Oxygen cost of exercise hyperpnoea is greater in women compared with men

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Key points summary

· The oxygen cost of breathing represents a significant fraction of total oxygen uptake during intense exercise.

· At a given ventilation, women have a greater work of breathing compared with men, and since work is linearly related to oxygen uptake we hypothesised that their oxygen cost of breathing would also be greater.

· For a given ventilation, women had a greater absolute oxygen cost of breathing and this represented a greater fraction of total oxygen uptake.

· Regardless of sex, those who developed expiratory flow limitation had a greater oxygen cost of breathing at maximal exercise.

· The greater oxygen cost of breathing in women indicates that a greater fraction of total oxygen uptake (and possibly cardiac output) is directed to the respiratory muscles, which may influence blood flow distribution during exercise.

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Abstract

We compared the oxygen cost of breathing ($\dot{V}O_{2RM}$) in healthy men and women over a wide range of exercise ventilations ($\dot{V}_E$). Eighteen subjects (9 women) completed four days of testing. First, a step-wise maximal cycle exercise test was completed for the assessment of spontaneous breathing patterns. Next, subjects were familiarized with the voluntary hyperpnoea protocol used to estimate $\dot{V}O_{2RM}$. During the final two visits, subjects mimicked multiple times (4-6) the breathing patterns associated with 5-6 different exercise stages. Each trial lasted 5 min and on-line pressure- and flow-volume loops were superimposed on target loops obtained during exercise to accurately replicate the work of breathing. At ~55 l min^{-1} $\dot{V}_E$, $\dot{V}O_{2RM}$ was significantly greater in women. At maximum ventilation, the absolute $\dot{V}O_{2RM}$ was not different (P>0.05) between the sexes, but represented a significantly greater fraction of whole-body $\dot{V}O_2$ in women (13.8±1.5 vs. 9.4±1.1% $\dot{V}O_2$). During heavy exercise at 92 and 100% $\dot{V}O_{2max}$, the unit cost of $\dot{V}_E$ was +0.7 and +1.1 mlO_2 l^{-1} greater in women (P<0.05). At $\dot{V}O_{2max}$, men and women who developed expiratory flow limitation had a significantly greater $\dot{V}O_{2RM}$ than those who did not (435±44 vs. 331±30 mlO_2 min^{-1}). In conclusion, women have a greater $\dot{V}O_{2RM}$ for a given $\dot{V}_E$ and this represents a greater fraction of whole-body $\dot{V}O_2$. The greater $\dot{V}O_{2RM}$ in women may have implications for the integrated physiological response to exercise.

Abbreviation list: EFL, expiratory flow limitation; $\dot{V}_E$, expired minute ventilation; $\dot{V}O_{2max}$, maximum oxygen uptake; $\dot{V}O_{2RM}$, oxygen uptake of the respiratory muscles; $\dot{V}O_{2tot}$, whole-body oxygen uptake; WOB, work of breathing.

Introduction

During dynamic exercise, ventilation rises in proportion to the metabolic demands of the locomotor muscles. This exercise-induced increase in minute ventilation ($\dot{V}_E$) results in an increased mechanical work of breathing (WOB) (Otis, 1964). Consequently, the metabolic and circulatory costs of exercise hyperpnoea are substantial. In healthy untrained humans, the oxygen uptake of the respiratory muscles ($\dot{V}O_{2RM}$) during maximal exercise represents ~10% of whole-body maximum oxygen uptake ($\dot{V}O_{2max}$) (Nielsen, 1936; Shephard, 1966; Aaron *et al.*, 1992b). In endurance trained men, who possess a high $\dot{V}O_{2max}$ and sustain high rates of ventilation, the $\dot{V}O_{2RM}$ can represent upwards of 15% of $\dot{V}O_{2max}$ (Aaron *et al.*, 1992b). Akin to other skeletal muscles, the contracting respiratory musculature requires sufficient blood flow to meet oxygen demand (Andersen & Saltin, 1985). Whilst direct blood flow measurements are not available in humans, at maximal exercise in ponies ~15% of cardiac output is directed towards the respiratory muscles (Manohar, 1990); this value is commensurate with estimates of blood flow in humans (Coast & Krause, 1993; Harms *et al.*, 1998b). Quantifying the metabolic demands of the respiratory muscles is necessary for understanding cardiorespiratory control during exercise. Specifically, high respiratory muscle work has been shown to alter blood flow distribution (Harms *et al.*, 1997) and reduce cardiac output by altering preload and afterload (Harms *et al.*, 1998b). Similar alterations in cardiac have also been demonstrated with externally imposed expiratory loading (Stark-Leyva *et al.*, 2004; Miller *et al.*, 2006).

There are well-documented sex differences with respect to airway anatomy and the respiratory mechanics associated with exercise hyperpnoea. When compared to height matched men, women have smaller lungs (Tan *et al.*, 2011) and conducting airways (Mead, 1980; Sheel *et al.*, 2009). During dynamic whole-body exercise, women develop expiratory flow limitation (EFL) more often (McClaran *et al.*, 1998; Guenette *et al.*, 2007) and have a greater mechanical WOB for a given $\dot{V}_E$ above ~65 l min^{-1} (Wanke *et al.*, 1991; Guenette *et al.*, 2009). It has been hypothesised that mechanical ventilatory constraints, such as EFL, are associated with a higher $\dot{V}O_{2RM}$ (Aaron *et al.*, 1992b), although to our knowledge this has not been systematically investigated. Therefore, it is important to consider the potential

independent effect of EFL on $\dot{V}O_{2RM}$. There have been limited attempts to compare the $\dot{V}O_{2RM}$ between men and women (Eckermann & Millahn, 1962; Topin *et al.*, 2003; Lorenzo & Babb, 2012). Unfortunately, methodological inadequacies and conflicting results render the findings difficult to interpret. For example, most of the studies assessed the $\dot{V}O_{2RM}$ in men and women at ventilations where sex-difference may not necessarily be present (<60 l min^{-1}). The importance of determining sex-based differences in $\dot{V}O_{2RM}$ is because cardiac output is finite during maximal exercise. As such, if women have a greater $\dot{V}O_{2RM}$ and must therefore dedicate a greater fraction of total blood flow towards their respiratory muscles during maximal exercise, performance may be impaired due to reduced locomotor muscle blood flow (Harms *et al.*, 2000).

Accordingly, we sought to compare $\dot{V}O_{2RM}$ in men versus women to address whether, for a given ventilation, women have a greater absolute $\dot{V}O_{2RM}$ and whether this represents a larger percentage of whole-body $\dot{V}O_2$ compared with men. A secondary aim was to determine the effect of EFL on $\dot{V}O_{2RM}$. We hypothesized that at submaximal and maximal ventilations where the WOB is greater compared to men, women have a greater $\dot{V}O_{2RM}$ and this constitutes a larger proportion of whole-body oxygen uptake. We further hypothesized that at maximal exercise, those who develop EFL will have a higher $\dot{V}O_{2RM}$.

Methods

Subjects. After providing written informed consent, eighteen (9 male, 9 female) healthy subjects participated in the study. Some subjects (13 of 18) had previously participated in a study designed to determine the reproducibility of $\dot{V}O_{2RM}$ (Dominelli *et al.*, 2014). The primary outcome measures in the current study did not overlap with any of the previous analyses. All procedures adhered to the *Declaration of Helsinki* and were approved by the Clinical Research Ethics Board at the University of British Columbia. Subjects had a wide range of exercise participation (recreational to national calibre athletics), did not report any current or previous cardiorespiratory ailments and had spirometry within normal limits (Tan *et al.*, 2011) (Table 1). Although not universally established, studies that have measured conjugates of oestrogen and progesterone have demonstrated significant inter- and intra-

subject variability with respect to hormone levels throughout the menstrual cycle, but with no effect on submaximal exercise ventilation (Beidleman *et al.*, 1999; MacNutt *et al.*, 2012). Therefore, we tested female subjects at random points throughout their menstrual cycle and oral contraceptive use was not an exclusion criterion.

Experimental design. Subjects completed 4 days of testing. Day 1 consisted of maximal incremental cycle exercise in order to obtain spontaneous ventilatory parameters during exercise. Day 2 served to familiarize subjects with the voluntary hyperpnoea protocol used to estimate $\dot{V}O_{2RM}$. Days 3 and 4 were experimental days, during which subjects mimicked their exercise breathing patterns at rest while $\dot{V}O_{2RM}$ was assessed. Days 1 and 2 were separated by at least 48 h, whereas the experimental days were separated by at least 24 h. Subjects were instrumented with oesophageal and gastric catheters on days 1, 3 and 4 for the assessment of respiratory pressures.

Maximal exercise (day 1). To obtain spontaneous breathing patterns, a step-wise incremental test on a cycle ergometer (Excalibur Sport; Lode, Groningen, The Netherlands) was performed to the limit of tolerance after insertion and placement of oesophageal and gastric balloon-tipped catheters. To ensure subjects exercised for similar durations, men began at 120 W and women began at 80 W, with a 20 W increase every 2 min for both groups. Testing was terminated when subjects could not maintain >60 rpm despite encouragement. Cardiorespiratory variables including EFL were assessed using customized hardware and software as described elsewhere (Dominelli *et al.*, 2011; Dominelli *et al.*, 2014).

Voluntary hyperpnoea (days 3 and 4). To estimate $\dot{V}O_{2RM}$, subjects rested on the cycle ergometer and mimicked tidal volume, frequency, $\dot{V}_E$, duty cycle and respiratory pressures associated with their exercise hyperpnoea (Dominelli *et al.*, 2014). End-tidal CO_2 tension was set to a level similar to each respective exercise stage. Briefly, each subject mimicked the breathing pattern associated with 4-5 submaximal exercise stages and maximal exercise. The experimental trials were performed in random order over two days. Each stage was mimicked 4-6 times sequentially and each trial was 5 min in duration. The first 4 min was used to provide feedback and ensure sufficient time for mixed expired gas fractions

to reach a steady-state. The final minute of each stage was used for subsequent analysis. During each of the voluntary hyperpnoea trials, the subjects maintained the same body position as during cycle exercise. Ample rest was allowed between trials, ranging from 5 min for lower intensity $\dot{V}_E$ (40% $\dot{V}_{Emax}$) to >30 min for higher levels of $\dot{V}_E$ (>75% $\dot{V}_{Emax}$). Heart rate and blood pressure were measured during the rest periods to ensure complete recovery before the subsequent hyperpnoea trial. Similar clothing was worn during exercise and voluntary hyperpnoea to avoid any clothing-induced changes in pulmonary mechanics and the ergometer configuration was identical for both conditions. We included a familiarization day as it significantly improves the accuracy of tidal volume and $\dot{V}_E$ and the matching of expiratory flow during voluntary hyperpnoea (Dominelli *et al.*, 2014). During the familiarization day, each hyperpnoea trial was mimicked several times and similar feedback (except oesophageal and gastric pressure) was provided.

Several procedures were used to ensure that the ventilatory responses to exercise were replicated during the voluntary hyperpnoea trials (Dominelli *et al.*, 2014). Numerical tidal volume was displayed to the subjects on a breath-by-breath basis and verbal feedback was provided throughout. Breathing frequency and duty cycle were maintained by breathing in time to a metronome. Directly in front of the subjects was a screen displaying online flow-volume and pressure-volume loops that were overlaid on loops obtained during exercise. Representative traces of a subject's oesophageal pressure during exercise and voluntary hyperpnoea are shown in Figure 1. Subjects were coached by the same investigator to match their on-line flow-volume and pressure-volume loops with the target loop. End-expiratory lung volume was monitored using the surrogate measure of end-expiratory oesophageal pressure. During each trial, the inspired gas was modified to ensure end-tidal CO_2 tension was similar to the respective exercise stage. In this regard, inspired percentage of CO_2 ranged from 2-6% whereas inspired O_2 was always ~21%.

In total, 442 experimental trials were completed, with equal distribution between the sexes. Each subject performed 20-30 trials, equally distributed across the experimental days. To determine the between-day reproducibly of $\dot{V}_{O_{2RM}}$, one subject repeated the entire

procedure six months after initial testing; all estimates were within 5-7% of the original measures over their full range of $\dot{V}_E$ (40-150 l min^{-1}).

Data analysis. Data were collected using a 16 channel analogue-to-digital data acquisition system (PowerLab/16Sp model ML 795, ADInstruments, Colorado Springs, CO, USA), sampled at 200 Hz, and stored on a computer for subsequent analysis using bespoke software ($GNAR^x$, developed in LabView 2013, Austin, Tx, USA). The final 30 s of each exercise stage was used for subsequent analysis. During voluntary hyperpnoea, the final minute was used for analysis. A longer time was used for the voluntary hyperpnoea protocols to ensure steady-state $\dot{V}O_2$. Flow-volume and pressure-volume loops for each trial were constructed from ensemble-averaged breaths. Tidal flow-volume loops were placed within the maximal expiratory flow-volume (MEFV) envelope by determining end-expiratory lung volume from an inspiratory capacity manoeuver (Guenette *et al.*, 2010). The WOB, extent of EFL and ventilatory capacity were determined using previously described methods (Dominelli *et al.*, 2013). Efficiency of the respiratory muscles was estimated by dividing the measured $\dot{V}O_{2RM}$ by the ideal oxygen uptake needed to perform the WOB (Aaron *et al.*, 1992a). To calculate the ideal oxygen uptake, the measured WOB was converted into units of oxygen with changes in respiratory exchange ratio accounted for. The maximal effective ventilation was defined as when the change in $\dot{V}O_{2RM}$ per unit of $\dot{V}_E$ equalled the change in whole body $\dot{V}O_2$ per unit $\dot{V}_E$ (Otis, 1954; Shephard, 1966). Once the maximal effective ventilation was determined, maximal exercise gas exchange parameters and the alveolar gas equation were used to predict the maximal alveolar ventilation and the corresponding $\dot{V}O_2$.

Statistics. Anthropometric and maximal exercise variables were compared between men and women using independent samples t-tests. An equation was fitted to each subject's relationship for WOB vs. $\dot{V}_E$, $\dot{V}O_{2RM}$ vs. WOB and $\dot{V}O_{2RM}$ vs. $\dot{V}_E$. The $\dot{V}O_{2RM}$ vs. WOB relationship was fit with a linear equation, whereas the WOB vs. $\dot{V}_E$ and $\dot{V}O_{2RM}$ vs. $\dot{V}_E$ were fit with an exponential equation. The respective constants for each equation were pooled and the sexes were compared using independent samples t-tests. To determine the specific $\dot{V}_E$ or WOB for which the groups were different, each subject's equation was solved for successive independent variables, with the resultants compared with t-tests and Bonferroni correction.

To determine sex-independent differences, subjects were grouped into those with and without EFL during exercise and similar comparisons were completed. Expiratory flow limitation was defined as >5% overlap of the tidal flow-volume loop with the MEFV curve. The effect of sex and EFL was also compared at different percentages of $\dot{V}_{Emax}$ (45, 60, 75 and 100%) using a two-factor (sex and % $\dot{V}_{Emax}$) repeated-measures ANOVA. When significant F ratios were detected, Tukey's post-hoc test was conducted. The percentages of $\dot{V}_{Emax}$ were selected because: (i) they spanned a wide range of ventilation, (ii) they represented ~10% increments in $\dot{V}O_{2max}$ (see Table 3) and (iii) all subjects had mimicked an exercise stage within this range. Statistical significance was set at $P<0.05$. All values are presented as mean ± SE unless otherwise noted.

Results

Subject characteristics and cardiorespiratory responses. Subject characteristics are presented in Table 1. Maximal cardiorespiratory and respiratory mechanics values are presented in Table 2. At peak exercise, men had significantly greater absolute and relative oxygen uptake, carbon dioxide output, tidal volume and $\dot{V}_E$ ($P<0.05$). However, there were no differences in respiratory exchange ratio, heart rate, end-tidal CO_2, ventilatory equivalents or operational lung volumes ($P>0.05$). At maximal exercise, men had significantly greater WOB owing to a greater $\dot{V}_E$ ($P<0.05$). For a given $\dot{V}_E$, however, women had a greater WOB due to a significantly greater resistive component ($P<0.05$) (Figure 2 and 3)

Work of breathing and $\dot{V}O_{2RM}$. Figure 4 shows the absolute and relative $\dot{V}O_{2RM}$ at different absolute and relative ventilations. While there was minimal within-subject variability for $\dot{V}O_{2RM}$, there was greater between-subject variability which was more pronounced at higher ventilations (Panel A). At a $\dot{V}_E$ of ~95 l min^{-1}, for example, the $\dot{V}O_{2RM}$ in women ranged from 200-400 ml min^{-1}. The variability in $\dot{V}O_{2RM}$ is explained by differences in the WOB vs. $\dot{V}_E$ relationship, which is dependent on airway size and presumably different in our groups. The order of trials had no effect on $\dot{V}O_{2RM}$. Specifically, when replicating maximal exercise ventilation the average $\dot{V}O_{2RM}$ for all subjects was not statistically different across trials (381 ± 32, 377 ± 31, 404 ± 34 and 389 ± 31 ml O_2 min^{-1} for

the 1st-4th trials, respectively; P>0.05). There was also no effect of order when the subjects were grouped by sex (P>0.05). At an iso-ventilation of ~55 l min^{-1}, women had a greater absolute $\dot{V}O_{2RM}$ (Panel B) (P<0.05). The group mean coefficient of variation for $\dot{V}O_2$ was 4.9, 4.9, 5.3 and 6.0% at 45, 60, 75 and 100% $\dot{V}_{Emax}$, respectively, with no difference between the sexes (P>0.05). When compared at relative ventilations, men and women had a similar absolute $\dot{V}O_{2RM}$ (P>0.05, Panel C). However, this represented a greater fraction of whole-body $\dot{V}O_2$ in women at 75 and 100% $\dot{V}_{Emax}$ (Panel D). At maximal exercise, $\dot{V}O_{2RM}$ represented 13.8% of whole body $\dot{V}O_2$ in women and 9.4% in men (P<0.05, Figure 5).

Without exception, every subject demonstrated a significant linear relationship between $\dot{V}O_{2RM}$ and WOB. During maximal intensity trials, however, the $\dot{V}O_{2RM}$ rose out of proportion to the increase in WOB (Figure 6). When WOB was related to $\dot{V}O_{2RM}$ as a % of total whole-body $\dot{V}O_2$, the average slope of the regression line was significantly greater in women (P<0.05, Figure 6B).

Table 3 displays variables for men and women during the voluntary hyperpnoea trials at different $\%\dot{V}_{Emax}$. Men had greater absolute $\dot{V}_E$ for all comparisons (P<0.05), primarily due to greater tidal volume. The changes from rest to hyperpnoea in heart rate, expiratory duty cycle and end-tidal carbon dioxide tension were not different between the sexes at any $\%\dot{V}_{Emax}$ (P>0.05). The $\dot{V}O_{2RM}/\dot{V}_E$ relationship increased in both sexes as $\dot{V}_E$ increased, and men were statistically lower at 75 and 100% $\dot{V}_{Emax}$ (P<0.05). The calculated efficiency of the respiratory muscles was greater in men at all ventilations (P<0.05). Women performed the hyperpnoea trials at significantly higher end-expiratory lung volume (P<0.05), with no difference in end-inspiratory lung volume (P>0.05).

Expiratory flow limitation. The effect of stratifying the subjects based on the appearance of EFL on $\dot{V}O_{2RM}$ is shown in Figure 7 and Table 4. There were similar numbers of men and women in each group and there was no difference between %EFL during exercise or hyperpnoea for either sex (men: 24±9% vs. 23±9%; women 22±8% vs. 18±6%; for exercise and hyperpnoea, respectively; P>0.05 for both). The MEFV curve was significantly larger in the group that did not develop EFL (Panel C, P<0.05). There were no differences in $\dot{V}O_{2max}$ or $\dot{V}_{Emax}$ (P<0.05); however, the $\dot{V}O_{2RM}$ was significantly greater in the EFL group

during the maximal ventilation trials (P<0.05, Panel B). At ≤75% $\dot{V}_{Emax}$, where there was no or minimal EFL (3 subjects, <20% overlap with the MEFV curve), the $\dot{V}O_{2RM}$ and $\dot{V}_E$ were similar between groups (Panel B). Although the absolute WOB was not different between groups (485±63 vs. 443±63 J min^{-1}, P>0.05), the resistive work contributed a significantly greater percent in the EFL group (79±1 vs. 72±2% of total WOB, P<0.05). At all ventilations lower than 100%, there were no differences between the EFL and NEFL groups (Table 4). At 100% $\dot{V}_E$, the EFL group had a greater breathing frequency and $\dot{V}O_{2RM}$ per $\dot{V}_E$ and a lower estimated respiratory muscle efficiency (P<0.05, Table 4).

Discussion

Major findings. The major findings from this study are three-fold. First, women have a greater absolute $\dot{V}O_{2RM}$ during submaximal and maximal rates of exercise hyperpnoea. Second, during strenuous and maximal exercise, the $\dot{V}O_{2RM}$ represents a significantly greater fraction of whole-body oxygen uptake in women. Finally, regardless of sex, those who develop EFL at maximal exercise have a greater $\dot{V}O_{2RM}$. Collectively, our findings indicate that the greater WOB and increased mechanical ventilatory constraints in women result in a greater absolute and relative $\dot{V}O_{2RM}$ at submaximal and maximal exercise intensities.

Sex-differences in $\dot{V}O_{2RM}$. We demonstrated that women have a greater absolute and relative $\dot{V}O_{2RM}$ compared to men. Given that oxygen uptake is linearly related to work, we hypothesized that at ventilations where women have a greater WOB than men, their $\dot{V}O_{2RM}$ would also be greater. Indeed, we found that women had a greater WOB at submaximal levels of $\dot{V}_E$ (Figure 2), a finding consistent with work from our laboratory (Guenette *et al.*, 2007) and others (Wanke *et al.*, 1991). The differences in WOB were due to increased resistive work (Figure 3). We found differences in $\dot{V}O_{2RM}$ between the sexes at ~55 l min^{-1}, which coincides with the $\dot{V}_E$ where the WOB is greater in women. A ventilation of ~55 l min^{-1} was achieved during submaximal exercise in both men and women, but represented a greater fraction of maximal ventilation in women. Therefore, we also used relative units to compare the sexes at similar fractions of $\dot{V}_{Emax}$. As shown in Figure 4C, when compared at similar relative $\dot{V}_{Emax}$, there were no differences in the absolute $\dot{V}O_{2RM}$. However, for the

comparisons presented in Figure 4C, the men had a significantly greater $\dot{V}_E$ and their whole-body $\dot{V}O_2$ was also greater (Table 3). To fully elucidate the comparisons, units on each axis should be relative, as shown in Figure 4D which displays the comparison between relative $\dot{V}_E$ and relative $\dot{V}O_{2RM}$. At ≥75% $\dot{V}_{Emax}$ (~90% of $\dot{V}O_{2max}$), a significantly greater fraction of whole-body $\dot{V}O_2$ was dedicated to the respiratory muscles in women. If the respiratory muscles in women command a greater percent of cardiac output, then blood flow to locomotor muscles may become compromised (see *Perspectives*)

Both sexes showed an increase in the unit rate of $\dot{V}O_{2RM}$ per $\dot{V}_E$ and were not different at 45 and 60% of $\dot{V}_{Emax}$. The progressive increase in $\dot{V}O_{2RM}/\dot{V}_E$ as ventilation increases towards higher levels has been observed by others (Aaron *et al.*, 1992b; Coast *et al.*, 1993). At 75% of $\dot{V}_{Emax}$, however, women showed marked increase in $\dot{V}O_{2RM}/\dot{V}_E$, whereas men only demonstrated a dramatic increase between 75 and 100% $\dot{V}_{Emax}$ (Table 3). While the $\dot{V}O_{2RM}/\dot{V}_E$ increased with ventilation, the $\dot{V}O_{2RM}$/WOB relationship did not change systematically in either sex and was consistently greater in women. Despite a linear relationship for $\dot{V}O_{2RM}$/WOB in both sexes, the efficiency of the respiratory muscles was significantly lower in women and this finding was most pronounced at maximal exercise (Table 3). While our study was not designed to determine the mechanism behind sex-based differences in respiratory muscle efficiency, our observations merit brief comment. Our primary concern with determining efficiency is that we are unable to account for all of the work done during breathing. For example, abdominal muscles contract to stabilize the abdominal wall during forceful expiration (De Troyer & Boriek, 2011), and work is done when the chest-wall is distorted at near maximal ventilations (>75% of $\dot{V}_{Emax}$) (Grimby *et al.*, 1968). Indeed, the work done to stabilize the abdominal wall and distort the chest wall is estimated to be upwards of 25% of total WOB (Goldman *et al.*, 1976). A further consideration is that the velocity of muscle shortening would have been greater in the women due to a higher maximal breathing frequency (Table 3), and this could also have necessitated greater work in order to stabilize the abdominal wall. Furthermore, the greater shortening velocity in women would be expected to result in an increased energy requirement (McCool *et al.*, 1986; McCool *et al.*, 1989). Accordingly, we cautiously speculate that decreased respiratory muscle efficiency in

women could arise from sex-differences in substrate utilization and morphology (Miller *et al.*, 1993; Hicks *et al.*, 2001) and/or blood vessel compression when the WOB is near maximal (Hunter, 2014).

How do our results for $\dot{V}O_{2RM}$ in men versus women compare to previous reports? To date, sex differences in $\dot{V}O_{2RM}$ have been found by some (Eckermann & Millahn, 1962; Topin *et al.*, 2003) but not all studies (Lorenzo & Babb, 2012). Eckermann and Millahn (1962) assessed ventilations up to ~120 l min^{-1} and concluded that women had a greater $\dot{V}O_{2RM}$. However, the absolute values for $\dot{V}O_{2RM}$ reported in their study were excessive (>2 l min^{-1}) and do not, therefore, represent a realistic estimation. Nonetheless, their estimation of respiratory muscle efficiency is similar to ours and others (Aaron *et al.*, 1992a), and they noted that men may be more efficient. Although more recent estimates of $\dot{V}O_{2RM}$ appear to be reasonable, there is still no consensus as to whether a sex-difference is apparent (Topin *et al.*, 2003; Lorenzo & Babb, 2012). A consideration when interpreting the two aforementioned studies is the narrow range of $\dot{V}_E$ investigated and the less than ideal accurate replication of exercise breathing patterns (i.e., lack of oesophageal pressure). Specifically, both studies estimated the $\dot{V}O_{2RM}$ in women at a $\dot{V}_E \leq 60$ l min^{-1}, which is approximately the threshold we found for a sex differences in $\dot{V}O_{2RM}$. Therefore, even with precise replication of exercise breathing patterns, a significant sex effect may have been masked by the low $\dot{V}_E$. A more suitable comparison for our data would be the work of Aaron *et al* (1992a,b). As in the current study, those authors accurately mimicked exercise breathing patterns, matched the WOB and had subjects perform multiple trials across a wide range of $\dot{V}_E$. When comparing our male subjects to those of Aaron *et al.* (1992 a,b) (who tested 7 men and 1 woman), our absolute $\dot{V}O_{2RM}$ was similar and we both estimated that maximal $\dot{V}O_{2RM}$ accounts for ~10% of whole-body oxygen uptake. The lone female subject in the previous study (Aaron *et al.*, 1992b) had a $\dot{V}O_{2RM}$ that represented ~15% of whole body oxygen uptake, which is commensurate with our results for women (13.8 ± 1.5% of $\dot{V}O_{2max}$). Notably, one woman in our study had a $\dot{V}O_{2RM}$ representing 24% of total oxygen uptake for two trials (Figure 5), which is remarkable considering others have shown that active muscle tissue can account for upwards of 85% of $\dot{V}O_2$ (Poole *et al.*, 1992). While we note that 24% is on the upper limit of

expected respiratory muscle oxygen uptake, others have reported similar values (Aaron *et al.*, 1992b). As expected, this subject developed EFL, used 85% of their ventilatory capacity and had an end-exercise $\dot{V}_E$ and WOB that was greater than the female average. Thus, many of the predisposing factors associated with sympathetically mediated blood flow redistribution are present and there is evidence from animal models to suggest the diaphragm may be less sensitive to vasoconstrictor activity (Aaker & Laughlin, 2002). Given the above influencing factors and the repeatability of our measures, we are confident our values are physiological. Overall, we conclude that women have a greater $\dot{V}O_{2RM}$ than men as a result of a greater WOB and decreased efficiency.

Mechanical ventilatory constraints. To investigate the role of mechanical ventilatory constraints on $\dot{V}O_{2RM}$, we categorized our subjects based upon the occurrence or absence of EFL during exercise. Expiratory flow limitation occurs when maximal flow plateaus despite an increase in driving pressure (Hyatt, 1983) and can arise in young healthy subjects during intense aerobic exercise (Johnson *et al.*, 1999; Babb, 2013). The occurrence of EFL during exercise is associated with an increase in operational lung volumes (Pellegrino *et al.*, 1993), exacerbated exercise-induced arterial hypoxaemia (Dominelli *et al.*, 2013) and reduced exercise performance (Iandelli *et al.*, 2002). Others have theorized that EFL is associated with a greater $\dot{V}O_{2RM}$ (Aaron *et al.*, 1992b) but no specific data were presented to support this postulate. Similarly, we found that those who developed EFL during maximum exercise had a greater $\dot{V}O_{2RM}$ (Figure 7). In addition, our flow limited and non-flow limited groups had similar $\dot{V}O_{2max}$, $\dot{V}_{Emax}$ and WOB. At submaximal exercise, minimal if any EFL was present and, as such, there were no statistical differences between the groups for any parameter (Figure 7). Furthermore, there was an equal distribution of sexes and both groups successfully replicated their exercise breathing patterns. Others have shown that aerobic fitness does not predict who does and does not develop EFL (Smith *et al.*, 2014) and we have argued that women develop EFL more often than men (Guenette *et al.*, 2007). In the current study, however, we found an equal distribution of EFL between the sexes. We intentionally recruited trained men in an attempt to ensure a similar distribution of flow-limited subjects in order to address our primary research question (regarding sex-differences in $\dot{V}O_{2RM}$) in the

most conservative fashion. If we did not recruit trained men, we anticipated that few, if any, of the male subjects would have developed EFL and we would be less able to accurately discern sex differences in $\dot{V}O_{2RM}$. In all cases, subjects who developed flow limitation during exercise did so during the hyperpnoea trials, and vice versa for the non-flow limited subjects (Figure 7). Therefore, variation in replicating spontaneous breathing patterns was not responsible for the greater $\dot{V}O_{2RM}$ noted in the flow limited group.

While we did not make anatomical estimations of airway size in the current study, those who develop EFL are thought to have smaller airways (McClaran *et al.*, 1998; Dominelli *et al.*, 2011). Smaller airways are consistent with the greater resistive WOB noted at maximal exercise in the EFL subjects, despite the total WOB being similar between groups (Table 4). As the maximal effective driving pressure for flow was approached, compression of the airways may have been initiated - a phenomenon termed "impending flow limitation" (Mead *et al.*, 1967; McClaran *et al.*, 1998). The impending flow limitation could have altered breathing patterns via compression of airways, thereby resulting in a decreased efficiency of the respiratory muscles. Other factors that could explain the greater $\dot{V}O_{2RM}$ in the EFL groups relates to those detailed above such as chest-wall deformation, abdominal stabilization and greater muscle shortening velocity from an increased breathing frequency. The chest-wall deformation and abdominal stabilization could lead to a greater $\dot{V}O_{2RM}$ through additional muscular contraction, yet the work may not be accounted for, which is seen by our similar WOB values (Table 4).

Technical considerations. We considered the possibility that respiratory muscle fatigue during the hyperpnoea trials could have affected our results. High intensity exercise to exhaustion has been shown to induce respiratory muscle fatigue (Johnson *et al.*, 1993; Taylor *et al.*, 2006), which may persist for up to 24 hr (Laghi *et al.*, 1995). Respiratory muscle fatigue is associated with a progressive increase in muscle sympathetic nerve activity (St Croix *et al.*, 2000; Derchak *et al.*, 2002), alterations in resting blood flow distribution (Sheel *et al.*, 2001) and reduced exercise capacity (Harms *et al.*, 2000; Taylor & Romer, 2008). Voluntary hyperpnoea has also been shown to elicit respiratory muscle fatigue (Renggli *et al.*, 2008). Thus, it is conceivable that our subjects developed respiratory muscle

fatigue and the associated neurovascular effects. In the absence of heavy exercise, however, respiratory muscle fatigue only develops when the WOB is significantly greater than that achieved during maximal exercise (Babcock *et al.*, 1995). In our study, the mechanical WOB did not exceed the maximal exercise values in any of the hyperpnoea trials. Furthermore, the trials were relatively short and the subjects were provided with substantial rest between trials. Finally, we found no effect of trial order on our estimates of $\dot{V}O_{2RM}$. If respiratory muscle fatigue was present, we would expect a systematic temporal change in the ability to replicate the exercise breathing pattern and/or $\dot{V}O_{2RM}$. Consequently, it is unlikely that fatigue developed and if it did, there does not appear to be any measurable effect on the $\dot{V}O_{2RM}$.

During the voluntary hyperpnoea trials there was a significant increase in heart rate beyond 60% $\dot{V}_{Emax}$. As such, myocardial work likely contributed in small part to the observed increase in $\dot{V}O_2$. However, the increases in heart rate were similar for men and women and we presume therefore that cardiac $\dot{V}O_2$ was also similar between the sexes.

Sex-based comparisons. A difficult and often encountered problem when designing and interpreting studies regarding sex-based differences is how to best compare men and women. Men, on average, are taller than women and therefore will have greater absolute lung volumes and flows. Due to a greater muscle mass, men will generally achieve a higher absolute $\dot{V}O_2$ and $\dot{V}_E$. The principle issue here is whether to compare the sexes using absolute or relative values, a concern shared in other fields (Hart & Charkoudian, 2014; Hunter, 2014). In the current study, we made several comparisons in order to individually address specific questions and collectively provide an overall interpretation.

Another confounding variable when assessing sex-based differences is whether subjects should be matched for one or more anthropometric or functional parameter (Sheel & Guenette, 2008). For example, men and women could be matched for height, lung size, lung function, aerobic fitness or body composition. However, matching may be best justified when attempting to isolate a single mechanism rather than attempting to understand the integrative whole-body response. For example, women appear to develop exercise-induced arterial hypoxaemia to a greater degree than men (Harms *et al.*, 1998a; Dominelli *et al.*, 2013), but when matched for height (and consequently lung size) and aerobic fitness the gas

exchange disparity is minimized (Olfert *et al.*, 2004). Another example to illustrate the effect of scaling stems from the current study. The woman with the lowest $\dot{V}O_{2RM}/\dot{V}_E$ was the tallest, had the largest lung volumes and greatest flows of all the women. Despite her high aerobic fitness (60 ml kg^{-1} min^{-1}), she did not develop EFL and her WOB was similar to the men. As such, when the sexes overlap in anatomical variables, the physiological sex differences appear to be minimized. However, we emphasize that many of the variables used to match men and women are themselves extensively influenced by sex. Matching men and women for lung size may allow for certain comparisons, but it would eliminate a consistent and population-wide sex-based difference, rendering the results less generalizable.

Perspectives. What are the implications of a greater $\dot{V}O_{2RM}$ in women on the integrative physiological response to exercise? During maximal exercise in men, the WOB influences active leg blood flow and the distribution of total cardiac output through a sympathetically mediated response (Harms *et al.*, 1997; Harms *et al.*, 1998b). As shown in Figure 6B, the slope of the $\dot{V}O_{2RM}$-WOB relationship is significantly greater in women compared with men. The greater slope of the $\dot{V}O_{2RM}$-WOB relationship in women indicates that for a given change in WOB, women have a greater change in the total $\dot{V}O_2$ dedicated to the respiratory muscles. Therefore, it could be hypothesized that when compared to men, women may show greater changes in leg blood flow when the WOB is altered by the same amount. Further support for the above hypothesis arises from findings on anesthetized male and female rabbits. Female rabbits dedicate a greater amount of blood towards the diaphragm in response to increases in ventilation elicited by hyperthermia (Lublin *et al.*, 1995). A caveat to the idea that women may dedicate greater blood flow to the respiratory muscles is the greater β-adrenergic receptor activity in pre-menopausal women resulting in a blunted response to sympathetically mediated vasoconstriction (Hart *et al.*, 2011). To date, the influence of WOB on blood flow distribution during exercise has not been studied in women. To accurately determine the potential effect of sex on WOB related alterations in blood flow, respiratory muscle work will need to be experimentally reduced while leg blood flow is directly measured.

Previous authors have argued for the existence of a maximal effective $\dot{V}_E$, defined as the ventilation beyond which further increases in external work would require the increase in $\dot{V}O_2$ to be dedicated solely to the respiratory musculature (Otis *et al.*, 1950). In men, the maximal effective ventilation is significantly above $\dot{V}_{Emax}$ (Aaron *et al.*, 1992b), but given the greater $\dot{V}O_{2RM}$ in women, we question if an effective ventilation could be attained. We found that the $\dot{V}O_{2RM}$ per $\dot{V}_E$ in women (Table 3) would need to be ~2.5x greater to equal the change in whole body $\dot{V}O_2$ per $\dot{V}_E$; men would require a value ~4x greater. To attain the maximal effective $\dot{V}_E$, the women would have to increase their maximal ventilation by 18 l min^{-1}, which would result in significant hypocapnia (end-tidal carbon dioxide <20 mmHg) and would not be sustainable. Using the alveolar gas equation, we estimate that the women's $\dot{V}O_{2max}$ would have to be 63% greater, or ~4.5 l min^{-1} (~80 ml kg^{-1} min^{-1}), for the greater $\dot{V}_E$ to be sustainable. Similarly, for the men to achieve their maximal effective ventilation, $t\dot{V}_{Emax}$ would have to increase 40 l min^{-1} and $\dot{V}O_{2max}$ would have to increase by 67% or to ~98 ml kg^{-1} min^{-1}. Accordingly, we conclude that women may be relatively closer to their maximal effective $\dot{V}_E$, but the corresponding oxygen uptake is only achievable in a small percentage of highly-trained athletes.

Conclusion. Three primary conclusions can be drawn from our study. First, at submaximal and maximal exercise intensities, $\dot{V}O_{2RM}$ is significantly greater in women compared to men. Second, during heavy exercise, the $\dot{V}O_{2RM}$ represents a greater fraction of whole body $\dot{V}O_2$ in women. Finally, subjects who develop expiratory flow limitation during exercise have a greater maximal $\dot{V}O_{2RM}$ than those who do not develop flow limitation. Overall, our findings indicate that the oxygen cost of exercise hyperpnoea is greater in healthy women than in healthy men, but neither sex readily achieves maximal effective ventilation. The greater $\dot{V}O_{2RM}$ in women may have implications for the integrated physiological response to exercise.

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Translational Perspective. We, and others, have shown that women have smaller diameter airways than men, even when matched for lung size. Thus, a woman matched for lung size to a man will have higher airway resistance, which is important under conditions of high ventilation such as exercise. We have also demonstrated that otherwise healthy young women have a higher mechanical work of breathing during exercise compared to men. In the present study we found that the oxygen cost of breathing during exercise is significantly higher in women. According to the Fick Equation, this suggests that women dedicate a greater fraction of cardiac output to respiratory muscles at the expense of blood flow to other exercising muscles. If our reasoning is correct, our findings become critical when considering exercise in disease. For example, pulmonary disorders are characterized by a reduced functional capacity of the respiratory system. A reduced capacity coupled with an innately accentuated respiratory muscle demand could result in sex-differences in exercise responses. Exercise is widely recognized as an integral component of pulmonary rehabilitation programs. Pulmonary rehabilitation improves perception of symptoms, exercise capacity, and health-related quality life. However, rehabilitation exercise guidelines typically do not differentiate between men and women. Differences in the oxygen cost of breathing between men and women are likely to be magnified when pulmonary disease is superimposed. Additional work is required to understand how our findings may contribute to activity-related breathlessness as well as sex-specific treatment plans for the management of patients with cardiopulmonary diseases.

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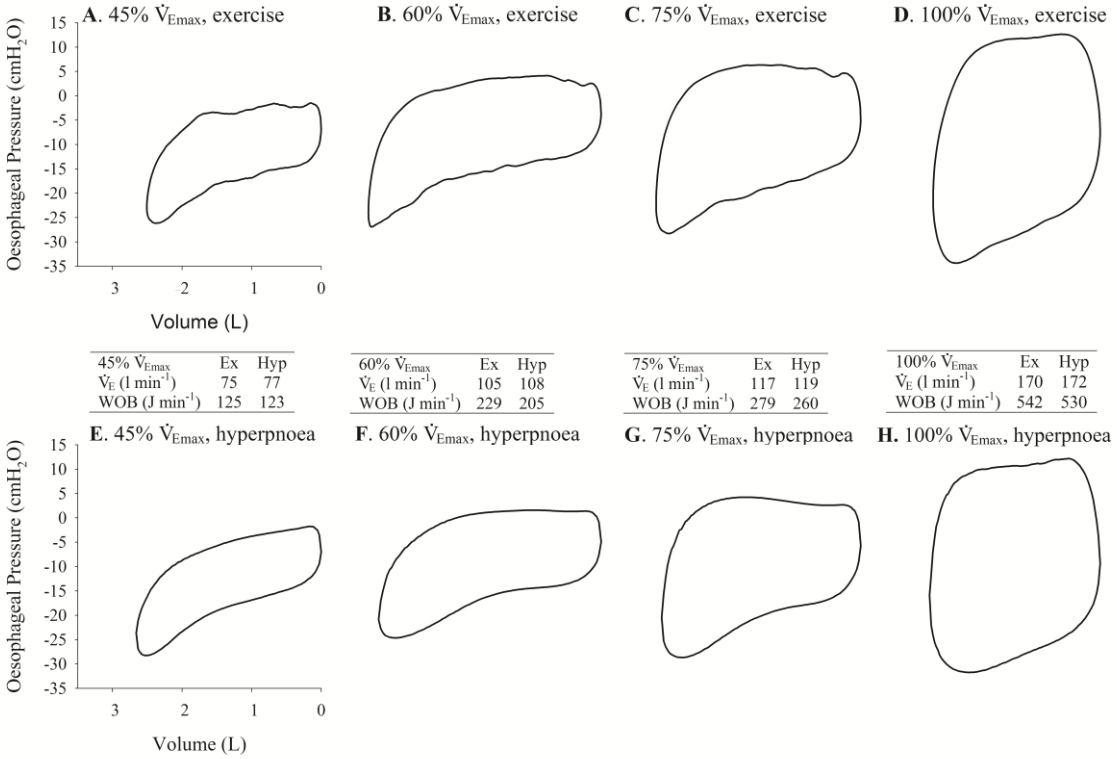
Author contribution. Conception of study: PBD, JNR, GEF, AWS. Design of experiment: PBD, JNR, GEF, AWS. Data collection, analysis and interpretation, drafting of article: PBD, JNR, YMS, GEF, LMR, AWS. All authors approved the final version of the manuscript.

Figure 1. Oesophageal pressure-volume loops for a representative male subject during exercise (Pane A-D) and voluntary hyperpnoea (Panel E-H). Loops representing exercise are an average composite from 30 seconds of data. Loops representing voluntary hyperpnoea are average composites of the final minute of several trials. Ventilation and work of breathing are presented in tables for each respective stage. $\dot{V}_{Emax}$, maximum minute ventilation; Ex, exercise; Hyp; hyperpnoea; $\dot{V}_E$, expired minute ventilation; WOB, work of breathing.



45% $\dot{V}_{Emax}$	Ex	Hyp
$\dot{V}_E$ (l min^{-1})	75	77
WOB (J min^{-1})	125	123

60% $\dot{V}_{Emax}$	Ex	Hyp
$\dot{V}_E$ (l min^{-1})	105	108
WOB (J min^{-1})	229	205

75% $\dot{V}_{Emax}$	Ex	Hyp
$\dot{V}_E$ (l min^{-1})	117	119
WOB (J min^{-1})	279	260

100% $\dot{V}_{Emax}$	Ex	Hyp
$\dot{V}_E$ (l min^{-1})	170	172
WOB (J min^{-1})	542	530

Figure 2. Relationship between work of breathing and minute ventilation during the voluntary hyperpnoea. The work of breathing is significantly greater in women at and above a ventilation of ~75 l min^{-1}. WOB, work of breathing; $\dot{V}_E$, expired minute ventilation/

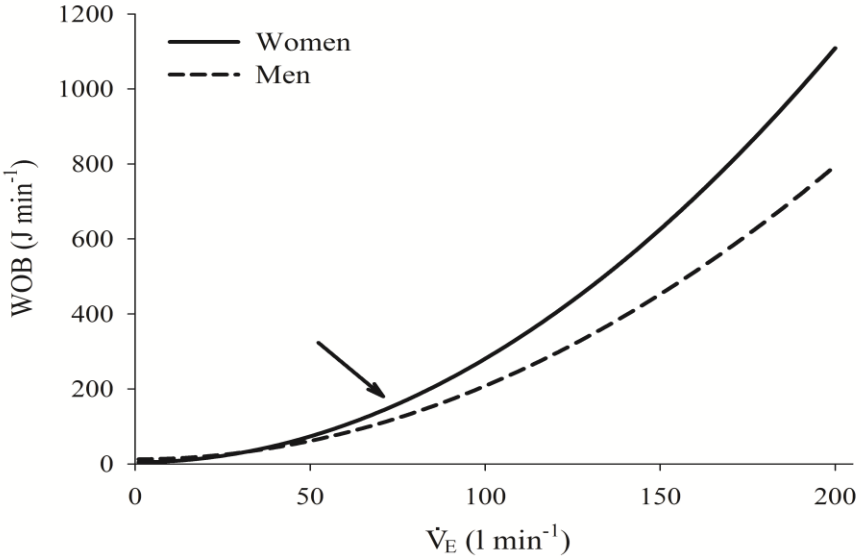


Figure 3. Relationship between elastic (Panel A) or resistive (Panel B) work of breathing and minute ventilation. Asterix represents a greater resistive work of breathing in women at iso-ventilation ($P<0.05$). Dagger represents a significantly greater elastic work of breathing and resistive work of breathing in men when maximum exercise ventilations are compared ($P<0.05$). $\dot{V}_E$, expired minute ventilation

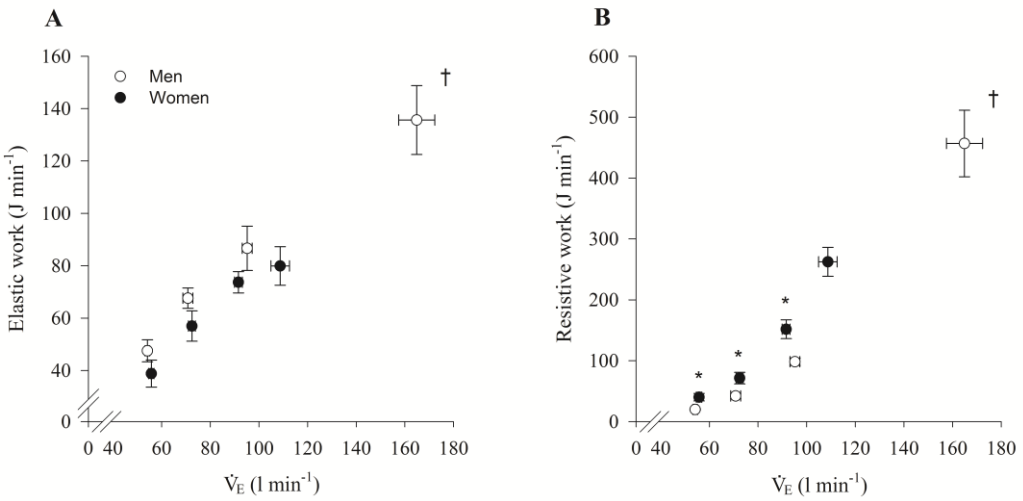


Figure 4. Panel A: average oxygen uptake for each stage of voluntary hyperpnoea performed by each subject. Panel B: regression lines for men and women performing voluntary hyperpnoea trials. The star, vertical line and arrow indicate that women have a significantly higher $\dot{V}O_{2RM}$ above a ventilation of ~55 l min^{-1}. Regression was fitted using the average of each subject's constants. Panel C: absolute $\dot{V}O_{2RM}$ at different percentages of maximal ventilation. Men had significantly greater ventilations at every comparison (see also Table 3). Panel D: $\dot{V}O_{2RM}$ as a percentage of whole-body oxygen uptake at different percentages of maximal ventilation. All average values are mean ± SE. $\dot{V}_E$, expired minute ventilation; $\dot{V}_{Emax}$, maximum minute ventilation; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_{2max}$, maximum oxygen uptake; $\dot{V}O_{2RM}$, oxygen uptake of the respiratory muscles. * Significantly greater in women ($P<0.05$).

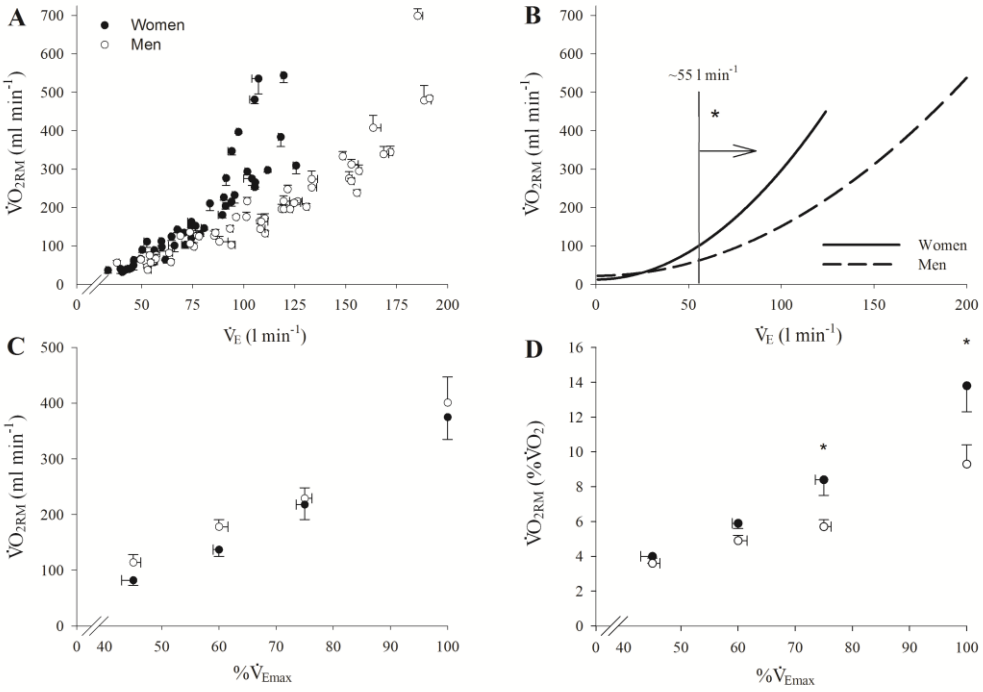


Figure 5. Box and whisker plot, showing individual subject data and group mean ± SE for $\dot{V}O_{2RM}$ as a percentage of whole-body oxygen uptake at maximal exercise in women and men. Squares in the box and whisker plot represent 5th and 95th percentiles and the horizontal line is the median. $\dot{V}O_{2RM}$, oxygen uptake of the respiratory muscles; $\dot{V}O_{2max}$, maximum oxygen uptake. * Significantly greater compared with men (P<0.05).

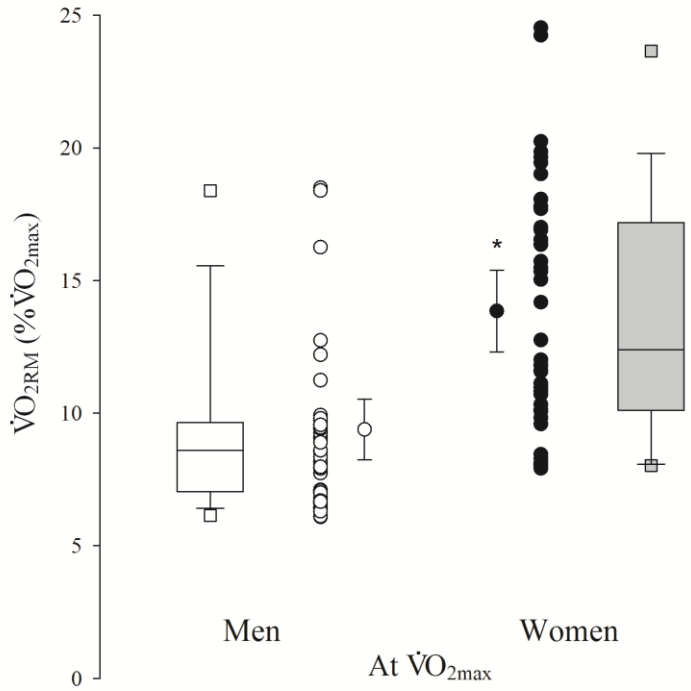


Figure 6. Oxygen uptake of the respiratory muscles in absolute (Panel A) and relative units (Panel B) at different WOB for each subject performing each trial. Group regression lines were developed by averaging each subject's regression and producing a composite. All subjects demonstrated a significant relationship between $\dot{V}O_{2RM}$ and WOB ($P<0.01$). For Panel A, there was no difference in the intercepts of the regression lines, but women had a significantly greater slope (1.29 ± 0.12 vs. 0.85 ± 0.05, $P<0.05$). Similarly, for Panel B, there was no difference in the intercepts of the lines, but women had a significantly greater slope (0.034 ± 0.002 vs. 0.012 ± 0.001, $P<0.05$). $\dot{V}O_{2RM}$, oxygen uptake of the respiratory muscles; WOB, work of breathing.

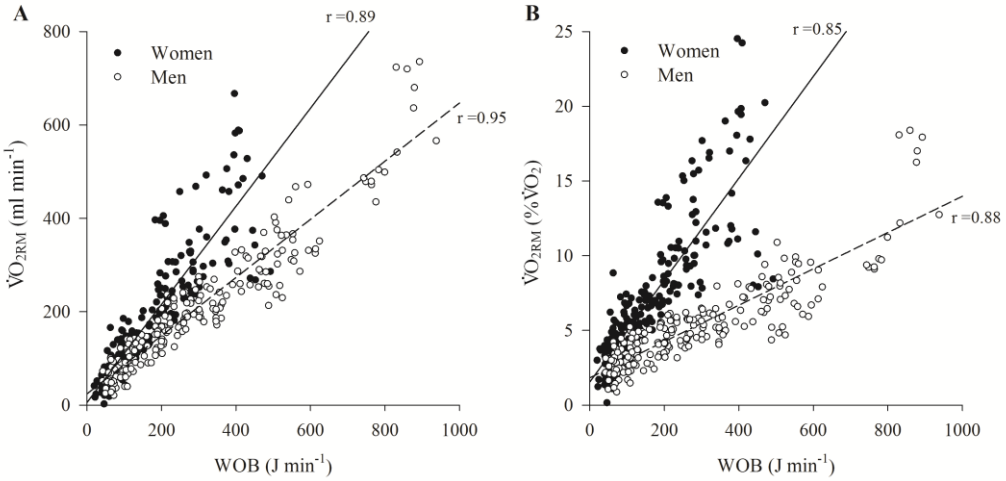


Figure 7. Composite average maximal expiratory flow-volume (MEFV) curves for subjects displaying expiratory flow limitation (EFL) (Panel A) and those with no expiratory flow limitation (NEFL) (Panel C). Placed within the MEFV curves are resting (thin solid lines) and the 100% $\dot{V}_{Emax}$ tidal flow-volume loops during maximal exercise and voluntary hyperpnoea. There was no difference in $\dot{V}O_{2max}$ or $\dot{V}_{Emax}$ between the groups. At 100% $\dot{V}_{Emax}$ the EFL group had a greater $\dot{V}O_{2RM}$, whether expressed as absolute (Panel B) or % of $\dot{V}O_{2max}$ - (13.5 vs. 9.2 % $\dot{V}O_{2max}$ for the EFL and NEFL groups, $P<0.05$). $\dot{V}O_{2max}$, maximum oxygen uptake; $\dot{V}_{Emax}$, maximum minute ventilation; $\dot{V}O_{2RM}$, oxygen uptake of the respiratory muscles. Values in Panel B are mean±SE. * significantly higher in EFL versus NEFL ($P<0.05$).

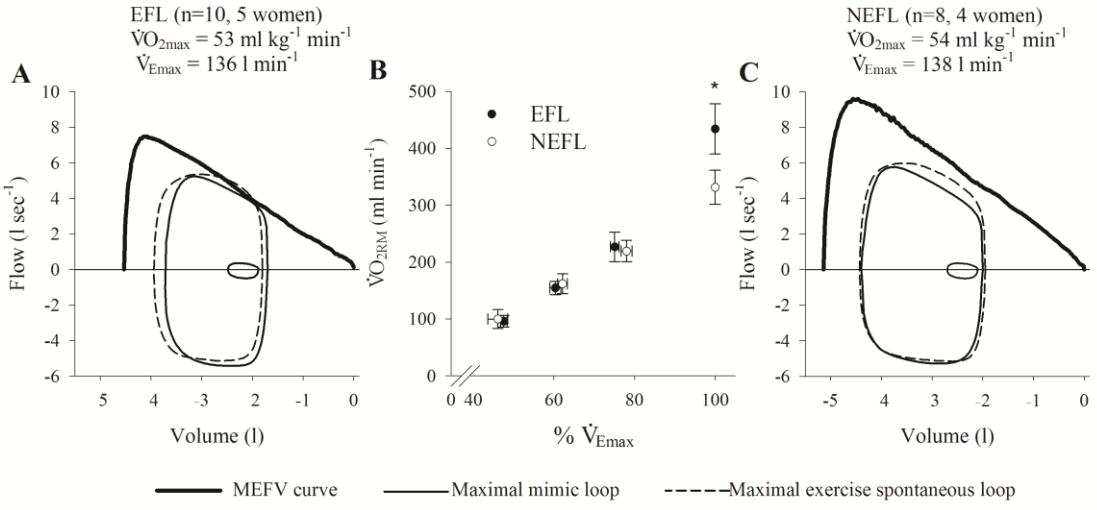


Table 1. Anthropometric and spirometric values.

	Men (n=9)	Women (n=9)
Age (y)	29±3	23±1*
Height (cm)	183±2	167±2*
Mass (kg)	75±3	58±2*
FVC (l)	5.8±0.2	4.0±0.2*
FVC (% predicted)	99±4	95±2
FEV_1 (l)	4.7±0.2	3.4±0.1*
FEV_1 (% predicted)	100±4	94±2
FEV_1/FVC	82±2	85±1
FEV_1/FVC (% predicted)	100±2	99±2

FVC, forced vital capacity; FEV_1, forced expired volume in 1 second; PEF, peak expiratory flow. * Significantly different compared to men ($P<0.05$). Values are mean±SE.

Table 2. Cardiorespiratory values at maximal exercise.

	Men (n=9)	Women (n=9)
$\dot{V}O_2$ (l min^{-1})	4.4±0.2	2.8±0.2*
$\dot{V}O_2$ (ml kg^{-1} min^{-1})	58.7±1.9	48.1±2.1*
Range	50.3-68.5	41.4-60.4
$\dot{V}CO_2$ (l min^{-1})	4.8±0.2	3.0±0.1*
V_T (l)	3.1±0.1	1.9±0.1*
f_b (breaths min^{-1})	56±3	61±3
$\dot{V}_E$ (l min^{-1})	173±10	114±4*
RER	1.11±0.02	1.10±0.02
HR (beats min^{-1})	183±2	189±3
$P_{ET}CO_2$ (mmHg)	28±1	28±1
$\dot{V}_E/\dot{V}CO_2$	36±1	38±1
$\dot{V}_E/\dot{V}O_2$	40±2	42±2
EELV (% FVC)	40±2	43±2
EILV (% FVC)	88±1	87±1
ΔP_{oe} (cmH_2O)	54±4	46±1*
WOB (J min^{-1})	605±59	354±19*
PTP_{oe} (cmH_2O s^{-1} min^{-1})	606±35	500±30*
PTP_{di} (cmH_2O s^{-1} min^{-1})	457±44	406±75
PTP_{oe}/PTP_{di}	0.77±0.07	0.84±0.11
$\dot{V}_{ECap}$ (l min^{-1})	220±15	164±9*
$\dot{V}_E/\dot{V}_{ECap}$ (%)	80±3	72±5
EFL (%)	23±9	21±8
EFL (n)	5	5

$\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide output; V_T, tidal volume; f_b, breathing frequency; $\dot{V}_E$, expired minute ventilation; RER, respiratory exchange ratio; H_R. heart rate; ΔP_{oe}, oesophageal pressure swing; $P_{ET}CO_2$, end-tidal carbon dioxide tension; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; WOB, work of breathing; PTP_{eso}, oesophageal pressure-time product; PTP_{dia}, diaphragmatic pressure-time product; $\dot{V}_{ECap}$, ventilatory capacity; EFL, expiratory flow limitation. * Significantly different compared to men ($P<0.05$). Values are mean±SE.

Table 3. Cardiorespiratory variables during voluntary hyperpnoea at different percentages of maximal exercise ventilation.

	45% $\dot{V}_{Emax}$		60% $\dot{V}_{Emax}$		75% $\dot{V}_{Emax}$		100% $\dot{V}_{Emax}$	
	Men	Women	Men	Women	Men	Women	Men	Women
$\dot{V}O_{2max}$ (%max)	70±3	72±3	83±1	83±2	92±1	92±2	100	100
V_T (l)	3.1±0.2	1.7±0.1 *	3.3±0.2	1.8±0.1 *	3.3±0.2	1.9±0.1 *	3.1±0.2	1.8±0.1 *
f_b (breaths min^{-1})	27±2	34±2*	33±2	39±2	41±3	46±2	53±2	60±2*
ΔH_R (beats min^{-1})	0±3	-2±3	7±2	6±4	7±1	11±3	20±3	25±3
T_e/T_{tot}	0.55±0.01	0.55±0.01	0.54±0.01	0.55±0.01	0.53±0.01	0.55±0.01	0.51±0.01	0.53±0.01
$P_{et}CO_2$ (mmHg)	40±1	37±1	40±1	37±1	35±1	36±1	31±2	35±2
$\dot{V}_E$ (l min^{-1})	81±7	55±2*	106±5	71±3*	133±7	88±3*	165±4	109±4*
$\dot{V}O_{2RM}/\dot{V}_E$ (ml O_2 l^{-1})	1.4±0.1	1.5±0.1	1.7±0.1	1.9±0.1	1.7±0.1	2.4±0.2 *	2.4±0.2	3.5±0.3 *
$\dot{V}O_{2RM}$/WOB (ml O_2 J^{-1})	0.8±0.1	1.1±0.1 *	0.8±0.05	1.2±0.1 *	0.7±0.04	1.1±0.1 *	0.7±0.0	1.1±0.1 *
$Efficiency_{RM}$ (%)	6.7±0.5	5.1±0.6 *	6.4±0.4	4.4±0.3 *	7.7±0.94	4.8±0.3 *	7.2±0.2	4.6±0.4 *
ΔP_{oe} (cmH_2O)	24±1	19±2	31±2	24±2	39±3	32±2	55±4	47±3*
WOB (J min^{-1})	142±21	75±8	232±23	122±12 *	347±38	199±15 *	593±60	339±27 *
WOB_{res} (% total)	40±3	51±5*	57±3	54±5	65±3	65±4	76±2	76±3
WOB_{el} (% total)	60±3	49±6*	43±3	46±5	35±3	35±4	24±2	24±3
EELV (% FVC)	35±2	44±3*	33±1	44±3*	32±1	43±2*	38±2	46±3*
EILV (% FVC)	83±2	83±3	85±2	86±3	85±2	88±2	87±1	88±1
$\dot{V}_E/\dot{V}_{ECap}$ (%)	38±3	33±3	52±3	40±3*	67±3	51±3*	74±4	67±4

$\dot{V}_E$, minute ventilation; $\dot{V}O_{2max}$, maximal oxygen uptake; V_T, tidal volume; f_b, breathing frequency; ΔH_R, change in heart rate from rest to mimic; T_e, expiratory time; T_{tot}, total breath time; $P_{et}CO_2$, end-tidal carbon dioxide tension; $\dot{V}O_{2RM}$, respiratory muscle oxygen uptake; WOB, work of breathing; $Efficiency_{RM}$, efficiency of the respiratory muscles determined by dividing the measured $\dot{V}O_{2RM}$ by the calculated ideal oxygen uptake needed to perform the work; ΔP_{oe}, oesophageal pressure swing; WOB_{res}, resistive work of breathing; WOB_{el}, elastic work of breathing; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; $\dot{V}$

$_{ECap}$, ventilatory capacity. * Significantly different compared to men ($P<0.05$). Values are mean±SE.

Table 4. Cardiorespiratory variables during voluntary hyperpnoea at different percentages of maximal exercise ventilation for the EFL (n=10, 50% men) and NEFL group (n=8, 50% men)

	45% $\dot{V}_{Emax}$		60% $\dot{V}_{Emax}$		75% $\dot{V}_{Emax}$		100% $\dot{V}_{Emax}$	
	EFL	NEFL	EFL	NEFL	EFL	NEFL	EFL	NEFL
% $\dot{V}O_{2max}$	74±2	69±4	83±1	84±2	93±1	92±1	100	100
V_T (l)	2.2±0.2	2.5±0.4	2.4±0.2	2.7±0.4	2.4±0.2	2.8±0.4	1.9±0.3	2.6±0.3
f_b (breaths min^{-1})	32±2	28±3	37±2	35±3	44±2	43±3	60±2*	53±3
ΔH_R (beats min^{-1})	-3±3	2±3	8±2	4±3	10±2	6±2	24±3	19±3
T_e/T_{tot}	0.56±0.01	0.54±0.01	0.56±0.01	0.53±0.01	0.54±0.01	0.53±0.01	0.53±0.01	0.52±0.01
$P_{et}CO_2$ (mmHg)	38±1	39±1	39±1	38±1	36±1	32±2	33±2	34±2
$\dot{V}_E$ (l min^{-1})	69±6	67±8	87±6	91±9	108±9	114±10	136±11	138±12
$\dot{V}O_{2RM}/\dot{V}_E$ (mlO_2 l^{-1})	1.4±0.1	1.5±0.1	1.8±0.1	1.8±0.1	2.2±0.3	2.0±0.1	3.3±0.4*	2.4±0.1
$\dot{V}O_{2RM}$/WOB (ml O_2 J^{-1})	0.9±0.1	1.0±0.2	1.0±0.1	1.0±0.1	0.9±0.1	0.8±0.1	1.0±0.1	0.8±0.1
Efficiency$_{RM}$ (%)	4.0±0.8	4.7±0.5	4.7±0.8	4.4±0.9	4.5±1.0	6.2±0.7	4.6±0.8*	6.2±0.5
ΔP_{oe} (cmH_2O)	23±1	20±2	28±2	28±3	35±2	37±3	52±3	49±3
WOB (J min^{-1})	114±15	108±25	168±19	183±33	265±33	296±45	485±63	443±67
WOB_{res} (% total)	50±5	43±2	56±4	54±4	67±3	64±4	79±1*	72±2
WOB_{el} (% total)	50±6	57±5	44±4	46±4	33±3	36±4	21±1	27±2
EELV (% FVC)	40±3	39±3	40±3	38±3	39±3	37±2	43±2	42±2
EILV (% FVC)	83±2	83±3	86±2	85±3	86±2	86±2	86±1	89±2
$\dot{V}_E/\dot{V}_{ECap}$ (%)	39±3	31±3	48±3	43±4	63±4	54±5	77±2*	63±3

EFL, expiratory flow limited; NEFL, non-expiratory flow limited; $\dot{V}O_{2max}$, maximal oxygen uptake; V_T, tidal volume; f_b, breathing frequency; ΔH_R, change in heart rate from rest to mimic; T_e, expiratory time; T_{tot}, total breath time; $P_{et}CO_2$, end-tidal carbon dioxide tension; $\dot{V}_E$, minute ventilation; $\dot{V}O_{2RM}$, respiratory muscle oxygen uptake; WOB, work of breathing; $Efficiency_{RM}$, efficiency of the respiratory muscles determined by dividing the measured $\dot{V}O_{2RM}$ by the calculated ideal oxygen uptake needed to perform the work; $\Delta P_{oe,}$ oesophageal pressure swing; WOB_{res}, resistive work of breathing; WOB_{el}, elastic work of breathing; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; $\dot{V}_{ECap}$, ventilatory capacity. * Significantly different compared to NEFL ($P<0.05$). Values are mean±SE.