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Manipulation of mechanical ventilatory constraint during moderate intensity exercise does not influence dyspnoea in healthy older men and women

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ABSTRACT

We sought to determine the effect of manipulating mechanical ventilatory constraint during submaximal exercise on dyspnoea in older men and women. *Methods:* Eighteen healthy subjects (60-80 y; 9 men, 9 women) completed two days of testing. On Day 1, subjects performed pulmonary function testing and a maximal incremental cycle exercise test. On Day 2, subjects performed three 6-min bouts of cycling at ventilatory threshold, in a single-blind randomized manner, while breathing: i) normoxic helium-oxygen (HEL) to reduce the work of breathing (W_b) and alleviate expiratory flow limitation (EFL); ii) through an inspiratory resistance (RES) of ~5 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ to increase W_b; and iii) ambient air as a control (CON). Oesophageal pressure, diaphragm electromyography, and sensory responses (using the category-ratio 10 Borg scale) were monitored throughout exercise. *Results:* During the HEL condition, there was a significant decrease in W_b (men: –21±6%, women: –17±10%) relative to CON (both p<0.01). Moreover, if EFL was present during CON (4 men, 5 women), it was alleviated during HEL. Conversely, during the RES condition, W_b (men: 42±19%, women: 50±16%) significantly increased relative to CON (both p<0.01). There was no main effect of sex on W_b (p=0.59). Across conditions, women reported significantly higher dyspnoea intensity than men (2.9±0.9 vs. 1.9±0.8 Borg scale units, p<0.05). Despite significant differences in the degree of mechanical ventilatory constraint between conditions, dyspnoea intensity was unaffected, independent of sex (p=0.46). *Conclusion:* When older men and women perform submaximal exercise at a moderate intensity, mechanical ventilatory constraint does not contribute significantly to the sensation of dyspnoea.

Key Words: aging, diaphragm electromyogram, heliox, sex-differences, work of breathing

Key Point Summary

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- The perceived intensity of exertional breathlessness (*i.e.* dyspnoea) is higher in older women than in older men, possibly due to sex-difference respiratory system morphology.
- During exercise at a given absolute intensity or minute ventilation, older women have a greater degree of mechanical ventilatory constraint (*i.e.* work of breathing and expiratory flow limitation) than their male counterparts, which may lead to a greater perceived intensity of dyspnoea.
- Using a single-blind randomized study design, we experimentally manipulated the magnitude of mechanical ventilatory constraint during moderate-intensity exercise at ventilatory threshold in healthy older men and women. We found that changes in the magnitude of mechanical ventilatory constraint within the physiological range had no effect on dyspnoea in healthy older adults.
- When older men and women perform submaximal exercise at a moderate intensity, mechanical ventilatory constraint does not contribute significantly to the sensation of dyspnoea.

INTRODUCTION

Dyspnoea, defined briefly as a subjective experience of breathing discomfort (American Thoracic Society, 1999), is a common sensory consequence of physical exertion (Sheel *et al.*, 2011). The magnitude of dyspnoea during exercise increases throughout the healthy aging process, whereby older individuals report higher levels of dyspnoea for a given absolute exercise intensity than their younger counterparts (Killian *et al.*, 1992; Mahler *et al.*, 2003). While our understanding of the mechanisms of dyspnoea is incomplete, exertional dyspnoea is generally thought to occur due to the perception of increased respiratory effort required to meet the ventilatory demands of exercise (Jensen *et al.*, 2011). Healthy aging is associated with a significant change to the structures of the respiratory system that leads to a progressive decline in pulmonary function (Janssens, 2005) and an increased ventilatory response to exercise (Patrick *et al.*, 1983). Consequently, older

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individuals have a greater magnitude of mechanical ventilatory constraint during exercise than younger individuals, as indicated by a greater work of breathing (W_b), higher operating lung volumes, and an increased propensity towards expiratory flow limitation (EFL) (Molgat-Seon *et al.*, 2018*a*). The magnitude of mechanical ventilatory constraint directly affects the degree of respiratory effort required to exercise at a given absolute intensity (O'Donnell *et al.*, 2000), and therefore is likely to influence the perception of dyspnoea.

It is becoming increasingly apparent that biological sex also affects dyspnoea during exercise in healthy older individuals. Activity-related dyspnoea is twice as common in women than men in the general population between the ages of 38 and 67 y (Ekström *et al.*, 2017). Moreover, we and others have shown that older women report higher levels of dyspnoea during exercise at a standardized rate of oxygen uptake ($\dot{V}O_2$) (Ofir *et al.*, 2008) and absolute work rate (Molgat-Seon *et al.*, 2018*a*) than older men. Although the precise causes of sex-differences in the perception of dyspnoea during exercise are likely multifactorial, it is possible that inherent differences in the structure of the respiratory system play a contributory role. Specifically, the smaller lungs and airways in women relative to men are thought to predispose women to mechanical ventilatory constraint during exercise (Molgat-Seon *et al.*, 2018*c*), which could result in a greater perception of breathing discomfort. We base this hypothesis on three primary lines of evidence. First, older women have a higher W_b for a given minute ventilation ($\dot{V}_E$) and are more likely to exhibit EFL during exercise than older men (Molgat-Seon *et al.*, 2018*a*). Second, indices of mechanical ventilatory constraint and respiratory effort during submaximal exercise have been shown to correlate with ratings of dyspnoea in older men and women (Molgat-Seon *et al.*, 2018*a*). Third, when the degree of mechanical ventilatory constraint is experimentally increased during exercise, using resistive loading or dead-space loading, the perception of dyspnoea is increased concomitantly (el-Manshawi *et al.*, 1986; Iandelli *et al.*, 2002; Jensen *et al.*, 2011). It follows that acute manipulation of mechanical ventilatory constraint during exercise in healthy older men and women would result in corresponding changes in the perceived intensity of dyspnoea. Furthermore, reducing mechanical ventilatory constraint in

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older women may eliminate the sex-differences in exertional dyspnoea observed in older individuals. However, this hypothesis remains untested.

The aim of the present study was to determine the effect of acutely altering the magnitude of mechanical ventilatory constraint during submaximal exercise on the perception of dyspnoea in healthy older men and women. We hypothesized that during submaximal exercise: i) reducing mechanical ventilatory constraint would decrease the perceived intensity of dyspnoea, and ii) that increasing mechanical ventilatory constraint would increase the perceived intensity of dyspnoea. We further hypothesized that the effect of manipulating mechanical ventilatory constraint would have a significantly greater effect on the perceived intensity of dyspnoea in women than in men.

METHODS

Ethical Approval. All subjects provided written informed consent, and all study procedures were approved by the Providence Health Care Research Ethics Board at the University of British Columbia (#H16-01732), which conforms to the standards set by the latest revision of the *Declaration of Helsinki*, except for registration in a database.

Subjects. Eighteen healthy, recreationally active older individuals (9 men, 9 women) between the ages of 60 and 80 y participated in the study. All subjects had normal pulmonary function based on predicted values (Burrows *et al.*, 1961; Black & Hyatt, 1969; Crapo *et al.*, 1982; Morris, 1988), a body mass index of 18-30 $kg \cdot m^{-2}$ and peak aerobic power ≥80% predicted (Blackie *et al.*, 1989). Subjects were excluded if they were current smokers, had previously smoked >5 pack-years, or had a history or current symptoms of cardiorespiratory disease or any contraindications to exercise testing.

Experimental Overview. Participants reported to the laboratory for two days of testing separated by ≥48 h. During Day 1, anthropometric measurements were taken, followed by pulmonary function testing and a maximal incremental cycle exercise test. Exercise data

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obtained during Day 1 were used to determine each subject's first ventilatory threshold (V_{Th}). During Day 2, subjects performed a series of constant-load cycle exercise trials at the work rate corresponding to their V_{Th} under 3 experimental conditions in a single-blind randomized fashion separated by periods of rest. The aim of these experimental trials was to manipulate the degree of mechanical ventilatory constraint during moderate-intensity exercise, and the primary outcome measure was the perception of dyspnoea.

Pulmonary Function Testing. Spirometry, whole-body plethysmography, single breath diffusing capacity for carbon monoxide, 12-s maximum voluntary ventilation, as well as maximum inspiratory and expiratory pressures were assessed using a pulmonary function testing system (Vmax Encore 229 with V62J Autobox; CareFusion, Yorba Linda, USA) according to standard recommendations (Green *et al.*, 2002; Miller *et al.*, 2005; Wanger *et al.*, 2005; MacIntyre *et al.*, 2005). Pulmonary function measurements were expressed in absolute units and as a percentage of predicted normal values (Burrows *et al.*, 1961; Black & Hyatt, 1969; Crapo *et al.*, 1982; Morris, 1988).

Exercise Protocol. During Day 1 and Day 2, exercise testing was conducted on an electronically braked cycle ergometer (ergoselect 200, ergoline GmbH, Bitz, Germany). During Day 1, exercise testing began with 6 min of rest followed by 1 min of unloaded (0 W) pedalling, then 20 W step-wise increases in workload (starting at 20 W) every 2 min until volitional exhaustion. Peak work rate was defined as the highest work rate sustained for at least 30 s. Day 2 involved 3 identical exercise trials. Each constant-load cycle exercise trial was preceded by a 6-min rest period followed by 1 min of unloaded pedalling. Then, power output progressively increased in a ramp fashion over 1 min up to each subject's predetermined work rate, which was then sustained for 5 min. The exercise intensity for the constant-load exercise trials was set at each subject's V_{Th}, which was determined based on gas exchange data obtained during the incremental exercise test performed on Day 1 using a combination of previously described methods (Caiozzo *et al.*, 1982; Beaver *et al.*, 1986).

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For each individual, the respiratory compensation point and V_{Th} were identified. The exercise intensity corresponding to V_{Th} was set for each subject based on the work rate that was most congruent among the different methods of V_{Th} determination. During the first experimental trial, subjects were free to choose any cadence they preferred (mean±SD: 85±5 rpm, range: 70-105) and were instructed to maintain a similar cycling cadence across all constant-load cycle exercise tests. Experimental trials were separated by at least 15 min of rest but were extended based on subject's personal preference (mean±SD: 22±6 min, range: 15-32 min). Prior to beginning the second and third constant-load exercise trials, we ensured that cardiorespiratory variables returned to the levels observed during the rest period prior to the first trial.

Experimental Conditions. To reduce the magnitude of mechanical ventilatory constraint, subjects breathed a normoxic helium-oxygen inspirate (HEL). Replacing nitrogen with helium as the backing gas reduces resistance to flow by promoting the laminar flow of air and increases the ability to generate flow (Papamoschou, 1995). Thus, helium reduces the potential for EFL by increasing ventilatory capacity ($\dot{V}_{ECAP}$) at a given lung volume (Babb, 1997*a*), and reduces the resistive component of W_b (Papamoschou, 1995). To increase mechanical ventilatory constraint, subjects breathed compressed ambient air through a resistor placed in the inspiratory circuit of the breathing apparatus (RES). The aperture of the resistor was individually set to increase inspiratory resistance to ~5 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ (mean±SD: 5.7±0.8 $cmH_2O \cdot l^{-1} \cdot s^{-1}$, range: 4.2-6.8 $cmH_2O \cdot l^{-1} \cdot s^{-1}$), thereby increasing inspired W_b for a given $\dot{V}_E$. The magnitude of inspiratory resistance was chosen in order to increase the resistive component of W_b to the same degree as the magnitude of the sex-difference in W_b at a given absolute $\dot{V}_E$ based on our previous work in healthy older men and women (Molgat-Seon *et al.*, 2018*a*). In other words, we wanted to increase the W_b in older men to a similar level as observed in women at the same absolute $\dot{V}_E$ and we wanted to increase the W_b in older women by an equivalent amount above their normally occurring W_b at a given

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$\dot{V}_E$. As a control condition, subjects breathed ambient air through an unobstructed breathing circuit (CON).

During all constant-load exercise trials, inspired gas was delivered by connecting a non-diffusing 100 l reservoir bag (Vacumed model 1196-100, Ventura, CA, USA) to the inspiratory limb of the breathing circuit. The reservoir bag was connected to a series of compressed-gas tanks that delivered gas through a humidifier. The order of the experimental conditions was randomized and we took several measures to ensure the subjects were blinded. First, the breathing apparatus was identical in appearance for each trial. Second, for all trials, compressed gas was delivered through a reservoir connected to the inspiratory limb of the breathing circuit. Finally, all calibration and setup procedures between trials were performed in an identical manner. After each trial, we asked subjects to guess which experimental condition they had completed; on average, subjects guessed correctly on 27±15% of occasions.

Flow, Respiratory Pressures, and Diaphragm Electromyogram. At rest and during exercise on both visits, subjects breathed through a mouthpiece connected to a two-way non-rebreathing valve (Hans Rudolph 2700B, Hans Rudolph, Kansas City, USA). Inspired and expired flow were measured using calibrated pneumotachographs (model 3813, Hans Rudolph, Kansas City, USA), and volume was obtained by numerical integration of the flow signals. On Day 2, each pneumotachograph was calibrated with helium-oxygen prior to the HEL condition, and with ambient air prior to the RES and CON conditions. Mouth pressure (P_{mo}) was measured through a port in the mouthpiece using a calibrated differential transducer (DP15-34, Validyne Engineering, Northridge, USA). During Day 2, subjects were instrumented with a multi-pair oesophageal electrode catheter equipped with two balloons, which was used to measure oesophageal pressure (P_{oe}), gastric pressure, and electromyogram of the crural diaphragm (EMG_{di}), the technical details of which are provided elsewhere (Luo *et al.*, 2008). P_{oe} and gastric pressure were measured by connecting the distal end of each respective balloon to independent, calibrated differential

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transducers (DP15-34, Validyne Engineering, Northridge, USA). EMG_{di} was measured by connecting the catheter to a grounded bio-amplifier (model RA-8, Yinghui Medical Technology Co. Ltd., Guangzhou, China).

Cardiorespiratory Responses. Standard cardiorespiratory measures were recorded at rest and during exercise using a commercially available metabolic cart (TrueOne 2400, Parvomedics, Sandy, USA). Heart rate and electrocardiogram changes were monitored continuously using a 12-lead electrocardiogram hidden from subject view (Cardiosoft Diagnostics System v6.71, GE Healthcare, Mississauga, Canada). Arterial oxygen saturation was estimated using a finger-pulse oximeter (Radical-7, Massimo Corporation, Irvine, USA). End-tidal CO_2 ($P_{ET}CO_2$) was sampled through a port in the mouthpiece connected to a calibrated CO_2 analyser (Vacumed model 17630, Ventura, USA). Since helium interferes with the infrared signal used by the CO_2 analysers, the CO_2 analysers were calibrated before each trial using two different calibration gases: one containing nitrogen as a backing gas (for the CON and RES conditions), the other containing helium as the backing gas (for the HEL condition).

Maximal Ventilatory Capacity and Operational Lung Volumes. Prior to and immediately following exercise on Day 1, subjects performed a series of forced vital capacity (FVC) manoeuvres at different efforts in order to construct maximum expiratory flow-volume (MEFV) curves by taking into account exercise-induced bronchodilation and thoracic gas compression (Guenette *et al.*, 2010). Breathing a helium-rich gas increases the ability to generate flow at a given lung volume (Papamoschou, 1995). Thus, to account for the effect of helium on the MEFV curve, the same series of FVC manoeuvers was repeated with helium instead of room air immediately after the last constant-load exercise trial during Day 2. Inspiratory capacity manoeuvres were performed at rest and during the last 15 s of each exercise stage on Day 1. On Day 2, inspiratory capacity manoeuvres were performed at rest and during the last 15 s of each constant-load exercise trial. End-inspiratory lung volume

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(EILV) and end-expiratory lung volume (EELV) were derived from each inspiratory capacity manoeuvre (Guenette *et al.*, 2013). Theoretical maximum ventilation ($\dot{V}_{ECAP}$) for rest, each incremental exercise stage, and for each constant-load exercise test were calculated based on the maximum expiratory airflow during a composite-averaged tidal breath (see *Data Processing and Analysis*) and the corresponding operating lung volumes as previously described (Johnson *et al.*, 1999). Fractional utilization of available ventilatory capacity ($\dot{V}_E/\dot{V}_{ECAP}$) was determined as the quotient of $\dot{V}_E$ and $\dot{V}_{ECAP}$. The presence of EFL was determined by positioning each flow-volume curve within the corresponding MEFV curve according to the measured EELV lung volume. The magnitude of EFL was then calculated as the % overlap between the expiratory portion of the tidal breaths and the MEFV curve, and EFL was present if ≥5% of the tidal flow-volume curve encroached on the MEFV curve.

Perceptual Responses. At rest and during exercise, subjects rated the intensity of "breathing discomfort" (dyspnoea) and "leg discomfort" using the modified category-ratio 10 Borg scale (Borg, 1982). Dyspnoea was defined as "the sensation of laboured or difficult breathing" and leg discomfort was defined as the "sensation of leg muscle fatigue". The endpoints of the scale were anchored such that 0 represented "no breathing/leg discomfort" and 10 represented "the most severe breathing/leg discomfort ever experienced or imagined". During Day 1, perceptual responses were recorded at rest and during the last 30 s of each exercise stage. During Day 2, perceptual responses were recorded at rest and during the last 30 s of each minute during all constant-load exercise tests. Given the subjective nature of perceived dyspnoea and leg discomfort, perceptual responses during Day 2 were assessed by an experimenter who was blinded to the condition.

Data Processing and Analysis. Airflow, respiratory pressures, $P_{ET}CO_2$, and EMG_{di} were collected using a 16-channel analogue-to-digital data acquisition system (PowerLab, ADInstruments, Colorado Springs, USA), sampled at 2000 Hz, then recorded using dedicated

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software (LabChart 7.3.7, ADInstruments, Colorado Springs, USA). Raw EMG_{di} signals were amplified and band-pass filtered between 20 and 1000 Hz (Biomedical Amplifier, Guangzhou Yinghui Medical Equipment Co Ltd, Guangzhou, China) and converted to a root mean square (RMS) using a time constant of 100 ms and a moving average window. EMG_{di} data were analysed on a breath-by-breath basis, whereby for each breath peak RMS data were obtained by manually selecting RMS signals falling between zones of cardiac artefact (Ramsook *et al.*, 2017). The electrode pair with the largest EMG_{di} amplitude for each breath was used for analysis, and the associated EMG_{di} data were then expressed as a percent of maximum EMG_{di} activity ($EMG_{di,max}$), defined as the highest level of EMG_{di} during an inspiratory capacity manoeuvre at rest or during exercise (Jolley *et al.*, 2009). The ratio between EMG_{di} expressed as a function of $EMG_{di,max}$ and tidal volume normalised to vital capacity was used as an index of neuromechanical (un)coupling (NMU) of the respiratory system (Schaeffer *et al.*, 2014; Guenette *et al.*, 2014). Flow, volume, and pressures were composite averaged using customized software, and W_b was then calculated by integrating the area within the oesophageal pressure–volume curve (Dominelli & Sheel, 2012). All cardiorespiratory and perceptual variables were analysed over the last 2 min of each constant-load exercise test.

Statistics. We performed an *a priori* sample size calculation using an estimated difference between means for dyspnoea of 1.0 unit on the Borg CR-10 scale, assuming a standard deviation (SD) of 0.75 and an α of 0.05 to yield a statistical power of 0.80. These estimates are based upon: i) the anticipated degree of change to the work of breathing (HEL vs. RES conditions), ii) our previous work in older men and women, wherein older women had a 1.0 unit on the Borg 0-10 scale differences in the perceived intensity of dyspnoea at a given work rate and relative $\dot{V}O_2$ than older men (Molgat-Seon *et al.*, 2018*a*), iii) the observation that a difference in dyspnoea of 1.0 unit on the Borg CR-10 scale is correlated with electrical activity of the diaphragm during exercise (Schaeffer *et al.*, 2014), iv) the recommended minimally clinically important difference for dyspnoea in patients with chronic obstructive

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pulmonary disease of 1.0 unit on the Borg CR-10 scale (Ries, 2005). The calculated sample size was 9 subjects per group.

Subject characteristics, pulmonary function, and peak exercise data were compared between the sexes using Student's unpaired *t*-test. A 2×3 (sex [male or female] by condition [CON, RES, and HEL]) repeated measures analysis of variance was used to test for differences in perceptual and cardiorespiratory variables during the last 2 min of the constant-load exercise tests. When significant *F* ratios were detected, Tukey's post hoc test was used to determine the location of group mean differences. The association between W_b and dyspnoea across conditions was assessed via random-coefficients regression (Xu, 2003). The occurrence of EFL during the constant-load exercise tests was expressed as frequency statistics; comparisons were made between conditions using Fischer's Exact Test. All analyses were performed using a statistical software package (SPSS v20.0, IBM, Armonk, USA) and the level of statistical significance was set at $p<0.05$. All data are presented as mean±SD unless otherwise stated.

RESULTS

Subject Characteristics and Pulmonary Function. Table 1 summarizes descriptive characteristics and pulmonary function data for all subjects. When expressed in absolute terms, the majority of pulmonary function measures were greater in men than women (all $p<0.05$), with the exception of the ratio of forced expiratory volume in 1 s to forced vital capacity ($p=0.16$), and forced expiratory flow between 25 and 75% of forced vital capacity ($FEF_{25\text{-}75\%}$) ($p=0.92$).

Incremental Exercise Responses. Data at peak exercise are shown in Table 2. There was a significant effect of sex on absolute $\dot{V}O_2$, carbon dioxide output, work rate, $\dot{V}_E$, tidal volume, and $\dot{V}_{ECAP}$ (all $p<0.05$). When $\dot{V}O_2$ peak was expressed as a percent of predicted, there was no significant effect of sex, indicating that subjects' relative fitness was similar. On average, subjects in both groups achieved a respiratory exchange ratio of 1.10±0.05 (range: 1.05-

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1.18) and near maximum heart rates based on predicted normal values (Tanaka *et al.*, 2001) (99±8%, range: 91-112%), indicating that maximal effort was exerted across groups. Ratings of perceived dyspnoea and leg discomfort are shown in Figure 1. Women had a higher perceived intensity of dyspnoea than men at 40, 60, 80, and 100 W (all $p<0.05$). However, when work rate was expressed as a function of peak work rate, the effect of sex was no longer present ($p>0.05$, data not shown). Additionally, no sex-differences in dyspnoea were noted when the perceived intensity of dyspnoea during incremental exercise was expressed as a function of $\dot{V}_E$/MVV or $\dot{V}_E/\dot{V}_{E\ CAP}$ (both $p>0.05$). Women reported greater leg discomfort at 80 W ($p<0.05$), but no significant differences were noted at any other absolute work rate (all $p>0.05$). Again, when work rate was expressed as a function of peak work rate, the effect of sex on leg discomfort was no longer evident ($p>0.05$, data not shown).

Exercise data at V_{Th} in both groups are presented in Table 3. On average, men and women reached V_{Th} at similar fractions of peak exercise $\dot{V}O_2$ ($p=0.74$), but since men were working at a higher absolute work rate, they had a higher $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, and tidal volume than women (all $p<0.05$). All other cardiorespiratory and perceptual variables at V_{Th} were similar between the sexes (all $p>0.05$).

Response to Constant-Load Exercise. Cardiorespiratory variables during the three constant-load cycle exercise trials are shown in Table 4. Across conditions, men had significantly higher $\dot{V}O_2$ and $\dot{V}CO_2$ than women (both $p<0.05$), while respiratory exchange ratio, heart rate, arterial oxygen saturation, and $P_{ET}CO_2$ were similar between the sexes (all $p<0.05$). There was no significant effect of condition on $\dot{V}O_2$, $\dot{V}CO_2$, respiratory exchange ratio, heart rate, arterial oxygen saturation, or $P_{ET}CO_2$ (all $p>0.05$). The ventilatory response to constant-load exercise under all three experimental conditions is depicted in Figure 2A. There was a significant effect of condition and sex on $\dot{V}_E$ (both $p<0.05$). Specifically, $\dot{V}_E$ was slightly, but significantly, lower during the RES relative to the CON condition ($p<0.05$), while $\dot{V}_E$ during the HEL condition was not significantly different from CON ($p=0.27$). However, there was no systematic effect of condition on tidal volume or breathing frequency (Table 4; both

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p>0.05). The fractional utilization of $\dot{V}_E/\dot{V}_{E\ CAP}$ is shown in Figure 2B. There was a significant main effect of condition (p<0.001), but not sex (p=0.76), whereby $\dot{V}_E/\dot{V}_{E\ CAP}$ was significantly lower during HEL relative to CON (p=0.03), but similar to CON during RES (p=0.93). There were no significant differences in operating lung volumes between the sexes or between conditions (all p>0.05; Figure 2C).

The W_b during constant-load exercise is depicted in Figure 3A. As expected, RES significantly increased W_b (men: 42±19%, women: 50±16%), while HEL significantly reduced W_b (men: –21±6%, women: –17±10%) relative to CON (both p<0.05). The relative increase in W_b during the RES condition and the relative decrease in W_b during the RES condition were similar between the sexes (both p>0.05). Figure 4 shows the W_b during each constant-load exercise test as a function of $\dot{V}_E$ and compared to values derived from sex- and age-specific regression equations (Molgat-Seon *et al.*, 2018*a*). The change in EMG_{di} activity followed a similar pattern between conditions as the W_b (Figure 3B), whereby, relative to CON, EMG_{di} (men: 35±18%, women: 22±17%) was significantly increased during RES (p=0.007), and significantly reduced (men: –7±6%, women: –12±8%) during HEL (p=0.03). Moreover, the pattern of change in EMG_{di} during HEL and RES conditions (as a % of CON) was similar between the sexes (both p>0.05). Figure 3C shows the degree of NMU during each constant-load exercise test. There was a significant effect of condition (p<0.001), but not sex (p=0.76), whereby NMU was higher during RES and lower during HEL relative to CON (both p<0.05).

The frequency of EFL during each constant-load exercise test is shown in Figure 5. During CON, 9 of 18 subjects were flow limited, and the frequency of EFL was not significantly different relative to CON during RES (5 of 18 subjects, p=0.31). However, 0 of 18 subjects were flow limited during the HEL condition - a significant reduction in the frequency of EFL relative to CON (p=0.001).

Perceptual Responses to Constant-Load Exercise. The perceptions of dyspnoea and leg discomfort during the constant-load exercise trials are shown in Figure 6. There was a significant effect of sex on dyspnoea, whereby women had a higher perception of dyspnoea

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than men across conditions (p=0.02, η^2=0.32; Figure 6 A); however, there was no significant effect of condition on the perception of dyspnoea during constant-load exercise (p=0.11, η^2=0.14). There was no significant correlation between W_b and dyspnoea across conditions (slope=0.01 units·J^{-1}·min^{-1}, r^2=0.61, p=0.10). Moreover, there was no significant effect of sex or condition on the perception of leg discomfort (Figure 6B).

DISCUSSION

Major Findings. We sought to determine the effect of experimentally manipulating mechanical ventilatory constraint during exercise on the perception of dyspnoea in healthy older men and women. The major findings from our study are twofold. First, women had a greater perception of dyspnoea during short-duration constant-load exercise at V_{Th} across experimental conditions. Second, acutely increasing or decreasing the degree of mechanical ventilatory constraint during submaximal exercise at the same relative intensity in healthy older men and women did not affect the perceived intensity of dyspnoea. Overall, our findings suggest that, in healthy older adults, sex-differences in exertional dyspnoea are not caused by sex-differences in mechanical ventilatory constraint, at least during exercise at V_{Th}.

Sex-differences in the Perception of Dyspnoea. During incremental exercise, women had significantly higher dyspnoea for a given absolute work rate at 40, 60, 80 and 100 W (Figure 1), an observation that is consistent with our previous data (Molgat-Seon *et al.*, 2018*a*) and those of others (Killian *et al.*, 1992; Ofir *et al.*, 2008). At V_{Th} during the incremental exercise test, women reported dyspnoea that were on average 0.6 Borg scale units greater than in men; however, this difference did not reach statistical significance (p=0.18, Table 3). Yet, during the constant-load exercise trials at V_{Th}, women reported significantly higher levels of dyspnoea than men by an average of 1.0 Borg scale unit across experimental conditions (Figure 6). The discrepancy between the presence of a significant sex-difference in dyspnoea during constant-load exercise at V_{Th} and the absence thereof at the same exercise intensity

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during incremental exercise likely reflects differences in the exercise protocol, the timing of dyspnoea measurements (i.e. once every 2 min *vs.* every minute for 6 min), the relatively small sample size, and the fact that multiple observations were made for each subject during the constant-load exercise trials. Nevertheless, the salient question is what mechanism causes the observed sex-differences in dyspnoea during exercise in healthy older individuals?

The neurophysiological mechanisms of dyspnoea are complex and multifactorial (Parshall *et al.*, 2012). Exertional dyspnoea in healthy individuals is thought to reflect the perception of increased respiratory effort required to meet the increased ventilatory demands. Sex-differences in the mechanical ventilatory response to exercise in healthy younger and older adults have previously been observed (Dominelli *et al.*, 2015*a*; Molgat-Seon *et al.*, 2018*a*). Regardless of age, women have a higher W_b for a given $\dot{V}_E$ ≥50-65 $l{\cdot}min^{-1}$ than men (Molgat-Seon *et al.*, 2018*a*); this has been ascribed to women having a higher resistive W_b (Guenette *et al.*, 2009; Dominelli *et al.*, 2015*a*). Additionally, older women appear to have a higher propensity towards EFL during exercise than older men (Molgat-Seon *et al.*, 2018*a*). In the present study, we noted that during exercise at a fixed relative intensity (*i.e.* at V_{Th}), women had a similar W_b (Figure 3A) but a higher perceived intensity of dyspnoea than men (Figure 6A). The similar W_b between the sexes implies that women are likely having to dedicate a greater fraction of whole-body $\dot{V}O_2$ to breathing than men based on the linear relationship between W_b and $\dot{V}O_2$ of the respiratory muscles (Dominelli *et al.*, 2015*b*). Therefore, we reasoned that if older women have a greater degree of mechanical ventilatory constraint (*i.e.* a similar W_b despite at lower $\dot{V}_E$) during exercise than do older men, that a relatively greater load would be imposed on their respiratory muscles. The perception of increased respiratory effort may explain the sex-differences in exertional dyspnoea in healthy older men and women. However, we acknowledge that there are likely other explanations for why women in our study had a higher perceived intensity of dyspnoea during exercise at V_{Th} than men, such psychological and/or sociocultural

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differences between the sexes that are known to influence the perception of dyspnoea (Bowden *et al.*, 2011).

Manipulations of Mechanical Ventilatory Constraint During Exercise. We experimentally altered the magnitude of mechanical ventilatory constraint during a series of short-duration constant-load exercise trials in a group of healthy older men and women. During the RES condition, we increased W_b so that it remained within the physiological range observed during incremental exercise. Based on data from our previous work in older men and women (Molgat-Seon *et al.*, 2018*a*), we increased W_b in men to a similar extent to what would be observed in older women at the same absolute $\dot{V}_E$ without breathing through a resistor (Figure 4). We also increased the W_b in women to a similar extent to that observed in men, albeit at a significantly lower absolute $\dot{V}_E$ (Figure 4). Thus, if the sex-difference in W_b contributed to sex-differences in dyspnoea, we would expect to observe an increase in dyspnoea in men to a similar level as women during the CON condition, and an increase in dyspnoea in women over and above their CON condition. However, regardless of sex, dyspnoea did not increase relative to CON during the RES condition (Figure 6A). Experimental studies in healthy young individuals involving the addition of external resistive loads during exercise have shown that dyspnoea increases in a resistance-dependent manner (Cotes *et al.*, 1985; el-Manshawi *et al.*, 1986). However, the level of added resistance in these previous studies ranged from 33-73 $cmH_2O·l^{-1}·s^{-1}$, which greatly exceeds the resistance of the intrathoracic airways of individuals with even the most profound degree of pathological airway obstruction (Hogg *et al.*, 1968), thereby limiting the generalizability of those findings. Conversely, another study used a similar experimental protocol but with a lower level of added resistance (~2.7 $cmH_2O·l^{-1}·s^{-1}$) and found that healthy individuals did not report higher levels of dyspnoea during exercise with the added external resistance relative to control (Lane *et al.*, 1987). In our study, the level of external inspiratory resistance was 5.7±0.8 $cmH_2O·l^{-1}·s^{-1}$, which resulted in an increase in W_b that never exceeded the absolute values observed during maximal exercise in a similar group of

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healthy older individuals (Molgat-Seon *et al.*, 2018*a*). Thus, our data suggest that increasing the W_b to physiologically relevant levels during constant-load exercise does not increase the intensity of perceived dyspnoea in healthy older adults, regardless of sex.

By using a normoxic helium-oxygen inspirate, we were able to reduce the magnitude of mechanical ventilatory constraint during the HEL condition. Breathing helium during exercise has been shown to eliminate EFL and reduce the resistive W_b in healthy younger individuals (Babb, 1997*a*; 1997*b*; Dominelli *et al.*, 2013). Since older women have a higher propensity towards EFL and a higher resistive component of W_b than older men (Molgat-Seon *et al.*, 2018*a*), we surmised that the HEL condition would result in a reduction in dyspnoea in women to a level equivalent to that of men during the CON condition, while having only a small positive effect on dyspnoea relative to the CON condition in men. Based on data from our previous work in older men and women (Molgat-Seon *et al.*, 2018*a*), the HEL condition reduced W_b in women to a similar extent to that observed in men at the same absolute $\dot{V}_E$, and we reduced W_b in men well below the values typically observed at the same absolute $\dot{V}_E$ (Figure 4). However, HEL had no significant effect on dyspnoea (Figure 6A). Therefore, our data suggest that decreasing the normally occurring W_b by 18±4% during constant-load exercise does not decrease the perceived intensity of dyspnoea in healthy older adults, regardless of sex.

The purpose of this study was to determine the effect of manipulating mechanical ventilatory constraint on dyspnoea during sub-maximal exercise in older men and women. However, given that older individuals have a lower resting arterial partial pressure of oxygen than younger individuals (Janssens, 2005), we were concerned about the possible effects exercise-induced reductions in arterial oxygen saturation influencing respiratory or limb sensations. In a separate trial (data not shown), all participants performed exercise whilst breathing a mildly hyperoxic gas mixture (FIO_2=0.26). This inspirate was selected to prevent any decrease in arterial oxygen saturation below resting values. Moreover, we avoided using a highly hyperoxic inspirate (*e.g.* FIO_2=0.6) as this would have reduced the drive to breathe and increased the arterial partial pressure of oxygen to a non-physiological state.

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We found that hyperoxia slightly lowered $\dot{V}_E$ relative to CON (men: –5±1 $l \cdot min^{-1}$, women: –3±1 $l \cdot min^{-1}$) and by association W_b (men: –8±3 $J \cdot min^{-1}$, women: –4±2 $l \cdot min^{-1}$) without a measurable change in the perceived intensity of dyspnoea or leg discomfort. As such, our measures of dyspnoea and our manipulations of mechanical constraint are unlikely to be confounded by the effect of arterial oxygenation.

Our observation that women had a higher perceived intensity of dyspnoea at a given work rate during incremental exercise (*i.e.* during Visit 1) is unsurprising due to differences in lung and airway size as well as absolute aerobic capacity. This observation agrees with our previous work (Molgat-Seon et al., 2018) as well as that of others (Killian et al., 1992; Ofir et al., 2008). However, in the present study, we had older men and women exercise at similar relative exercise intensities (*i.e.* at V_{Th}), which resulted in lower work rate and $\dot{V}_E$ in women than in men. Despite these differences, women and men utilized a similar fraction of $\dot{V}_{ECAP}$ (Figure 2B) and had a statistically similar W_b (Figure 3 and Figure 4). This is an important point because in this situation we were able to test whether manipulating W_b had a greater effect on the perceived intensity of dyspnoea during exercise in older women than older men. However, despite increasing and decreasing the degree of mechanical ventilatory constraint during exercise, there was no effect of condition on dyspnoea (Figure 6A). Moreover, there was no significant association between W_b and dyspnoea across conditions, which we interpret to mean that the magnitude of mechanical ventilatory constraint is not the primary determinant of exertional dyspnoea, regardless of sex.

Mechanisms of Dyspnoea in Healthy Aging. During exercise, the mechanisms of dyspnoea are complex and multifactorial (Killian & Jones, 1994). Broadly speaking, the perceived intensity of dyspnoea is thought to increase, in part, due to a mismatch between respiratory motor output and the mechanical response to this output, also known as NMU (Jensen *et al.*, 2009). Previous studies have used EMG_{di} as a surrogate for neural respiratory drive to the diaphragm (Luo *et al.*, 2008), and while this approach has several limitations (Faisal *et al.*, 2016; Martinez-Valdes *et al.*, 2018), it is commonly employed in combination with

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normalized measures of tidal volume to provide a quantitative estimate of NMU in both health and disease (Schaeffer *et al.*, 2014; Guenette *et al.*, 2014; Ciavaglia *et al.*, 2014; Elbehairy *et al.*, 2016). In the present study, we manipulated the degree of mechanical ventilatory constraint during exercise in healthy older men and women, which correspondingly altered EMG_{di} (Figure 3B). However, changes in EMG_{di} were not accompanied by proportional changes in normalized measures of tidal volume, which implies that we also experimentally manipulated NMU (Figure 3C). Based on our results, we conclude that NMU is not the primary determinant of dyspnoea during exercise in healthy older adults, at least during short-duration exercise at V_{Th}. Moreover, our results do not support the hypothesis that sex-differences in exertional dyspnoea observed in healthy older individuals are caused by sex-differences in mechanical ventilatory constraint. The question then becomes, if mechanical ventilatory constraint does not explain sex-differences in dyspnoea during exercise in healthy older individuals, what does?

Dyspnoea is a complex sensation that arises through the interaction of mechanical, chemical, neural, affective, and sociocultural factors (Parshall *et al.*, 2012). Our study aimed to manipulate experimentally one of these contributing factors, and therefore other factors are likely to explain the observed sex-differences in exertional dyspnoea. If we narrow our perspective to physiological factors that are known to differ during exercise on the basis of biological sex, possible explanations include the pulmonary vascular response to constant-load exercise, and sex-differences in respiratory muscle activation during exercise. Recent data in healthy older men and women during moderate intensity exercise at approximately 72-74% of age-predicted maximal heart rate show that older women have a greater pulmonary artery wedge pressure compared to older men at the same relative exercise intensity (Esfandiari *et al.*, 2017). It is possible, albeit speculative, that the increased dyspnoea in older women observed in the present study was the result of sex-differences in the hemodynamic response to exercise in healthy older adults. We have recently shown that older and younger women rely on scalene and sternocleidomastoid muscles to a greater extent during exercise than older and younger men (Molgat-Seon *et al.*, 2018*b*). The

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increased motor output to the scalene and sternocleidomastoid muscles may also increase the perception of dyspnoea (Gigliotti, 2010). Nevertheless, the multifactorial nature of the mechanisms of dyspnoea cannot be overstated. The notion that a single causative factor can explain sex-differences in dyspnoea in older individuals is appealing due to its conceptual tidiness,

but is likely an oversimplification. Therefore, future studies that consider a host of potentially "dyspnogenic" factors in a large population of healthy men and women are needed to improve our understanding of the mechanistic basis of sex-differences in exertional dyspnoea.

Limitations. There are several limitations of our study that should be acknowledged. First, the constant-load exercise bouts were performed at a moderate exercise intensity (*i.e.* V_{Th}) and the results of our study cannot be generalized to higher or lower intensities. Nevertheless, we chose to perform experimental trials at V_{Th} (*i.e.* equivalent to ~74% of peak $\dot{V}O_2$ in our subjects) because it is physiologically equivalent between the sexes and commensurate with an exercise intensity that most individuals are able to sustain for relatively long periods of time. Second, given the moderate intensity and short-duration of each exercise bout, the absolute dyspnoea ratings in our study were relatively low ('slight' to 'moderate'). Therefore, it is possible that there is a perceptual (or perhaps even mechanical) threshold above which acute alterations in mechanical ventilatory constraints may influence dyspnoea. Third, as is the case with any study involving a subjective primary outcome variable, the placebo effect may have confounded our results. However, we took great care in ensuring that the subjects and the experimenter tasked with asking the subjects to rate their perceptions of dyspnoea were blinded to the experimental conditions. This was accomplished by standardizing the gas delivery method across trials, performing the same calibration procedures in the same order between trials, and instructing subjects not to speak for at least 1 min after the end of each trial due to the effect of helium on voice pitch. Fourth, although our study was appropriately powered to detect a 1.0 unit on the

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Borg CR-10 scale difference in dyspnoea between groups, the study was not powered to detect a smaller effect. Therefore, it is possible that mechanical ventilatory constraint may still contribute to sex-differences in the perceived intensity of dyspnoea during exercise, albeit to a small extent. Fifth, V_{Th} is a discrete boundary between two exercise intensity domains. We were careful in our determination of V_{Th} (Caiozzo *et al.*, 1982; Beaver *et al.*, 1986), and this approach is similar to that of others who have made between-group comparisons during dynamic exercise (Babb, 1997*a*). However, it is possible that during experimental trials some participants were exercising slightly above V_{Th} while others were slightly below V_{Th}, which may have had an impact on our observed findings. Specifically, the perceptual responses to an increase or a decrease in mechanical ventilatory constraint during exercise may be differ based on whether participants are exercising above or below V_{Th}. To account for this limitation, future studies should consider performing similar experiments with participants exercising at fixed fractions of peak work rate above and below V_{Th}. Lastly, our manipulations of mechanical ventilatory constraint were relatively modest. Although we could have used a proportional assist ventilator to further reduce the W_b (Dominelli *et al.*, 2016; 2017), the reductions in W_b would have been the result of decreases in both the resistive and viscoelastic components of W_b, and would have made blinding subjects to the experimental condition impossible. Similarly, we could have used a higher resistive load, but this would not have been representative of the resistive work associated with exercise hyperpnoea in healthy individuals.

Perspectives. Our study is the first to investigate the mechanisms of sex-differences in exertional dyspnoea by experimentally manipulating mechanical ventilatory constraint during exercise in healthy older men and women. We found that acutely manipulating the degree of mechanical ventilatory constraint during short bouts of exercise at V_{Th} did not have a significant effect on the perceived intensity of dyspnoea in healthy older men and women. We recognize that the contextual nature of our study limits the generalizability of our findings. Therefore, we provide the following perspectives. First, the perception of

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dyspnoea during the constant-load exercise tests was considered 'slight' to 'moderate' according to the Borg scale (Borg, 1982). Although the degree of mechanical ventilatory constraint did not appear to contribute to dyspnoea at V_{Th}, our findings cannot be extrapolated to higher exercise intensities where the perception of dyspnoea is greater. Moreover, due to the complexities associated with the precise detection of V_{Th}, some participants may have been exercising slightly above V_{Th} while others were exercising slightly below V_{Th}. Although it is well established that exercise intensity has a substantial effect on the perception of dyspnoea during exercise (Killian & Jones, 1994), it is unclear how changes in exercise intensity modulate the perceptual responses to increasing or decreasing the magnitude of mechanical ventilatory constraint. Second, our comparisons between older men and older women were made at a similar relative exercise intensity, but for short periods of time (*i.e.* 6 min). It is unknown how the time course of dyspnoea would change during longer bouts of exercise, or how mechanical ventilatory constraint might influence this time course. Lastly, the finding of sex-differences in the perception of dyspnoea during exercise is not unique to healthy older individuals; sex-differences in the perception of activity-related breathlessness have been reported in studies involving healthy young individuals (Schaeffer *et al.*, 2014; Cory *et al.*, 2015), asthmatics (Chhabra & Chhabra, 2011), and individuals with chronic obstructive pulmonary disease (de Torres *et al.*, 2006; 2007; Guenette *et al.*, 2011). While it is tempting to generalize our findings to other populations, it is currently unclear how aging, biological sex, and respiratory disease interact to influence the perception of breathing discomfort during physical exertion.

Conclusions. Acutely manipulating the magnitude of mechanical ventilatory constraint during short bouts of moderate-intensity exercise in healthy older men and women did not have an effect on the perception of dyspnoea. Although sex-differences in respiratory mechanics are evident in healthy older adults, they do not appear to contribute to the magnitude of exertional dyspnoea, at least during short bouts of submaximal exercise. Thus, the higher levels of dyspnoea observed in older women relative to older men may be caused

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by physiological mechanisms that were not assessed in the present study, or by non-physiological factors. Future work is required to determine the mechanisms that lead to sex-differences in dyspnoea in older adults.

ADDITIONAL INFORMATION

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Author contributions: YMS, PBD, JDR, JAG, and AWS designed the study. YMS, AHR, PBD, and MRS enrolled subjects and conducted data collection. YMS CMP, and PBD analysed the data. All authors had complete access to the study data, contributed to drafting and critically revising the manuscript. All authors approved the final version of the manuscript and take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGENDS

Figure 1. Perceptions of dyspnoea (panel A) and leg discomfort (panel B) during incremental cycle exercise in men and women. The highest equivalent work rate achieved by all subjects was 100 W. Dashed lines within each group connect the 100 W data point to the peak exercise data point. The work rates corresponding to V_{Th} are depicted by the grey dotted line for men and the black dotted line for women. * p<0.05, men vs. women.

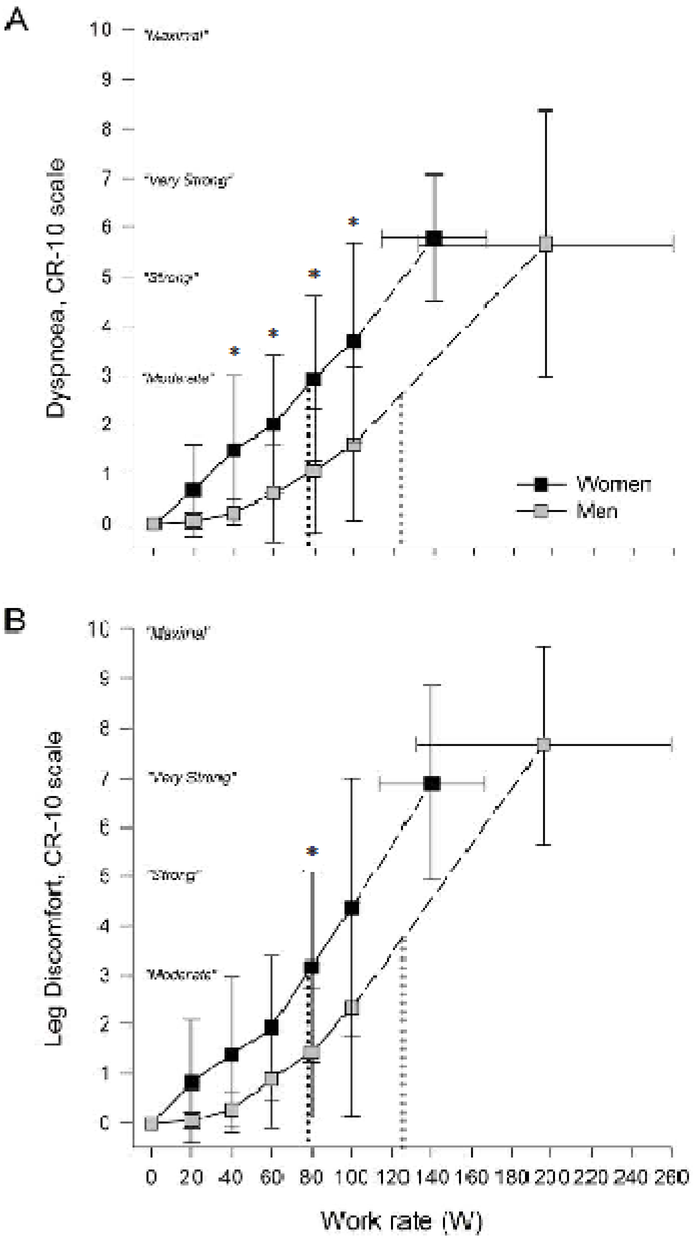

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Figure 2. Group mean $\dot{V}_E$ (panel A), $\dot{V}_E/\dot{V}_{E\ CAP}$ (panel B), and operating lung volumes (panel C) during the last 2 min of each constant-load exercise condition. In panel C, the grey shaded area represents average resting operating lung volumes for all subjects. $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}_{E\ CAP}$, fractional utilization of ventilatory capacity; CON, control condition; RES, resistor condition; HEL, helium condition. *p<0.05, effect of sex, † p<0.05, effect of condition.

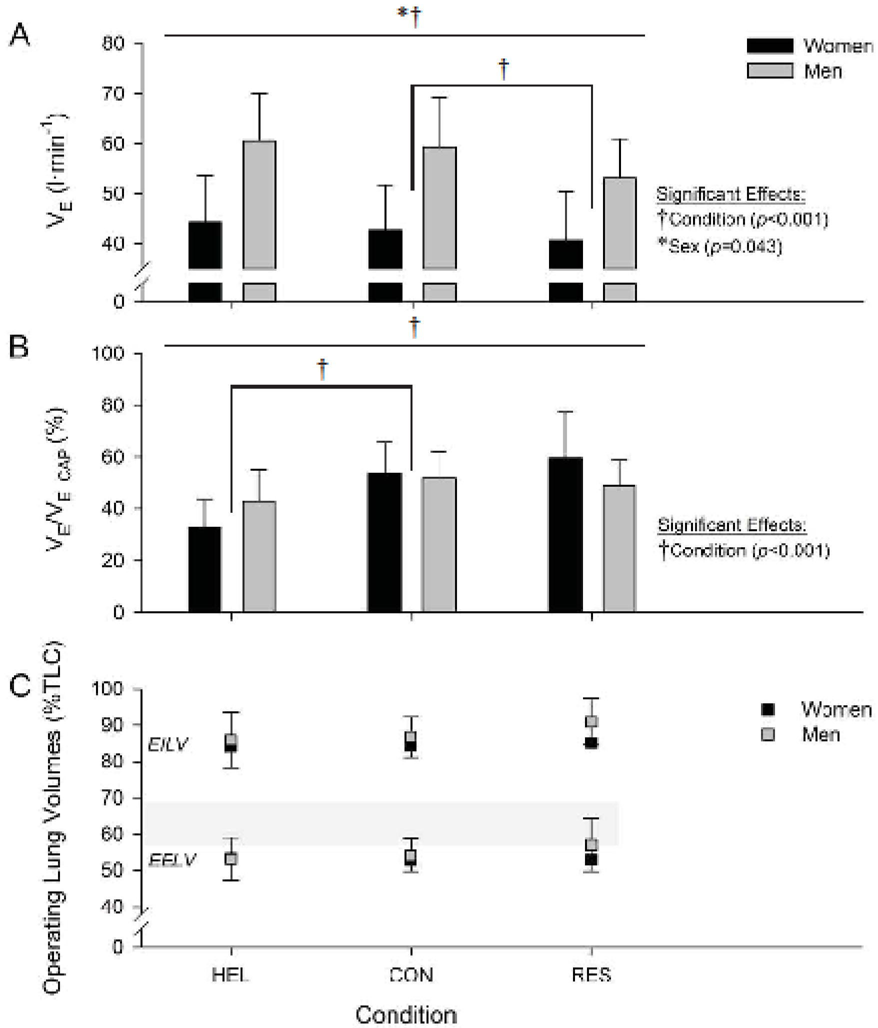

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Figure 3. Group mean W_b (panel A), EMG_{di} (panel B), and NMU (panel C) during the last 2 min of each constant-load exercise condition. W_b, work of breathing; EMG_{di}, diaphragm electromyogram; $EMG_{di,max}$, maximum EMG_{di} activity; NMU, neuromechanical uncoupling; V_T, tidal volume; VC, vital capacity; CON, control condition; RES, resistor condition; HEL, helium condition. † p<0.05, effect of condition.

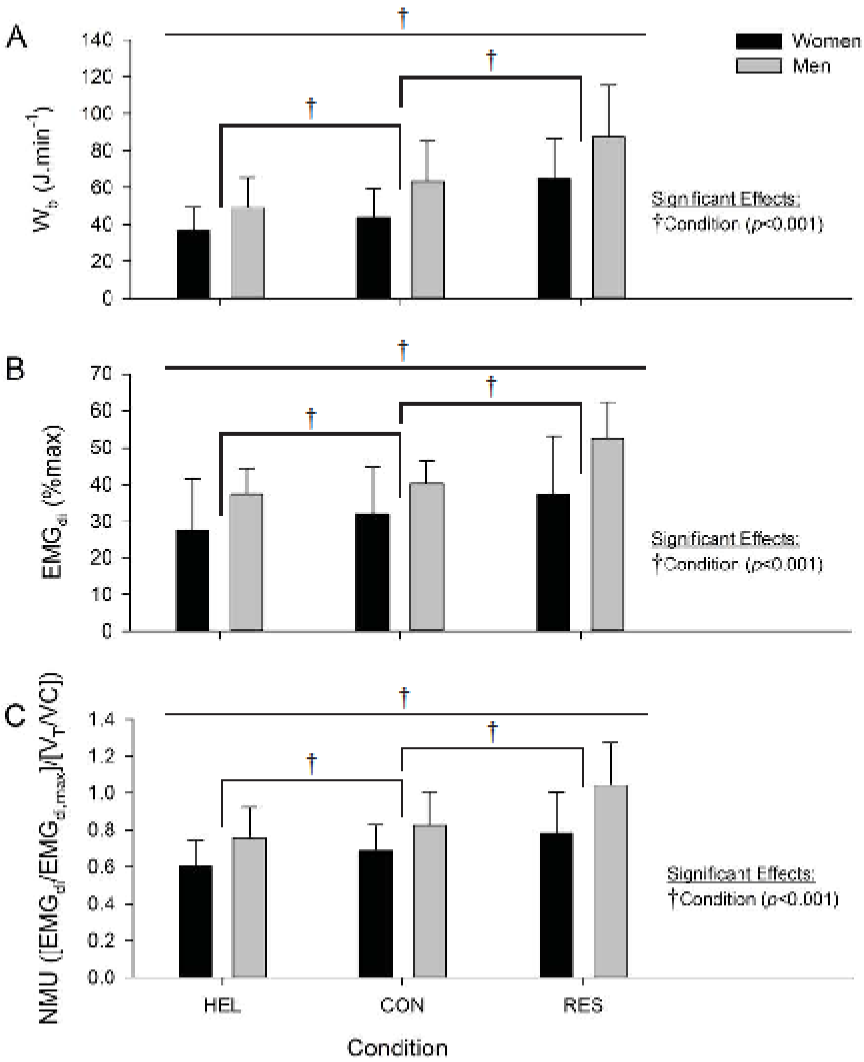

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Figure 4. W_b during the last 2 min of each constant-load exercise condition. In panel A, mean values for men and women are shown for each condition and juxtaposed over regression lines for men and women from a previous study in a separate group of subjects aged 60-80 y (Molgat-Seon *et al.*, 2018*a*). In panel B, mean values for men and women pooled together are shown for each condition and juxtaposed over a single regression lines for men and women from a previous study in a separate group of subjects aged 60-80 y (Molgat-Seon *et al.*, 2018*a*). W_b, work of breathing; CON, control condition; RES, resistor condition; HEL, helium condition. † p<0.05, effect of condition.

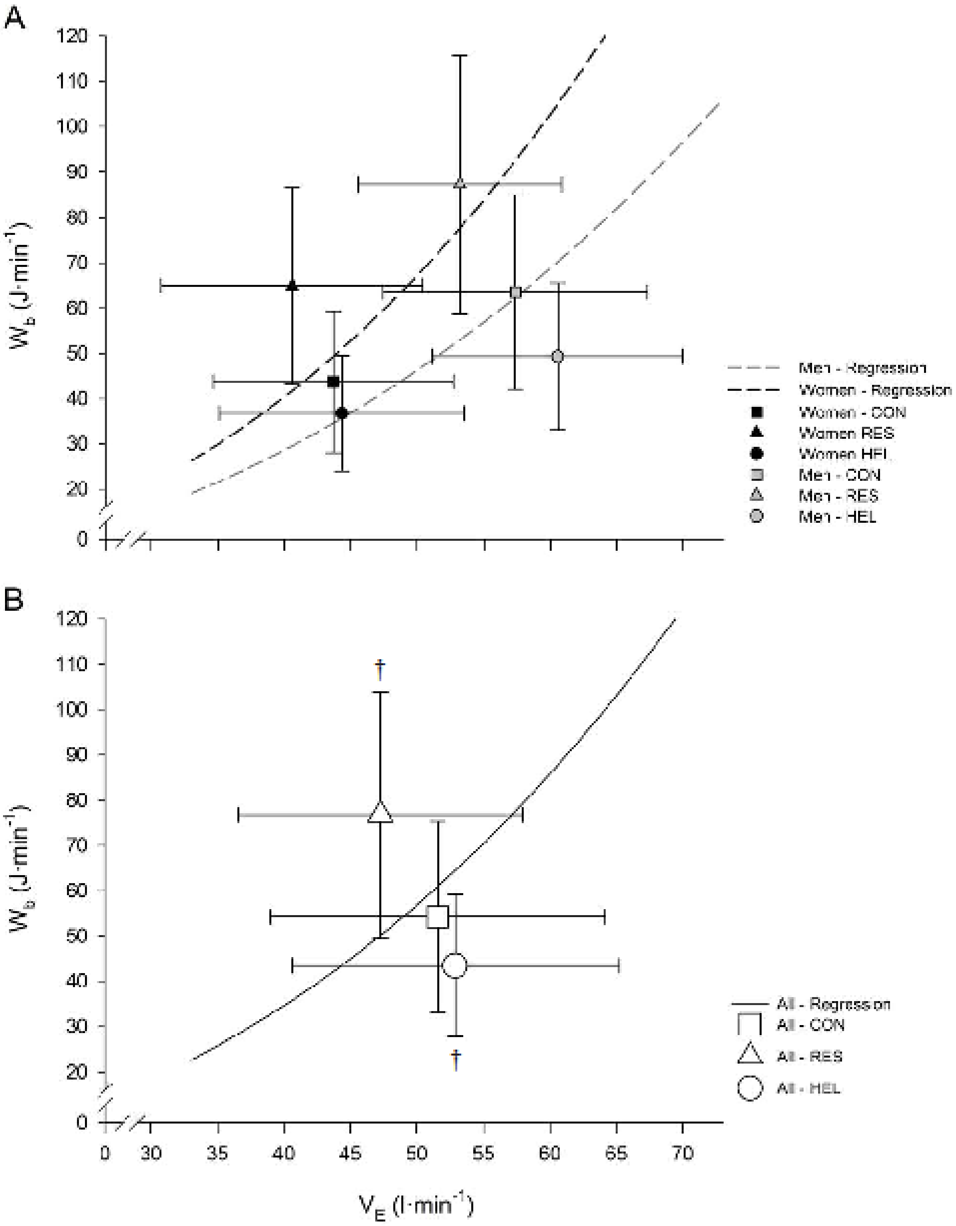

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Figure 5. The number of expiratory-flow limited subjects in each group during the last 2 min of each constant-load exercise test. EFL; expiratory flow limitation; CON, control condition; RES, resistor condition; HEL, helium condition. † p<0.05, effect of condition.

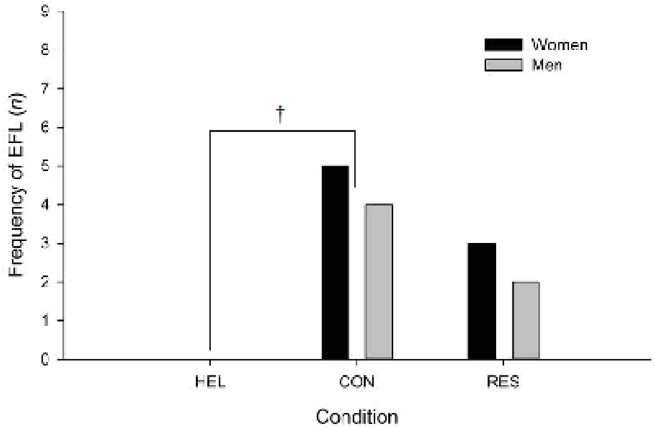
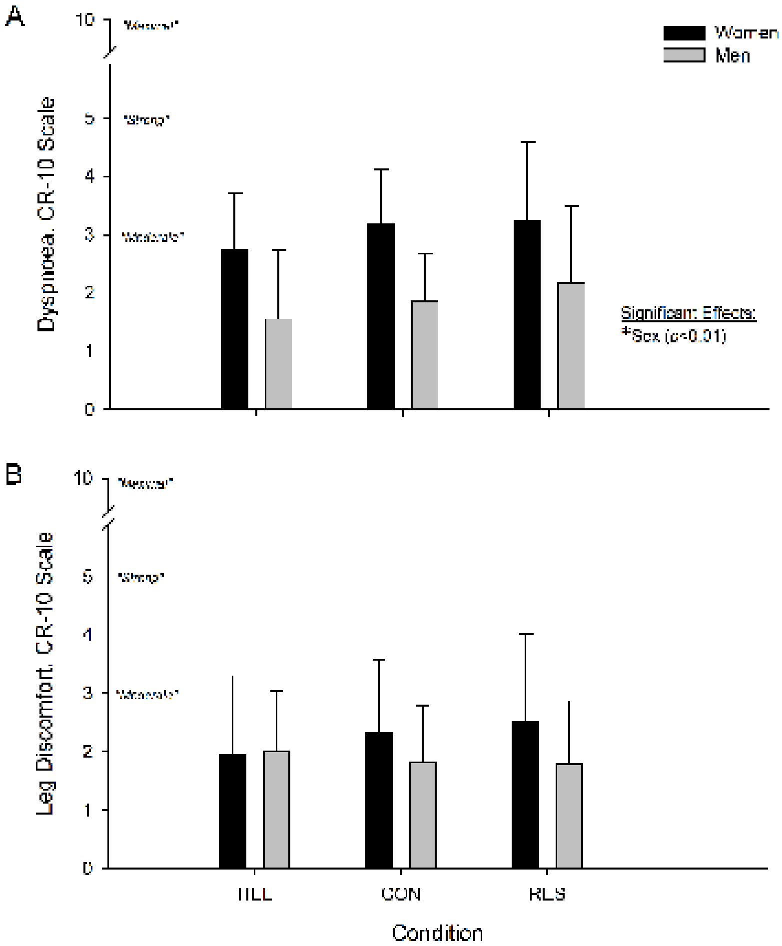


Figure 6. Group mean perceptions of dyspnoea (panel A) and leg discomfort (panel B) during the last 2 min of each constant-load exercise test. CON, control condition; RES, resistor condition; HEL, helium condition. * p<0.05, effect of sex.



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First Author Bio: Yannick Molgat-Seon completed his PhD under the supervision of Dr. A. William Sheel in the School of Kinesiology at the University of British Columbia in Vancouver, Canada. His doctoral thesis examined how sex-based differences in respiratory system morphology affect the integrative physiological and sensory responses to exercise in healthy adults across the lifespan. He is currently a postdoctoral fellow at the Centre for Heart Lung Innovation at St. Paul's Hospital and in the Department of Physical Therapy at the University of British Columbia in Vancouver working under the supervision of Dr. Jordan A. Guenette. His current research focuses on studying the mechanisms of breathlessness and exercise limitation in patients with chronic lung disease.

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TABLES

Table 1. Subject characteristics and pulmonary function data.

	Men			Women			
Age, y	69	±	7	65	±	5	
Height, cm	177	±	7	165	±	6	*
Body mass, kg	78	±	10	61	±	7	*
BMI, kg m^{-2}	25	±	3	22	±	2	*
FVC, l	4.84	±	0.98	3.50	±	0.56	*
FVC, % predicted	107	±	13	108	±	15	
FEV_1, l	3.38	±	0.71	2.61	±	0.43	*
FEV_1, % predicted	105	±	14	110	±	15	
FEV_1/FVC	70	±	5	75	±	4	
FEV_1/FVC, %predicted	98	±	8	102	±	6	
FEF_{25-75}, $l{\cdot}s^{-1}$	2.12	±	0.91	2.08	±	0.73	
FEF_{25-75}, %predicted	81	±	32	84	±	27	
MVV, $l{\cdot}min^{-1}$	147	±	32	105	±	19	*
TLC, l	7.40	±	1.01	5.30	±	0.72	*
TLC, % predicted	106	±	10	102	±	10	
VC, l	5.07	±	1.06	3.58	±	0.52	*
VC, % predicted	107	±	13	110	±	12	
IC, l	3.15	±	0.71	2.33	±	0.53	*
IC, % predicted	100	±	24	96	±	19	
FRC, l	4.25	±	1.08	2.97	±	0.35	*
FRC, % predicted	91	±	18	100	±	7	
RV, l	2.33	±	0.29	1.72	±	0.38	*
RV, % predicted	92	±	9	88	±	16	
DL_{CO}, $ml{\cdot}min^{-1}{\cdot}mmHg^{-1}$	28	±	4	20	±	2	*
DL_{CO}, % predicted	106	±	10	92	±	8	*
MIP, cmH_2O	-110	±	17	-76	±	21	*
MIP, % predicted	104	±	15	107	±	25	
MEP, cmH_2O	153	±	43	103	±	12	*
MEP, % predicted	77	±	21	76	±	9	

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEF_{25-75}, forced expired flow between 25 and 75% of FVC; MVV, maximum voluntary ventilation; TLC, total lung capacity; VC, vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; DL_{CO}, diffusion capacity of the lung for carbon monoxide; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure. * $p<0.05$, men vs. women.

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Table 2. Cardiorespiratory and perceptual responses at peak exercise during the incremental exercise test.

	Men	Women	
Work rate, W	196 ± 63	129 ± 27	*
$\dot{V}O_2$, $l \cdot min^{-1}$	2.55 ± 0.62	1.62 ± 0.29	*
$\dot{V}O_2$ $ml \cdot kg^{-1} \cdot min^{-1}$	32.9 ± 10.4	26.8 ± 4.0	
$\dot{V}O_2$, % predicted	108 ± 19	109 ± 18	
$\dot{V}CO_2$, $l \cdot min^{-1}$	2.84 ± 0.69	1.76 ± 0.25	*
RER	1.12 ± 0.05	1.09 ± 0.07	
HR, $beats \cdot min^{-1}$	158 ± 12	156 ± 16	
HR % predicted	99 ± 7	97 ± 8	
S_pO_2, %	97 ± 2	97 ± 3	
V_T, l	2.55 ± 0.43	1.69 ± 0.28	*
F_b, $breaths \cdot min^{-1}$	41 ± 10	37 ± 5	
$\dot{V}_E$, $l \cdot min^{-1}$	103 ± 20	62 ± 12	*
$\dot{V}_E/\dot{V}O_2$	41.5 ± 7.7	38.9 ± 7.8	
$\dot{V}_E/\dot{V}CO_2$	37.6 ± 5.5	35.4 ± 5.4	
$P_{ET}CO_2$, mmHg	33.0 ± 3.6	34.6 ± 4.8	
EELV, % TLC	57 ± 7	55 ± 4	
EILV, % TLC	91 ± 5	88 ± 3	
$\dot{V}_{ECAP}$, $l \cdot min^{-1}$	141 ± 29	102 ± 10	*
$\dot{V}_E/\dot{V}_{ECAP}$, %	73 ± 14	62 ± 13	
$\dot{V}_E$/MVV, %	71 ± 14	61 ± 14	
Dyspnoea	5.7 ± 2.6	5.8 ± 1.3	
Leg Discomfort	7.7 ± 2.0	6.9 ± 2.0	

Abbreviations: $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$; carbon dioxide output; RER; respiratory exchange ratio; HR, heart rate; S_pO_2, oxygen saturation by pulse oximetry; V_T, tidal volume; F_b, breathing frequency; $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; $\dot{V}_{ECAP}$, ventilatory capacity; MVV, maximum voluntary ventilation. * $p<0.05$, men vs. women.

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Table 3. Cardiorespiratory and perceptual responses at V_{Th} during the incremental exercise test.

	Men			Women			
Work rate, W	124	±	50	78	±	20	*
$\dot{V}O_2$, $l{\cdot}min^{-1}$	1.90	±	0.50	1.17	±	0.23	*
$\dot{V}O_2$, %max	74	±	5	74	±	7	
$\dot{V}CO_2$, $l{\cdot}min^{-1}$	1.88	±	0.49	1.14	±	0.20	*
RER	0.99	±	0.06	0.97	±	0.07	
HR, $beats{\cdot}min^{-1}$	123	±	23	130	±	20	
S_pO_2, %	97	±	2	96	±	3	
$\dot{V}_E$, $l{\cdot}min^{-1}$	57	±	11	35	±	7	*
V_T, l	2.14	±	0.40	1.40	±	0.25	*
F_b, $breaths{\cdot}min^{-1}$	27	±	7	25	±	3	
$\dot{V}_E/\dot{V}O_2$	30.6	±	5.1	29.9	±	4.1	
$\dot{V}_E/\dot{V}CO_2$	31.6	±	4.0	31.1	±	3.4	
$P_{ET}CO_2$, mmHg	40.8	±	3.8	40.9	±	3.6	
EELV, % TLC	54	±	5	53	±	7	
EILV, % TLC	83	±	6	80	±	8	
$\dot{V}_{ECAP}$, $l{\cdot}min^{-1}$	113	±	33	83	±	31	*
$\dot{V}_E/\dot{V}_{ECAP}$, %	56	±	17	48	±	16	
$\dot{V}_E$/MVV, %	40	±	8	39	±	10	
Dyspnoea	2.1	±	1.2	2.7	±	0.8	
Leg Discomfort	2.8	±	0.8	2.8	±	1.7	

Abbreviations: $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$; carbon dioxide output; RER; respiratory exchange ratio; HR, heart rate; S_pO_2, oxygen saturation by pulse oximetry; V_T, tidal volume; F_b, breathing frequency; $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for oxygen; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; $\dot{V}_{ECAP}$, ventilatory capacity; MVV, maximum voluntary ventilation. * $p<0.05$, men vs. women.

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Table 4. Cardiorespiratory variables during the three constant-load cycle exercise conditions.

	HEL		CON		RES		
	Men	Women	Men	Women	Men	Women	
Work rate, W	124 ± 50	78 ± 20	124 ± 50	78 ± 20	124 ± 50	78 ± 20	*
$\dot{V}O_2$, l·min^{-1}	2.20 ± 0.51	1.48 ± 0.29	2.11 ± 0.51	1.45 ± 0.20	2.08 ± 0.47	1.41 ± 0.23	*
$\dot{V}CO_2$, l·min^{-1}	2.15 ± 0.35	1.42 ± 0.20	2.00 ± 0.43	1.34 ± 0.15	2.08 ± 0.59	1.33 ± 0.17	*
RER	0.98 ± 0.05	0.96 ± 0.08	0.96 ± 0.06	0.93 ± 0.07	0.98 ± 0.08	0.95 ± 0.06	
HR, beats·min^{-1}	120 ± 11	127 ± 14	121 ± 18	126 ± 8	121 ± 16	128 ± 12	
S_pO_2, %	97 ± 1	98 ± 2	97 ± 1	98 ± 1	97 ± 1	97 ± 2	
V_T, l	2.33 ± 0.46	1.55 ± 0.22	2.36 ± 0.38	1.58 ± 0.23	2.51 ± 0.46	1.63 ± 0.26	*
F_b, breaths·min^{-1}	25 ± 4	28 ± 5	25 ± 4	26 ± 5	22 ± 4	24 ± 4	
$P_{ET}CO_2$, mmHg	39.6 ± 4.2	39.9 ± 5.3	40.9 ± 3.5	40.9 ± 4.3	41.3 ± 3.4	41.8 ± 4.8	

Abbreviations: $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$; carbon dioxide output; RER; respiratory exchange ratio; HR, heart rate; S_pO_2, oxygen saturation by pulse oximetry; V_T, tidal volume; F_b, breathing frequency; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide. * p<0.05, men vs. women.

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