217–221. https://doi.org/10.1055/s-2008-1025762

Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J, Initiative ERSGLF (2012) Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 40(6):1324–1343. https://doi.org/10.1183/09031936.00080312

Romer LM, McConnell AK (2004) Inter-test reliability for non-invasive measures of respiratory muscle function in healthy humans. Eur J Appl Physiol 91(2–3):167–176. https://doi.org/10.1007/s00421-003-0984-2

Romer LM, Lovering AT, Haverkamp HC, Pegelow DF, Dempsey JA (2006) Effect of inspiratory muscle work on peripheral fatigue of locomotor muscles in healthy humans. J Physiol 571(Pt 2):425–439. https://doi.org/10.1113/jphysiol.2005.099697

Ross E, Middleton N, Shave R, George K, McConnell A (2008) Changes in respiratory muscle and lung function following marathon running in man. J Sports Sci 26(12):1295–1301. https://doi.org/10.1080/02640410802104904

Sheel AW, Derchak PA, Morgan BJ, Pegelow DF, Jacques AJ, Dempsey JA (2001) Fatiguing inspiratory muscle work causes reflex reduction in resting leg blood flow in humans. J Physiol 537(Pt 1):277–289. https://doi.org/10.1111/j.1469-7793.2001.0277k.x

Sheel AW, Boushel R, Dempsey JA (2018) Competition for blood flow distribution between respiratory and locomotor muscles: implications for muscle fatigue. J Appl Physiol 125(3):820–831. https://doi.org/10.1152/japplphysiol.00189.2018

Smith JR, Cross TJ, Van Iterson EH, Johnson BD, Olson TP (2018) Resistive and elastic work of breathing in older and younger adults during exercise. J Appl Physiol 125(1):190–197. https://doi.org/10.1152/japplphysiol.01105.2017

Sylvester KP, Clayton N, Cliff I, Hepple M, Kendrick A, Kirkby J, Miller M, Moore A, Rafferty GF, O'Reilly L, Shakespeare J, Smith L, Watts T, Bucknall M, Butterfield K (2020) ARTP statement on pulmonary function testing 2020. BMJ Open Respir Res. https://doi.org/10.1136/bmjresp-2020-000575

Tanaka H, Seals DR (2003) Invited review: dynamic exercise performance in masters athletes: insight into the effects of primary human aging on physiological functional capacity. J Appl Physiol 95(5):2152–2162. https://doi.org/10.1152/japplphysiol.00320.2003

Taylor BJ, Johnson BD (2010) The pulmonary circulation and exercise responses in the elderly. Semin Respir Crit Care Med 31(5):528–538. https://doi.org/10.1055/s-0030-1265894

Tong TK, Fu FH, Quach B, Lu K (2004) Reduced sensations of intensity of breathlessness enhances maintenance of intense intermittent exercise. Eur J Appl Physiol 92(3):275–284. https://doi.org/10.1007/s00421-004-1094-5

Turner LA, Tecklenburg-Lund SL, Chapman R, Shei RJ, Wilhite DP, Mickleborough T (2016) The effect of inspiratory muscle training on respiratory and limb locomotor muscle deoxygenation during exercise with resistive inspiratory loading. Int J Sports Med 37(8):598–606. https://doi.org/10.1055/s-0042-104198

Verges S, Devouassoux G, Flore P, Rossini E, Fior-Gozlan M, Levy P, Wuyam B (2005) Bronchial hyperresponsiveness, airway inflammation, and airflow limitation in endurance athletes. Chest 127(6):1935–1941. https://doi.org/10.1378/chest.127.6.1935

Volianitis S, McConnell AK, Koutedakis Y, Jones DA (2001) Specific respiratory warm-up improves rowing performance and exertional dyspnea. Med Sci Sports Exerc 33(7):1189–1193. https://doi.org/10.1097/00005768-200107000-00017

Wilkie SS, Dominelli PB, Sporer BC, Koehle MS, Sheel AW (2015) Heliox breathing equally influences respiratory mechanics and cycling performance in trained males and females. J Appl Physiol 118(3):255–264. https://doi.org/10.1152/japplphysiol.00400.2014

Wilson GD, Welch HG (1980) Effects of varying concentrations of N2/O2 and He/O2 on exercise tolerance in man. Med Sci Sports Exerc 12(5):380–384

Witt JD, Guenette JA, Rupert JL, McKenzie DC, Sheel AW (2007) Inspiratory muscle training attenuates the human respiratory muscle metaboreflex. J Physiol 584(Pt 3):1019–1028. https://doi.org/10.1113/jphysiol.2007.140855