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Sex differences in the oxygen delivery, extraction and uptake during moderate walking exercise transition

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Running head

Aerobic response to moderate intensity walking in women and men.

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Abstract

Previous studies in children and older adults demonstrated faster oxygen uptake ($\dot{V}O_2$) kinetics in males compared to females, but young health adults have not been studied. We hypothesized that young men would have faster aerobic system dynamics in response to the onset of exercise than women. Interactions between oxygen supply and utilization were characterized by the dynamics of $\dot{V}O_2$, deoxyhemoglobin (HHb), tissue saturation index (TSI), cardiac output ($\dot{Q}$) and calculated arteriovenous O_2 difference ($a - vO_2diff$) in women and men. Eighteen healthy active young women and men (9 of each sex) with similar aerobic fitness level volunteered for this study. Participants performed an incremental cardiopulmonary treadmill exercise test and three moderate intensity treadmill exercise tests (at 80 % $\dot{V}O_2$ of gas exchange threshold). Data related to the moderate exercise were submitted to exponential data modeling to obtain parameters related to the aerobic system dynamics. The time constants of $\dot{V}O_2$, $a - vO_2diff$, HHb and TSI (30 ± 6 , 29 ± 1 , 16 ± 1 and 15 ± 2 s, respectively) in women were statistically ($p < 0.05$) faster than the time constants in men (42 ± 10 , 49 ± 21 , 19 ± 3 and 20 ± 4 s, respectively). Although $\dot{Q}$ dynamics were not statistically different ($p = 0.06$) between groups, there was a trend to slower $\dot{Q}$ dynamics in men corresponding with the slower $\dot{V}O_2$ kinetics. These results indicated that the peripheral and pulmonary oxygen extraction dynamics were remarkably faster in women. Thus, contrary to the hypothesis, $\dot{V}O_2$ dynamics measured at the mouth at the onset of submaximal treadmill walking were faster in women compared to men.

Keywords. Sex influences, aerobic system, cardiac output, NIRS, walking, oxygen uptake kinetics.

Introduction

The characterization of the oxygen uptake ($\dot{V}O_2$) dynamics during exercise transition can be used to investigate the adjustments of the aerobic response to supply a new energetic demand (Krogh and Lindhard 1913). The rate at which the $\dot{V}O_2$ increases at the beginning of exercise seems to be determined by the integrative control of several mechanisms involving the O_2 transport by the circulation and its utilization by the myocyte (Hughson and Morrissey 1983, Grassi et al. 1996, Macdonald et al. 1997, Rossiter et al. 1999, Hughson 2009, Beltrame and Hughson 2017).

The greater maximal aerobic power of men compared to women is well recognized (Cureton et al. 1986). Nevertheless, the sex influences over the aerobic response dynamics during moderate exercise transition are not fully understood. Previous studies observed faster $\dot{V}O_2$ kinetics in pre-pubertal and adolescent males compared to females (Fawcner and Armstrong 2004, Franco et al. 2014, Lai et al. 2016). In older adults, sex-differences explained some variation in $\dot{V}O_2$ kinetics (Chilibeck et al. 1995), but another study observed no difference between men and women in healthy or diabetic populations (O'Connor et al. 2012). Other factors in women including better autonomic control of heart rate (Rossy and Thayer 1998, Dart et al. 2002) and higher predominance of slow-twitch muscle fibers (Nygaard 1981) might be expected to speed $\dot{V}O_2$ dynamics during exercise transition (Hughson 1984, Powers et al. 1985, Barstow et al. 1996), but there are no data to address this in young men and women. Despite potential differences in the aerobic responses between sexes, some studies (Bauer et al. 2007, Endo et al. 2007) investigated the $\dot{V}O_2$ dynamics in men and women as a single group which could mislead the interpretation of the results and underlying mechanisms if sex-differences are involved in $\dot{V}O_2$ control.

No investigation to date performed measurements in men and women that allowed the simultaneous investigation of $\dot{V}O_2$ kinetics and the contributions of the O_2 delivery-utilization systems during exercise transition. Near infrared spectroscopy (NIRS) and estimation of cardiac output ($\dot{Q}$) can be used to assess the O_2 delivery-utilization distortions *in vivo* (Ferrari et al. 1997, Faisal et al. 2010, Murias et al. 2011). These variables, when obtained simultaneously with $\dot{V}O_2$ data, offer the opportunity to study how the O_2 delivery-utilization balance differs between women and men, and how this might impact the rate at which the aerobic system supplies the energy demand.

Therefore, the purpose of this cross-sectional study was to further explore how sex influences the $\dot{V}O_2$ response during exercise transition with simultaneous measurement of NIRS and $\dot{Q}$. We hypothesized that in healthy young adults, similar to previous studies of children, men would have faster $\dot{V}O_2$ dynamics in comparison to women, and that this would be supported by a better O_2 delivery and extraction in men.

Methods

Participants

Eighteen healthy, recreationally active young adults (9 women and 9 men) of similar age and body mass index (women = age 23 ± 3 years, height 164 ± 7 cm, weight 62.9 ± 5.9 kg, and BMI 23.2 ± 1.2 kg/m² and men = age 29 ± 6 years, height 181 ± 8 cm, weight 81.1 ± 11.1 kg, and BMI 24.6 ± 2 kg/m²) without any cardiovascular or orthopedic complications volunteered for this study. Women and men presented similar submaximal fitness level evaluated by gas exchange threshold (*GET*). Participants were evaluated during walking activities on a previously calibrated treadmill (error lower than 1% for speeds between 0.5 to 8 km·h⁻¹) (Bodyguard, St-Georges, QB,

Canada). Walking, instead of cycling, was performed to incorporate the most common activity of daily living. Participants signed a written informed consent after receiving detailed information about the experimental procedures and potential risks involved. They were aware of their right to withdraw from the study at any time. The study procedures were reviewed and approved by the Office of Research Ethics at the University of Waterloo and in agreement with Declaration of Helsinki. It was requested of all participants to not consume a large meal within 2 h prior testing, not drink alcohol and caffeinated beverages as well as not perform high intensity exercise for 24 h prior testing.

Experimental Design

Data were collected on two separate visits. The first visit consisted of incremental cardiopulmonary exercise testing, while the second visit consisted of three moderate walking exercise tests. Following the measurement of height and weight, a 3-lead electrocardiogram (ECG) electrodes were applied over the participant's skin and an air cushion mask was fitted to the participant's face to allow measurement of gas exchange. Prior to testing, all individuals were trained to step on the treadmill in motion according to speed and inclination requirements and familiarized with the protocols. Experiments were performed in a quiet room with temperature and humidity relatively constant (22.4 ± 0.5 °C, $23.4 \pm 0.9\%$ respectively) and barometric pressure of 728.7 ± 4.4 mmHg.

Experimental Protocols

The incremental cardiopulmonary exercise testing protocol consisted of 1-minute baseline, 6-minute warm-up at $4.5 \text{ km}\cdot\text{h}^{-1}$ no slope, followed by a new increment in speed

(individual maximum walking speed of $\sim 6 \text{ km} \cdot \text{h}^{-1}$) and then progressive increments in grade ($1\% \cdot \text{min}^{-1}$). The test was terminated when subjects reached 80% of their predicted maximal heart rate. This protocol was performed in order to obtain individual *GET* (Beaver et al. 1986) that was used to calculate the relative moderate work rate performed in the following laboratory visit. On the second visit, participants performed three identical walking exercises at a work rate corresponding to 80% of their $\dot{V}O_2$ at *GET* (Ozyener et al. 2001). This protocol included 1 minute of baseline standing at the treadmill edge followed by 6 min walking at individual selected speeds and grades and 6 minutes of recovery.

To minimize any carry over effect between exercise bouts, seated recovery periods between all constant work rate exercise tests lasted at least 20 min. The treadmill was operating at the target speed even during baseline for at least 5 min to avoid anticipatory responses. To indicate when participants should start walking on the treadmill, a computer monitor was placed at the participant's eye level to control the transitions.

Data acquisition

Breath-by-breath measurements of pulmonary $\dot{V}O_2$ and carbon dioxide output ($\dot{V}CO_2$) were taken during tests. A low dead space, bidirectional, low resistance turbine was used to measure inhale/exhale air volumes and flows (UVM-1725, Vacumed, Ventura, California, USA) and it was attached to an air cushion mask (Vacumed, Ventura, California, USA) for a total system dead space of 170 mL. A 3 L syringe using different flow rates (0.5 to $2 \text{ L} \cdot \text{s}^{-1}$) was used to calibrate the turbine prior to each test bout. Air samples inside the mask were sent to a mass spectrometer (Amis 2000, Innovision, Odense, Denmark) by a short sample line ($\sim 1.5 \text{ m}$). The system gas concentration calibration was performed using gas tanks with known O_2 , CO_2 , N_2 ,

and Ar concentrations. The turbine and mass spectrometer signals were synchronized and utilized in the estimation of $\dot{V}O_2$ and $\dot{V}CO_2$ (Hughson et al. 1991).

The heart rate beat-by-beat calculation was derived from the ECG signal (Pilot 9200, Colin Medical Instruments, San Antonio, TX, USA) recorded with LabChart 7.3.7 (ADInstruments, Colorado Springs, CO, USA). The finger arterial pressure signal (Finometer, Finapres Medical System, Arnhem, The Netherlands) was used to provide a beat-by-beat estimate of $\dot{Q}$ as previously validated for exercise (Faisal et al. 2009). The total arteriovenous O_2 difference ($a - vO_2diff$) was calculated by the ratio $\dot{V}O_2/\dot{Q}$ and it was used as a proxy of the total venous O_2 content during exercise transition (Barstow et al. 1990).

A multi-distance continuous-wave single channel near infrared spectroscopy (NIRS) (PortaLite, Artinis Medical Systems B.V., Elst, The Netherlands) evaluated changes in *Gastrocnemius Lateralis* muscle oxy- (O_2Hb) and deoxy-hemo/myoglobin (HHb) concentrations (expressed in μM) sampled at a rate of 10 Hz. The light emitting probe was composed by three light-emitting diodes operating at two wavelengths ($\lambda_1=845$ and $\lambda_2=759$ nm) with an average light in/out distances of ~ 35 mm. The probe was placed in the target area and the device was warmed-up for at least 30 min before the data collection. To avoid any motion artifact and ambient light influences, the probe was fixed by tape and then a dark cloth was gently wrapped around the calf.

The tissue saturation index (TSI) was calculated as the percent of O_2 for a given capillary blood volume. Any probe movement was checked in real-time by the correlation level (r^2) between the light in/out distance and the optical density. During the entire data collection, the r^2 was $> 98\%$ indicating appropriate signal quality. The adipose tissue thickness (ATT) was determined by measurements of the *Gastrocnemius* lateral head skinfold thickness using a

skinfold caliper. The *ATT* did not exceed the minimum penetration depth of the NIRS system calculated as the half of the light in/out distance ($35 \text{ mm}/2 = 17.5 \text{ mm}$). The average *ATT* was $7.06 \pm 2.57 \text{ mm}$, or $\sim 40\%$ lower than the NIRS light penetration depth. The *ATT* was not correlated to any variable evaluated in this study. The selected *HHb* and *O₂Hb* signals were related to the deepest penetrating transmitter of the NIRS (i.e., highest light in/out distance) in order to diminish the influence of skin blood flow over the target signals.

Data analysis

The data from the constant work rate protocols were linearly interpolated and re-sampled at 1 Hz. The signals for each of the three constant work rate exercise transitions were time-aligned with time zero matching the onset of walking exercise. The data from the three repetitions were ensemble-averaged generating a single exercise dataset per participant. Afterwards, a 5-s moving average was used for filtering to reduce the influence of the inter-breath oscillations (Lamarra et al. 1987), narrowing the confidence interval of the parameters to be estimated (Keir et al. 2014). Finally, the kinetics of $\dot{V}O_2$, $\dot{Q}$, *HR* and *a-vO₂diff* were analyzed by the bi-exponential model following previous literature (Hughson et al. 1988):

$$VO_2, \dot{Q}, HR \text{ or } a - vO_2diff_{(t)} = a_0 + a_1 * \left(1 - e^{\left(-\frac{t-TD_1}{\tau_1}\right)}\right) + a_2 * \left(1 - e^{\left(-\frac{t-TD_2}{\tau_2}\right)}\right); \text{ where: "t"}$$

is time (independent variable); "*a*₀" is the mean value during baseline; "*a*₁" and "*a*₂" are the steady-state amplitudes for the cardio-dynamic and fundamental phases, respectively; "*τ*₁" and "*τ*₂" are time constants for each phase; "*TD*₁" and "*TD*₂" are time delays for each phase. For all variables, the steady-state of the cardio-dynamic phase (i.e., $4*[\tau_1+TD_1]$) coincided with the beginning of the fundamental phase (i.e., *TD*₂), so that phase 1 had minimal impact on fitting of phase 2. The mean response time (*MRT*) was calculated by the sum of *TD*₂ and *τ*₂ (i.e.,

$MRT = TD_2 + \tau_2$) and used as an index to describe the overall kinetic response during transition (Linnarsson 1974). The quality of the fitting was assured by the analysis of residuals, degree of linear correlation between the experimental data and fitted function (r), 95% confidence interval band (CI_{95}) (Fawcner et al. 2002, Keir et al. 2016) and the significance level (p value) of the estimated parameters.

The NIRS signals were normalized by the average of the data during 30 s prior the onset of exercise for better data visualization. The HHb and TSI time constants were obtained following a previously described method (DeLorey et al. 2003, Murias et al. 2011). Data not directly associated to the muscular $\dot{V}O_2$ dynamics (DeLorey et al. 2003) were excluded based on the detection of two nadir values for each individual exercise transition dataset. The first portion of excluded data was related to the muscle pump. The first nadir occurred at 11 ± 0.6 and 11.6 ± 1.3 s for women and men, respectively. This period was characterized by a sudden decrease in HHb signal (Figure 1A) with a simultaneous increase in TSI as a consequence of an elevated initial blood flow that surpasses the $\dot{V}O_2$ increase (Tschakovsky et al. 2006) decreasing the O_2 extraction (Murias et al. 2014). After this first nadir, the HHb increased and TSI decreased following an exponential-like function. It is believed that this behavior is a consequence of the $\dot{V}O_2$ dynamics characteristics during exercise transition, and therefore the phase of interest (Figure 1A) (Murias et al. 2011).

Instead of studying the influence of data window selection over the parameters estimation by arbitrarily choosing different time intervals (Dumanoir et al. 2010, Murias et al. 2011, Keir et al. 2016), the end of the data window was selected according to the identification of a second nadir (Bauer et al. 2004). Due to the late overshooting characteristics of the HHb signal (Bauer et al. 2007) usually more pronounced in women, the second nadir was set when a systematic

increase in capillary blood volume assessed by the total hemoglobin ($tHb = HHb + O_2Hb$) was observed after a brief period of steady-state (— in Figure 1B). This increment in the capillary blood volume (Truijen et al. 2012) might be occurring due to temperature increase that elevates skin blood flow and/or due to the local metabolites action over the capillary bed. The second nadir occurred after 37 ± 8 and 41 ± 11 s for women and men, respectively. To avoid misinterpretation of the HHb dynamics associated to non-steady capillary blood volume (Kime et al. 2013), both nadirs were used to select the optimized data window to be fitted.

(Figure 1)

To facilitate comparison with previous literature (Murias et al. 2011, 2014), we implemented an exponential fitting procedure on the selected data. The HHb data contained between the two nadirs were fitted by the equation: $HHb_{(t)} = a_0 + a_1 * \left(1 - e^{\left(\frac{t-TD_1}{\tau_1}\right)}\right)$, as depicted in Figure 1A. The equation parameters are the same as previously described. The selected TSI data were fitted by the same equation but instead of adding the exponential component to the a_0 , it was decreased from the a_0 . Since the response can be interpreted as a non-delayed local response, the MRT of the HHb and TSI ($HHb-MRT$ and $TSI-MRT$, respectively) was also calculated by the sum of τ_1 and TD_1 and considered as the only time constant for these variables (Murias et al. 2011, Allart et al. 2012). All data modeling parameters were calculated by a G-language computer program developed by a certified LabVIEW programmer (LabVIEW 2012, National Instruments, Austin, TX, USA). This program fitted the data using a nonlinear curve fit function that finds the lowest sum of the squared errors by a standard Levenberg-Marquardt algorithm.

Statistical Analysis

Data were expressed as mean $\pm$ SD. The one-way repeated measures ANOVA was used to compare the $\dot{V}O_2$ baseline between the three bouts of moderate walking exercise to confirm no carryover effects prior to ensemble averaging to achieve a single exercise transition per participant. For comparison of the parameters obtained by the kinetics analysis between women and men, Shapiro-Wilk test was used to assess data distribution. The t-test or Mann-Whitney Rank Sum test was used for comparisons between men and women for normal and non-normal data distribution, respectively. The established cut-off significance level was 5% ($p < 0.05$). Statistical analysis was performed using SigmaPlot 12.5 software (Systat Software Inc, San Jose, CA, USA).

Results

The incremental treadmill test was terminated at 80% predicted maximal heart rate. At this point of peak exercise, the HR was not different ($p > 0.05$) between women (149.0 ± 2.6 bpm) and men (152.7 ± 5.5 bpm). However, absolute and relative $\dot{V}O_2$ in men (2945 ± 648 ml $\cdot$ min $^{-1}$ and 36.27 ± 6.09 ml $\cdot$ min $^{-1} \cdot$ kg $^{-1}$, respectively) were higher ($p = 0.003$ and $p = 0.001$, respectively) than in women (1870 ± 211 ml $\cdot$ min $^{-1}$ and 29.80 ± 2.72 ml $\cdot$ min $^{-1} \cdot$ kg $^{-1}$, respectively).

The selected treadmill grade at 80% of GET was not different between groups (6 ± 1 % for women and 6 ± 2 % for men, $p < 0.05$). Women were shorter than men ($p < 0.05$) thus, as expected, the treadmill speed at 80% of GET was also slower in women (3.4 ± 0.0 km $\cdot$ h $^{-1}$ for women and 3.9 ± 0.2 km $\cdot$ h $^{-1}$ for men, $p < 0.05$). The $\dot{V}O_2$ at GET was not different between groups (26 ± 3 ml $\cdot$ min $^{-1} \cdot$ kg $^{-1}$ for women and 30 ± 5 ml $\cdot$ min $^{-1} \cdot$ kg $^{-1}$ for men, $p < 0.05$).

The one-way repeated-measures ANOVA indicated that there were no statistically significant differences between the $\dot{V}O_2$ baseline (initial condition) of three bouts of moderate walking exercise. Figure 2A displays the normalized second-by-second group response of the $\dot{V}O_2$ during exercise transitions. According to Figure 2B, the $\dot{V}O_2$ -MRT was significantly faster in women in comparison to men ($p < 0.05$). The $\dot{Q}$ -MRT approached statistical significance ($p = 0.06$), with women having faster MRT than men. The HR-MRT was not statistically ($p > 0.05$) different between women and men.

(insert Figure 2)

The second-by-second *HHb* and *TSI* data (Figures 3A and 3B, respectively) for the region of interest (selected as described in Figure 1) revealed a statistically ($p < 0.05$) faster adaptation in women. The exponential characteristics of the response were evident and the data modeling presented low residuals, as well as low CI_{95} and p values.

(insert Figure 3)

Table 1 shows the comparison of the data fitting parameters between women and men. The statistical analysis indicated that women presented lower $\dot{V}O_2$ - a_2 relative to weight or absolute values ($p < 0.05$) and faster $\dot{V}O_2$ - τ_2 in comparison to men, but no differences for the parameters τ_1 , TD_1 and TD_2 . The parameters a_0 and a_1 relative to weight were not different between women and men ($p > 0.05$). However, the a_0 and a_1 absolute values were higher ($p = 0.002$ and $p = 0.011$, respectively) in men in comparison with women. The initial cardio-

dynamic component of the $\dot{Q}$ response (i.e., $\dot{Q}-a_1$) was less pronounced in women ($p < 0.05$). The $\dot{Q}-\tau_2$ was not different between women and men. In addition, no differences ($p > 0.05$) were found in $\dot{Q}$ for the parameters a_0 , a_2 , τ_1 , τ_2 and TD_1 . The $\dot{Q}$ baseline amplitude (i.e., a_0) and the $\dot{Q}-TD_2$ also approached statistical significance between groups ($p = 0.06$) being both lower in women. In comparison to men, the faster local oxygen extraction (faster $HHb-MRT$) found in women was also associated with faster pulmonary O_2 extraction investigated by $a - vO_2diff$ - τ_2 . The $a - vO_2diff$ parameters a_0 , a_1 , a_2 , τ_1 , TD_1 and TD_2 were not different ($p > 0.05$) between groups. Like $\dot{Q}$, the MRT for $a - vO_2diff$ also approached statistical significance ($p = 0.06$) with women having a faster response than men. The $HR-a_2$ was higher ($p < 0.05$) in women in comparison to men. However, the HR parameters a_0 , a_1 , τ_1 , τ_2 , TD_1 and TD_2 did not present statistical differences ($p > 0.05$) between groups.

(Table 1)

Discussion

To the best of our knowledge, this was the first time that the integrative cardiovascular and metabolic responses have been compared in young, healthy men and women during the dynamic adaptive phase of moderate intensity walking exercise. The main finding of the current study showed that women presented faster $\dot{V}O_2$ dynamics in comparison to men. This was contrary to our initial hypothesis, but consistent with a strong trend for faster central O_2 transport ($\dot{Q}$), as well as remarkably faster peripheral and pulmonary O_2 extraction dynamics in women in comparison to men.

In contrast to previous studies that reported faster $\dot{V}O_2$ kinetics in younger boys compared to girls (Fawcner et al. 2002, Franco et al. 2014, Lai et al. 2016) and an investigation of 55-year-old men and women that reported no difference in $\dot{V}O_2$ kinetics between the sexes (O'Connor et al. 2012), we observed significantly faster responses in young, healthy women compared to men. The current study demonstrated that sex influenced the aerobic adaptation during moderate walking. In the rest to exercise transition, women presented $\dot{V}O_2$ dynamics ~28 % faster in comparison to men as indicated by the faster τ_2 (Figure 2A) and MRT (Table 1). In addition, as depicted in Figure 3, the HHb and TSI adaptive responses (MRT) in women were respectively 19 % and 22 % faster than men, indicating a faster peripheral O_2 extraction (HHb) and O_2 desaturation (TSI) dynamics, respectively. Despite the lack of statistical significance of the $\dot{Q}$ temporal dynamics (i.e., $\dot{Q}$ - MRT) between groups, the mean effect size of $\approx 25\%$ associated with a statistical significance level (p) of 0.06 cannot be overlooked. The observed faster $\dot{V}O_2$ dynamics in women might be also associated with faster $\dot{Q}$ dynamics reflecting O_2 transport in addition to the statistically significant faster O_2 extraction. Consequently, the blood with lower O_2 content might be reaching the lungs faster in women which would support, according to Fick principle, the remarkable faster pulmonary $\dot{V}O_2$ observed in this group.

The faster $\dot{V}O_2$ dynamics for the same relative metabolic demand (80% GET) showed that women were able to utilize aerobic rather than anaerobic metabolism to supply the energetic demand during exercise transition. This is true even if faster $\dot{Q}$ dynamics might distort the interpretation of muscle $\dot{V}O_2$ dynamics (Hoffmann et al. 1992, 2013). The mechanisms that underlie the more rapid increase in $\dot{V}O_2$ are complex. The capillary density of the gastrocnemius muscle seems to be similar between women and men (Coggan et al. 1992), but women have lower hemoglobin concentration (Vahlquist 1950) and possibly different respiratory function

(Harms and Rosenkranz 2008) which contributes with $\dot{Q}$ dynamics to affect convective O_2 transport.

In order to diminish the influence of other variables beyond sex over the aerobic response (Lundsgaard and Kiens 2014), women and men were similar in their age, BMI and *GET*. Differences between matched men and women in observed pulmonary $\dot{V}O_2$ might also reflect muscle metabolic potential. Women apparently have a higher slow-twitch muscle fiber composition which has a better oxidative capacity (Staron et al. 2000, Lundsgaard and Kiens 2014, Haizlip et al. 2015). Different muscle type compositions has an impact over the $\dot{V}O_2$ measured at the mouth and as expected greater recruitment of slow-twitch fiber will speed up the aerobic system energy supply during exercise transitions (Crow and Kushmerick 1982, Barstow et al. 1996). In addition, it was reported that women have similar cytochrome *c* oxidase (Rouleau et al. 1995) activity in comparison to matched men. In addition, the mitochondrial content and myocyte respiration was reported to be similar between women and men for the same muscle fiber type (Thompson et al. 2013). Therefore, the observed faster aerobic adjustment in the current study might be accounted for in part by a higher composition or recruitment of slow-twitch muscle in women.

Women have a greater reliance on fat oxidation in comparison to men during dynamic exercise (Tarnopolsky et al. 1990, Tarnopolsky 2008) which should also influence the $\dot{V}O_2$ dynamics during exercise transition (Molé and Hoffmann 1999). However, $\dot{V}O_2$ dynamics were slowed during a high fat diet intervention (Raper et al. 2014), contrary to the observed faster $\dot{V}O_2$ adjustment in women of the current study. Nonetheless, despite the impossibility of exactly identifying the intracellular mechanisms that trigger a faster $\dot{V}O_2$ dynamics in women, the faster peripheral O_2 extraction in the capillary bed lead to a faster detachment of the O_2 from the O_2Hb ,

accelerating the dynamics of HHb concentration and the blood O_2 desaturation (i.e. TSI) (Figure 3). As previously described (Hughson 2009), interactions of O_2 transport and O_2 delivery mechanisms establish the rate of increase in $\dot{V}O_2$ accounting for differences between men and women.

Regarding the quality of the parameters estimation, the data modeling presented elevated reliability which allowed us to infer about the aerobic system response profile based on the parameters estimated from the $\dot{V}O_2$ data measured at the mouth (Lamarra et al. 1987, Keir et al. 2014). The CI_{95} of the $\dot{V}O_2\text{-}\tau_2$ (main variable) was not statistically ($p > 0.05$) different between women (2.2 ± 0.5 s) and men (2.6 ± 0.5) and corresponded to ~ 7 and ~ 6 % of the women's and men's group mean response, respectively.

Study Limitations

Comparison studies of sex-differences in responses to exercise are complicated by multiple factors. Women are smaller and have relatively greater fat mass, on average, than men (Charkoudian and Joyner 2004). In addition to the lower hemoglobin concentration (Vahlquist 1950), women have smaller stroke volume and reduced total systemic oxygen transport (Wheatley et al. 2014). Differences in maximal aerobic power when expressed per kg body mass are partially compensated when expressed per kg lean body mass, but an average 15% difference still exists (Peltonen et al. 2013). Lower maximal aerobic power or $\dot{V}O_2$ at GET might be explained by training status or by leg strength (Neder et al. 1999). In the current study, the statistically similar $\dot{V}O_2$ at GET in men and women might indicate that the women were relatively more physically fit which could account for the faster $\dot{V}O_2$ kinetics in women. This seems, though, to be unlikely in the current study as the levels of physical activity were similar

in the young, healthy students studied. Future studies should systematically address these issues related to fitness and normalization of metabolic demand.

Cardiovascular responses to exercise across the menstrual cycle have not been extensively studied, nor extensively compared to men. Peak reactive hyperemia is greatest in the late follicular phase of the menstrual cycle highlighting the impact of hormonal concentrations on vascular endothelial function (Adkisson et al. 2010). Muscle blood flow is greater in women than men with single leg knee extension and forearm exercise when tested in the early follicular (first 5-7 days) of the menstrual cycle (Parker et al. 2007, Kellawan et al. 2015). For young women tested in the follicular and luteal phases of the menstrual cycle, there were no differences in $\dot{V}O_2$ kinetics or muscle deoxygenation patterns at the onset of moderate intensity exercise (Gurd et al. 2007). In the current study, we did not standardize the phase of the menstrual cycle, but we did find clear differences between men and women. These results establish a basis for continued research to explore mechanisms related to muscle blood flow and its distribution patterns as well as explorations of metabolic control at the onset of exercise in women as well as in men.

The current study used treadmill exercise rather than the more commonly studied cycle ergometer exercise. The kinetics of $\dot{V}O_2$ are reported to be similar for cycling and treadmill (Koschate et al. 2016), but to date the exercise modes have only been compared in men. It is not known if women might respond differently to treadmill exercise.

Conclusion

In spite of no difference in submaximal aerobic fitness as indicated by the $\dot{V}O_2$ at gas exchange threshold, women presented a faster $\dot{V}O_2$ dynamics during walking exercise transition,

indicating a faster aerobic system adjustment to supply the energetic demand. Women also presented a remarkably faster O_2 extraction dynamics in comparison to men at both peripheral and pulmonary compartments. The observed faster aerobic system adjustment in women during treadmill walking at a submaximal intensity was a consequence of faster intracellular O_2 handling in combination with faster central O_2 delivery.

Conflict of interest disclaimer

The authors report no conflicts of interest associated with this manuscript.

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Tables

Table 1: Parameters obtained from the kinetic analysis of the oxygen uptake ($\dot{V}O_2$), cardiac output ($\dot{Q}$), total arteriovenous O_2 difference ($a - vO_2diff$) and heart rate (HR) during moderate walking exercise transition in women and men.

		Women (<i>n</i> = 9)	Men (<i>n</i> = 9)
$\dot{V}O_2$	a_0 (ml·kg ⁻¹ ·min ⁻¹)	4.75±0.48	4.38±0.53
	a_1 (ml·kg ⁻¹ ·min ⁻¹)	7.62±1.31	8.79±1.93
	a_0 (ml·min ⁻¹)	296±23	351±35 *
	a_1 (ml·min ⁻¹)	480±107	717±207 *
	τ_1 (s)	4.04±2.56	3.98±2.28
	TD_1 (s)	0.55±0.59	1.21±1.56
	a_2 (ml·kg ⁻¹ ·min ⁻¹)	11.97±1.19	14.99±2.46 *
	a_2 (ml·min ⁻¹)	753±111	1216±276 *
	τ_2 (s)	30.30±6.42	42.40±10.00 *
	TD_2 (s)	18.26±4.70	16.98±6.24
$\dot{Q}$	a_0 (l·min ⁻¹)	4.22±0.72	5.18±1.17 #
	a_1 (l·min ⁻¹)	4.36±0.85	5.95±1.92 *
	τ_1 (s)	4.26±2.89	5.78±3.20
	TD_1 (s)	1.00±0.72	1.33±1.70
	a_2 (l·min ⁻¹)	3.06±0.77	5.07±2.80
	τ_2 (s)	20.78±12.59	27.37±8.88
	TD_2 (s)	14.91±7.21	20.32±2.84 #
$a - vO_2diff$	a_0 (mlO ₂ ·(l·b) ⁻¹)	71.80±10.18	72.77±30.72
	a_1 (mlO ₂ ·(l·b) ⁻¹)	24.62±11.33	34.90±19.73
	τ_1 (s)	4.90±7.83	0.67±0.88
	TD_1 (s)	3.90±8.28	1.32±1.60
	a_2 (mlO ₂ ·(l·b) ⁻¹)	40.47±12.61	65.35±67.93
	τ_2 (s)	29.22±12.5	49.94±21.96 *
	TD_2 (s)	28.49±11.23	24.45±2.52
	MRT (s)	57.71±12.16	74.39±21.37 #
HR	a_0 (bpm)	86.43±9.33	78.48±10.12
	a_1 (bpm)	24.65±13.63	27.50±7.32
	τ_1 (s)	6.65±8.49	7.36±4.18
	TD_1 (s)	0.44±0.77	1.38±3.44
	a_2 (bpm)	29.53±5.56	22.81±6.93 *
	τ_2 (s)	60.67±45.13	75.20±52.33
	TD_2 (s)	26.67±32.47	30.45±5.79

Abbreviation: a_0 is the baseline value; a_1 and a_2 are the steady state amplitude of the response above a_0 and a_1 , respectively; τ_1 and τ_2 are time constants (i.e. speed of the adaptation) for each phase; TD_1 and TD_2 are time delays of each phase and MRT is the mean response time. Please see text for further details regarding the parameters. *

means statistically different ($p < 0.05$) between women and men and # means statistical significance level of $p = 0.06$.

Draft

Figure Captions

Figure 1. Group mean response ($n = 18$) of the deoxyhemoglobin (A, HHb) and total hemoglobin (B, tHb) changes (in $\Delta\mu M$) during walking exercise transition. The method used to select the data to be fitted by an exponential function was based on the identification of two nadir values (see text).

Figure 2. A: Mean $\pm$ SD (vertical lines) of the normalized pulmonary oxygen uptake ($\dot{V}O_2$) of women ($n = 9$) and men ($n = 9$) during moderate walking exercise transition. To display the function used for data fitting, the mean $\dot{V}O_2$ response was fitted by a bi-exponential model (—, see text for further details). B: The smaller bar graphs show the speed of the signal adjustment (represented by the mean response time, MRT) of $\dot{V}O_2$, cardiac output ($\dot{Q}$) and heart rate (HR). *: Statistically ($p < 0.05$) faster (i.e., lower MRT) in women and #: Statistical significance level of $p = 0.06$.

Figure 3. Mean $\pm$ SD of the normalized deoxy-hemoglobin (A, HHb) and tissue saturation index (B, TSI) of women ($n = 9$) and men ($n = 9$) during moderate walking exercise. The smaller bar graphs show the speed of the signal adjustment (represented by the mean response time or “ MRT ”) of each variable. *: statistically ($p < 0.05$) faster (i.e., lower MRT) in women.

Group mean response ($n = 18$) of the deoxyhemoglobin (A, HHb) and total hemoglobin (B, tHb) changes (in $\Delta\mu\text{M}$) during walking exercise transition. The method used to select the data to be fitted by an exponential function was based on the identification of two nadir values (see text).

113x42mm (300 x 300 DPI)

A: Mean $\pm$ SD (vertical lines) of the normalized pulmonary oxygen uptake ($\dot{V}O_2$) of women (n = 9) and men (n = 9) during moderate walking exercise transition. To display the function used for data fitting, the mean $\dot{V}O_2$ response was fitted by a bi-exponential model (— , see text for further details). B: The smaller bar graphs show the speed of the signal adjustment (represented by the mean response time, MRT) of $\dot{V}O_2$, cardiac output (Q) and heart rate (HR). *: Statistically ($p < 0.05$) faster (i.e., lower MRT) in women and #: Statistical significance level of $p = 0.06$.

121x47mm (300 x 300 DPI)

Mean $\pm$ SD of the normalized deoxy-hemoglobin (A, HHb) and tissue saturation index (B, TSI) of women (n = 9) and men (n = 9) during moderate walking exercise. The smaller bar graphs show the speed of the signal adjustment (represented by the mean response time or “MRT”) of each variable. *: statistically ($p < 0.05$) faster (i.e., lower MRT) in women.

114x42mm (300 x 300 DPI)

Draft