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IN
KINESIOLOGY

THESIS TITLE: SEX DIFFERENCES IN HEMODYNAMIC RESPONSE TO HIGH INTENSITY INTERVAL EXERCISE

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THE THESIS HAS BEEN ACCEPTED BY THE THESIS COMMITTEE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN KINESIOLOGY.

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Sex Differences in Hemodynamic Response to High Intensity Interval Exercise
Abstract
Sex differences in the cardiorespiratory and hemodynamic response to exercise exist due to differences in heart size, blood volume, and hemoglobin mass, eliciting a higher maximal oxygen uptake (VO2max) in men versus women. Data are equivocal on whether sex differences in training responsiveness occur. This study investigated potential sex differences in the hemodynamic response (stroke volume (SV) and cardiac output (CO)) to high intensity interval exercise (HIIE). Habitually active men (n=15) and women (n=13) underwent VO2max testing, followed by three HIIE sessions consisting of the 4X4, 10X1, and reduced exertion high intensity training (REHIT), whose order was randomized. During exercise, oxygen uptake (VO2) and hemodynamic responses were determined. Results showed no sex difference in peak relative VO2 (p=0.263), CO (p=0.277), or SV (p=0.116), although absolute values were higher in men (p<0.05). Peak absolute (127.3 ± 20.6 vs. 115.2 ± 16.6 mL/beat, p=0.004, d=0.66) and relative SV (111.0 ± 15.5 vs. 100.7 ± 11.1 %max, p=0.005, d=0.78) were higher with REHIT versus 4X4. No sex differences in mean relative VO2, CO, or SV occurred (p>0.05). Data showed lower mean VO2 during REHIT versus 4X4 (59.3 ± 6.8 vs. 65.8 ± 5.8 %VO2max, p<0.001, d=1.05) and 10X1 (59.3 ± 6.8 vs. 69.1 ± 7.4 %VO2max, p<0.001, d=1.4). Mean CO was lower in REHIT than 10X1 (79.8 ± 8.6 vs. 84.0 ± 7.4 %max, p=0.012, d=0.53). Previously reported differences in VO2max response to HIIE may not be due to unique hemodynamic responses.

Keywords
high intensity interval exercise; cardiac output; stroke volume; intermittent exercise; oxygen uptake; sprint interval training
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1. Introduction

Compared to women, men have a greater heart size, blood volume, and hemoglobin mass\(^1\) that elicits a 10% higher maximal oxygen uptake (VO\(_{2\max}\)).\(^2\) It has been shown that VO\(_{2\max}\) is higher in men compared to women (22% vs. 15%) after 1 year of moderate intensity continuous training (MICT). Diaz-Canestro and Montero\(^3\) reviewed a total of eight studies describing the VO\(_{2\max}\) response to chronic MICT. Their aggregate data concluded that MICT confers superior increases in VO\(_{2\max}\) in men versus women, although in three studies, women exhibited greater increases in VO\(_{2\max}\) versus men.\(^3\) These unique responses to training are plausible considering the aforementioned differences in the capacity for \(O_2\) transport between sexes.\(^1,4,5\) Although LV function does not differ between sexes, women tend to have smaller LV mass (25 - 38%) in comparison to men, which is consistent with smaller dimensions and wall thickness.\(^6\) This difference may be due to discrepancies in body size, hormone levels and hypertrophy of myocytes.\(^4,6\) Overall, these alterations in cardiac structure and function are important in mediating differences in VO\(_{2\max}\), as the Fick Equation (\(VO_2 = (HR \times SV) \times (a-vO_2)\), where cardiac output (CO) = HR \times SV) denotes that oxygen uptake is determined by CO and peripheral oxygen extraction.

VO\(_{2\max}\) represents the cardiovascular system’s ability to transport oxygen to working muscle and subsequent consumption by mitochondria to support aerobic metabolism. Research reveals that having a VO\(_{2\max}\) above 19 mL/kg/min for men and 16.5 mL/kg/min for women is associated with a low risk of all-cause mortality (< 1%).\(^7\) Consequently, augmenting VO\(_{2\max}\) can be a goal of exercise programming in clinical populations and healthy adults for its health-promoting effects.
One primary barrier to MICT is a perceived lack of time. Only 47% of adults meet the aerobic physical activity guidelines, and only 24% meet both aerobic and resistance training guidelines. A time-saving alternative to MICT is high-intensity interval training (HIIT) which elicits a comparable or superior increase in VO\textsubscript{2}max with a lower training volume when compared to MICT. HIIT requires short (10 s – 5 min) bouts of vigorous efforts at intensities slightly below, at, or greater than those associated with VO\textsubscript{2}max interspersed with recovery. It is established that the increase in blood flow seen with MICT, increases heart rate and cardiac output (CO) leading to higher VO\textsubscript{2}max levels, and some suggest that similar responses are seen with HIIT, suggesting that a greater oxygen delivery mediates the increase in cardiorespiratory fitness resulting from interval-based exercise.

Differences in oxidative capacity and fatigue resistance also occur between men and women. It is apparent that women have a reduced reliance on nonoxidative metabolism versus men, which may reduce the level of metabolic stress experienced during HIIE. These innate physiological differences suggest potential for sex differences in the adaptive response to HIIT, as the acute response to exercise may mediate part of the chronic response. For example, 12 weeks of sprint interval training (SIT) led to attenuated increases in VO\textsubscript{2}max in men versus women (6% vs. 19%), which is opposed by recent data exhibiting a greater increase in VO\textsubscript{2}max (28% vs. 14%) in men compared to women undergoing 12 weeks of low-volume SIT. However, another study reported no sex difference in VO\textsubscript{2}max response to six sessions of SIT when men and women were matched for baseline VO\textsubscript{2}max. Notably, these studies are characterized by relatively small sample sizes, which may limit the ability to detect potential sex differences in the training response.
The acute changes in CO and stroke volume (SV) are related to chronic cardiovascular responses to exercise training.\textsuperscript{19} Cardiac output increases markedly from rest (5 L/min) to approximately 20-40 L/min at VO\textsubscript{2max}, which contributes to the variability in VO\textsubscript{2max}.\textsuperscript{20} Similarly, SV increases during exercise but typically plateaus at approximately 50% VO\textsubscript{2max},\textsuperscript{19} and the continued rise in HR mediate subsequent increase in CO. The magnitude of change in SV and CO during acute exercise increases LV dilation and mass long-term, which may elicit a higher VO\textsubscript{2max} post-training.\textsuperscript{21}

To our knowledge, no study has documented potential sex differences in the CO response to acute high intensity interval exercise (HIIE) which may shed light on the limiting factors to training-induced changes in VO\textsubscript{2max}. Since HIIT leads to significant increases in VO\textsubscript{2max} in many adults,\textsuperscript{18,22} its adoption may have profound effects on population health. However, if men and women reveal discrepant cardiovascular responses to acute HIIE, this may partially mediate the sex differences in VO\textsubscript{2max} response to HIIT previously reported.\textsuperscript{16,17} It is possible that exercise prescription may need to elicit higher relative workloads for women to elicit similar hemodynamic responses and in turn, similar increases in VO\textsubscript{2max} compared to men.

The primary aim of this study was to examine potential sex differences in the acute CO response to HIIE, as CO is the primary determinant of VO\textsubscript{2max}.\textsuperscript{23} The secondary aim was to identify differences in acute hemodynamic responses between unique HIIE protocols. It was hypothesized that a higher CO and SV response (expressed as %CO\textsubscript{max} and %SV\textsubscript{max}) will occur in women versus men, due to their smaller heart size and lower blood volume, which may elicit a greater relative load on the heart at similar intensities to men. A secondary hypothesis is that there will be a lower CO\textsubscript{max} in response to low-volume sprint interval exercise (SIE) than in response to higher volume HIIE protocols.
2. Materials and Methods

2.1 Participants

Initially, 33 men (n = 17) and women (n = 16) provided informed consent and participated in VO2max testing, but five withdrew from the study for personal reasons. A total of 28 men (n = 15) and women (n = 13) subsequently completed all requirements of this study. Their physical characteristics are revealed in Table 1, and their race and ethnicity are reported in Figure 1. They were between the ages of 20-49 years and were not obese (percent body fat ≤ 25% in men and, ≤ 33% in women). Each participant performed 150 minutes/week of moderate or 75 minutes/week of vigorous physical activity throughout the previous year, which was verified with a questionnaire. They completed resistance training, aerobic exercise, non-competitive sport, and/or surfing, yet none was training for a particular sport. They were also healthy and free of any condition which may preclude intense cycling. Initially, the participant provided written informed consent and filled out a health history questionnaire and PARQ to confirm eligibility. This protocol was approved by the University Institutional Review Board.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men (n = 15)</th>
<th>Women (n = 13)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29 ± 8*</td>
<td>22 ± 2</td>
<td>20-49</td>
</tr>
<tr>
<td>Physical Activity (h/wk)</td>
<td>6 ± 3</td>
<td>6 ± 3</td>
<td>1.5-12.0</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>78.9 ± 9.8*</td>
<td>60.1 ± 7.3</td>
<td>47.0-94.8</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>25.0 ± 2.6*</td>
<td>21.9 ± 2.5</td>
<td>18.3-31.0</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>14 ± 4*</td>
<td>22 ± 4</td>
<td>7-26</td>
</tr>
</tbody>
</table>

* = p < 0.05 versus women
2.2 Experimental Design

This study used a randomized, within-subjects crossover design. On day one, VO$_2$max was determined during ramp exercise and a subsequent verification test (VER). The subsequent three sessions were held at the same time of day within subjects, and HIIE protocols varying in volume and structure were performed. During all sessions, pulmonary gas exchange data was acquired, and thoracic impedance was used to assess the hemodynamic response to exercise. Prior to all sessions, participants refrained from strenuous exercise for 24 hours, fasted for 2 hours, and were instructed to consume 1 L of water in the 2 hours before their visit. Participants were also asked to record all food and drink consumption 24 hours prior to the initial HIIE session and were encouraged to replicate this intake before the last two sessions. All test sessions were separated by at least 48 hours.
2.3 Assessment of VO2max and Body Composition

Initially, height and weight were assessed to determine body mass index (BMI in kg/m²). Percent body fat was calculated by measuring subcutaneous fat at three sites in rotational order, chest, abdominal and thigh in men and, triceps, supra-iliac and thigh in women. Body density and percent body fat were calculated using sex and race-specific equations. Before exercise, the metabolic cart (ParvoMedics True One, Sandy, UT) was calibrated according to manufacturer guidelines. During exercise, VO₂, carbon dioxide output (VCO₂), ventilation, and respiratory exchange ratio (RER) were measured every 10 s.

A ramp-based test was conducted on an electrically-braked cycle ergometer (Velotron Dynafit Pro, Racermate, Spearfish, SD) during which pulmonary gas exchange data were obtained using the metabolic cart. Participants began with a 2-min warm-up at 40-70 W and work rate was increased by 20-35 W/min until cadence declined below 50 rev/min. Peak power output (PPO) and maximal heart rate (HR) were identified as the peak values attained when cadence declined below 50 rev/min. Participants underwent a cooldown for 2 min at 50 W followed by a 5 min passive recovery. Immediately following passive recovery, participants pedaled for 2 min at 20% PPO followed by 1 min at 50% PPO. Intensity was immediately increased to 85% PPO and participants pedaled until volitional fatigue where cadence declined below 50 rev/min in order to verify VO₂max attainment. VO₂max was identified as the mean of the ramp and VER-derived values, with maximum values from ramp and VER determined as the average of the two highest consecutive values at volitional exhaustion. Blood lactate concentration (BLa) was measured 3 min after the verification test from a 0.7 µl blood sample via a fingertip puncture using a lancet (Owen Mumford Inc., Marietta, GA) and portable analyzer (Lactate Plus, Sports Research Group, New Rochelle, NY). Prior to measurement, the fingertip
was cleaned with a damp paper towel, then it was dried, punctured, and the first drop of blood
was wiped away.

2.4 Assessment of Thoracic Impedance

An impedance cardiograph device (PhysioFlow Enduro, Manatec, Strasbourg, France) was used to estimate CO during all sessions.26,27 Prior to exercise, participants sat quietly for 5 min after which resting blood pressure (Omron Tru-Gage Cuff, Omron Healthcare, Vernon Hills, IL) was determined at the brachial artery twice, with a 1 min period between measurements. Then, a total of six electrodes (PhysioFlow Versa Trode, Nissha Medical Technologies, Devon, UK) were placed on each participant, two on the left supraclavicular fossa at the base of the neck, one on the right pectoralis major, one on the left rib closest to V6, and two directly left of the spine (on the transverse xiphoid process line and directly below). Each site was prepared by cleaning with an alcohol swab then rubbing an electrode gel (NuPrep; Weaver and Company, Aurora, CO) into the skin. A 30-beat calibration procedure ensued to derive resting values of HR, SV, and CO. During exercise, HR, CO, and SV were averaged every 10 seconds. Intraclass correlations for repeated measures of SV and CO at VO_{2max} in our lab from similarly-trained men and women performing ramp exercise on the identical cycle ergometer are equal to 0.90-0.95.27 In addition, the minimum difference in CO in response to Wingate tests performed on separate days is equal to 1.8 L/min.27 Similar to previous studies,28 hemodynamic variables as well as VO_{2} were reported as mean and peak values for each protocol and expressed as a percent of the maximal value derived from VO_{2max} testing, which are then considered the relative values. Peak values were determined as the mean of the two highest consecutive 10-s values at either 25, 50, 75, or 100% of protocol duration. Mean values were determined as the average from the entire session, not including pre-exercise, warmup, or post-recovery. Arteriovenous
oxygen difference (a-vO$_2$diff) was calculated as the quotient of VO$_2$ max (mL·min$^{-1}$)/CO (L·min$^{-1}$) and expressed in mL/dL.

2.5 Description of HIIE Protocols

All sessions were held at the same time of day within participants (0600 am – 1700 pm). Three different protocols (Table 2) were completed in a randomized order. Each protocol included a 3 min warm-up at 20% PPO and a 2 min recovery post-exercise. For each protocol, BLa was measured pre-exercise after a 5 min seated rest, during exercise halfway through the protocol, and 3 min post-exercise using the same methods as denoted previously. During the 10 X 1 protocol, 29 participants performed ten 1 min bouts of cycling at 85% PPO followed by 1 min of recovery at 20% PPO. The 4 X 4 protocol consisted of four 4 min bouts of cycling at 85-95% HRmax interspersed by 3-minutes at 20% PPO. Power output was continuously altered during each 4-minute interval to maintain HR within this range. The third session consisted of reduced exertion high-intensity training (REHIT) which required two 20-second all-out sprints at a workload equal to 5% body mass within a 10-minute session.

Table 2. Summary of the HIIE protocols used in this study

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Bout duration</th>
<th>Recovery duration</th>
<th>Intensity (%PPO, %HRmax, or %BM)</th>
<th>Total duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>10X1</td>
<td>60 s</td>
<td>60 s</td>
<td>85%PPO</td>
<td>23</td>
</tr>
<tr>
<td>4X4</td>
<td>240 s</td>
<td>180 s</td>
<td>85-95%HRmax</td>
<td>28</td>
</tr>
<tr>
<td>REHIT</td>
<td>20 s</td>
<td>180 s</td>
<td>5%BM</td>
<td>10</td>
</tr>
</tbody>
</table>
2.6 Statistical Analysis

Data are expressed as mean ± SD and analyzed using SPSS Version 28.0 (IBM, Armonk, NY, USA). Normality was assessed using the Shapiro–Wilk test. An unpaired t-test was used to compare demographic and maximal gas exchange data between men and women. Two-way repeated measures ANOVA was used to compare differences in the SV and CO response between men and women, with one within-subjects factor equal to HIIE condition (3 levels), and the between-subjects factor equal to sex (men vs. women). Similar analyses were conducted for the peak and mean value of these outcomes. If a significant F ratio was obtained, Tukey’s post hoc test was used to detect differences between means. Cohen’s d was used as an estimate of effect size between 0.15 and < 0.40 representing “small,” between 0.40 and < 0.75 representing “moderate,” and ≥ 0.75 representing “large.” Statistical significance was set at P < 0.05

3. Results

3.1 Maximal gas exchange and hemodynamic data

Table 3 shows that men exhibited higher (p < 0.05) absolute VO₂max, PPO, COmax, SVmax, and a-vO₂diff than women, although relative VO₂max, HRmax, and PPO (W/kg) were similar (p > 0.05).

Table 3. Maximal gas exchange, hemodynamic, and BLa data between men and women (mean ± SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n= 15)</th>
<th>Women (n= 13)</th>
<th>P value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂max (L/min)</td>
<td>3.1 ± 0.5*</td>
<td>2.3 ± 0.3</td>
<td>&lt;0.01</td>
<td>2.0</td>
</tr>
<tr>
<td>VO₂ max (mL/kg/min)</td>
<td>39.5 ± 3.4</td>
<td>38.2 ± 4.6</td>
<td>0.21</td>
<td>0.33</td>
</tr>
<tr>
<td>PPO (W)</td>
<td>293 ± 42*</td>
<td>217 ± 25</td>
<td>&lt;0.01</td>
<td>2.24</td>
</tr>
<tr>
<td>Variable</td>
<td>Men (n= 15)</td>
<td>Women (n= 13)</td>
<td>P value</td>
<td>Cohen’s d</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>PPO (W/kg)</td>
<td>3.7 ± 0.3</td>
<td>3.6 ± 0.5</td>
<td>0.62</td>
<td>0.26</td>
</tr>
<tr>
<td>HRmax (b/min)</td>
<td>178 ± 14</td>
<td>184 ± 9</td>
<td>0.07</td>
<td>0.59</td>
</tr>
<tr>
<td>COmax (L/min)</td>
<td>21.6 ± 3.6*</td>
<td>18.8 ± 3.2</td>
<td>0.02</td>
<td>0.86</td>
</tr>
<tr>
<td>SVmax (mL/beat)</td>
<td>126.6 ± 20.2*</td>
<td>105.8 ± 17.7</td>
<td>0.004</td>
<td>1.14</td>
</tr>
<tr>
<td>a-VO₂diff max (mL/dL)</td>
<td>14.6 ± 2.4*</td>
<td>12.3 ± 1.5</td>
<td>0.006</td>
<td>1.17</td>
</tr>
<tr>
<td>BLa (mmol/L)</td>
<td>11.9 ± 2.4</td>
<td>10.3 ± 1.8</td>
<td>0.06</td>
<td>0.77</td>
</tr>
</tbody>
</table>

PPO = peak power output; HR = heart rate; CO = cardiac output; SV = stroke volume; a-VO₂diff = arteriovenous oxygen difference; BLa = blood lactate concentration; *= p < 0.05 versus women
Figure 2. Representative changes in a) HR, b) SV, c) CO, and d) VO\textsubscript{2} in response to different HIIE protocols in a 25 year old female with VO\textsubscript{2max} = 37.0 mL/kg/min.

3.2 Peak hemodynamic and metabolic data

Figure 2 reveals typical changes in HR, SV, CO, and VO\textsubscript{2} in response to various HIIE protocols in a representative participant. There was no main effect of protocol (p = 0.197) or protocol X sex interaction (p = 0.469) in peak VO\textsubscript{2} (L/min) across protocols, yet a main effect of sex occurred as men show greater values than women (p < 0.001) (Table 4). No main effect of protocol (p = 0.478), sex (p = 0.263), or protocol X sex interaction (p = 0.744) was found for relative VO\textsubscript{2} (%VO\textsubscript{2max}). Peak absolute CO was higher in men versus women sex (p = 0.012), but no effect of protocol (p = 0.094) or protocol X sex interaction (p = 0.445). Relative CO (%CO\textsubscript{max}) showed no main effect of protocol (p = 0.097) or sex (p = 0.277) and there was no
protocol X sex interaction (p = 0.277). Peak absolute SV was different across protocols as REHIT revealed higher values than 4 X 4 (p = 0.004, d = 0.66), and men exhibited significantly greater values than women (p = 0.002), yet no protocol X sex interaction was found (p = 0.559). Relative SV (%SVmax) was significantly different across protocol (REHIT > 4 X 4; p = 0.005, d = 0.78), but there was no main effect of sex (p = 0.116) or protocol X sex interaction (p = 0.652). Peak HR (bpm) shows a protocol effect only (REHIT < 10 X 1, p < 0.001, d = 0.59), yet no effect of sex (p = 0.197) or protocol X sex interaction (p = 0.427). Results showed that relative HR (%HRmax) had a main effect of protocol (REHIT < 10 X 1; p < 0.001, d = 1.1), yet no main effect of sex (p = 0.526) or protocol X sex interaction (p = 0.483).

3.3 Mean hemodynamic and metabolic data

There was a main effect of protocol for mean absolute VO2 (REHIT < 10 X 1 and 4 X 4; p < 0.001 and p < 0.001; d = 0.83 and 0.57) and a main effect of sex (p < 0.001), yet no protocol X sex interaction (p = 0.164) (Table 4). Additionally, relative VO2 during REHIT is lower than 4 X 4 and 10 X 1 (p < 0.001 and < 0.001; d = 1.05 and 1.4, respectively), yet no effect of sex (p = 0.261) or protocol X sex interaction was found (p = 0.368). Mean CO (L/min) shows a protocol effect (REHIT < 10 X 1; p = 0.008, d = 0.35) and a significant main effect of sex, as men show greater values than women (p = 0.007), yet no protocol X sex interaction (p = 0.863). Mean relative CO (%COmax) also showed a main effect of protocol (REHIT < 10 X 1; p = 0.012, d = 0.53), but no effect of sex (p = 0.899) or protocol X sex interaction (p = 0.918). Stroke volume (mL/beat) was not different across protocol (p = 0.252) and no protocol X sex interaction (p = 0.664), although values were greater in men than women (p < 0.001). Relative SV (%SVmax) showed no effect of protocol (p = 0.207), protocol X sex interaction (p = 0.668) or main effect of sex (p = 0.309). Mean HR (bpm) shows a protocol effect (REHIT < 10 X 1 and 4 X 4; p < 0.001 and < 0.001; d = 0.99 and 0.91, respectively) yet no effect of sex as (p = 0.065) or protocol X sex
interaction \((p = 0.358)\). Mean relative HR (%HRmax) shows the same protocol effect (REHIT < 10 X 1 and 4 X 4; \(p < 0.001\) and < 0.001; \(d = 1.59\) and 1.58), yet no effect of sex \((p = 0.195)\).

**Table 4.** Peak and mean hemodynamic and metabolic responses to various HIIE protocols (mean ± SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n= 15)</th>
<th>Women (n= 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 X 4</td>
<td>10 X 1</td>
</tr>
<tr>
<td><strong>Peak</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO2 (L/min)*</td>
<td>2.7 ± 0.5</td>
<td>2.6 ± 0.5</td>
</tr>
<tr>
<td>VO2 (%max)</td>
<td>86 ± 10</td>
<td>84 ± 13</td>
</tr>
<tr>
<td>CO (L/min)*</td>
<td>19.7 ± 2.5</td>
<td>21.3 ± 3.7</td>
</tr>
<tr>
<td>CO (%max)</td>
<td>95 ± 10</td>
<td>103 ± 14</td>
</tr>
<tr>
<td>SV (mL/beat)*</td>
<td>123.1 ± 10.9**</td>
<td>132.2 ± 28.5</td>
</tr>
<tr>
<td>SV (%max)</td>
<td>102 ± 12**</td>
<td>109 ± 19</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>162 ± 12</td>
<td>168 ± 18**</td>
</tr>
<tr>
<td>HR (%max)</td>
<td>91 ± 3</td>
<td>94 ± 4**</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO2 (L/min)*</td>
<td>2.1 ± 0.3**</td>
<td>2.2 ± 0.4**</td>
</tr>
<tr>
<td>VO2 (%max)</td>
<td>68 ± 6**</td>
<td>70 ± 8**</td>
</tr>
<tr>
<td>CO (L/min)*</td>
<td>17.6 ± 2.0</td>
<td>18.1 ± 2.7**</td>
</tr>
</tbody>
</table>
Table 5 reveals that REHIT elicits higher (p < 0.001) BLa versus 10 X 1 (d = 0.79) and 4 X 4 (d = 1.42), yet lower (p < 0.001) relative HR versus these protocols (d = 1.13 and 0.63, respectively). Peak HR was significantly higher (p < 0.001) in response to 10 X 1 versus all other protocols. No main effect of sex was shown for BLa (p = 0.05), absolute HR (p = 0.19), or relative HR (p = 0.52).

### Table 5. Peak metabolic values from HIIE protocols (mean ± SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>4 X 4</th>
<th>10 X 1</th>
<th>REHIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLa (mmol/L)</td>
<td>7.1 ± 2.3*</td>
<td>8.7 ± 2.2*</td>
<td>10.6 ± 2.7*</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>166 ± 12</td>
<td>170 ± 15*</td>
<td>163 ± 12</td>
</tr>
<tr>
<td>HR (%max)</td>
<td>92 ± 3</td>
<td>94 ± 4</td>
<td>90 ± 4**</td>
</tr>
</tbody>
</table>

* = p < 0.05 versus other protocols; ** = p < 0.05 versus 10 X 1
4. Discussion

The primary purpose of this study was to examine potential sex differences in the acute CO response to HIIE, which may shed light on previously reported differences in the VO₂ max response to MICT or HIIT between men and women. The secondary purpose was to identify potential differences in acute hemodynamic response between different HIIE paradigms. Our results show that SV and CO expressed as percentages of maximal values do not differ in men versus women, suggesting a similar hemodynamic response to vigorous exercise.

4.1 Sex differences in hemodynamic responses to HIIE protocols

Prior findings suggest that HIIE protocols are not interchangeable in men versus women due to inherent differences in cardiovascular and metabolic responses to exercise, which may diminish the magnitude of stress in women compared to men. This may be due to women’s enhanced resynthesis of ATP between bouts compared to men independent of intensity and perceived exertion. Our data oppose our hypothesis yet corroborate prior results showing a higher absolute SV and CO in men in response to three unique HIIE protocols. However, these differences disappeared when outcomes are expressed according to %SV/COmax. In addition, no sex differences were exhibited in peak %VO₂ max across protocols. In the present study, relative VO₂ max was similar between sexes which may minimize the resultant magnitude of differences in the acute response to HIIE. In addition, there is potential for a ceiling effect leading to no sex differences in these outcomes. Stroke volume typically plateaus in untrained adults at 50% VO₂ max, and the interval intensities are well above this. Moreover, SV attained near-maximal values by the first or second bout of 10 X 1 and 4 X 4. Overall, our data suggest that reported sex differences in the VO₂ max response to HIIE are not due to unique acute hemodynamic responses between men and women.
Blood lactate concentration was significantly lower in women versus men in response to REHIT, which corroborates data denoting sex differences in BLa to acute HIIT and SIT. One explanation for this finding is the significantly higher peak (8.0 ± 1.6 W/kg vs. 6.9 ± 0.6 W/kg; p = 0.012; d = 0.92) and mean power output (6.6 ± 1.1 W/kg vs. 6.0 ± 0.4 W/kg; p = 0.035; d = 0.73) revealed by men compared to women in response to REHIT. It is likely that sex differences in muscle fiber type, oxidative capacity, and muscle mass explain this result. Lactate has also been identified as an energy sensor associated with molecular signaling which is related to the adaptive response and may partially explain why a prior study requiring SIT exhibited significantly greater increases in CRF in men versus women. These BLa data exhibit that women experience less metabolic strain than men when performing interval protocols requiring intensities greater than that associated with VO\textsubscript{2max} (REHIT). However, HIIE protocols requiring longer bouts at lower absolute intensities such as 4 X 4 may not require any modification due to a similar BLa response between men and women. Further work is needed using muscle biopsy to elucidate the metabolic responses to HIIT between men and women.

4.2 Differences in hemodynamic responses to various HIIE protocols

Our data show that REHIT elicits a higher relative peak CO and SV versus 4 X 4, but a lower mean relative VO\textsubscript{2} (Table 4). These data refute our hypothesis that SIT would elicit lower CO\textsubscript{max} than higher-volume HIIT. Adami et al. required active men to complete cycling at 120% PPO, and data revealed a faster time constant for CO than that of VO\textsubscript{2} kinetics. In active adults, Astorino et al. reported significantly higher SV and lower VO\textsubscript{2} in response to SIT versus values derived from VO\textsubscript{2max} testing. This lower VO\textsubscript{2} is also attributed to lower reliance on aerobic metabolism during REHIT and SIT that elicits intensities above 200% PPO. Overall, the circulatory system rapidly adjusts to these high intensities to optimize oxygen delivery to the exercising legs, allowing attainment of maximal CO values (Table 4).
The attainment of peak SV and CO during acute interval exercise is significant because peak cardiovascular stress may be important for optimizing changes in VO2max in response to exercise training.38 We identified peak values as the highest of the average of two consecutive values at either 25, 50, 75, or 100% of protocol duration. Previous studies (e.g. Balci et al.)39 frequently report peak values of SV and CO, yet do not denote how they are identified, leading to uncertainty related to how the outcome is calculated and therefore, potential discrepancies in values across studies. Additional discrepancies may be due to differences in exercise protocols or modality as well as participants’ sex, age, and fitness level across studies.40 Similarly, prior research28,39 reports mean SV and CO, but do not denote whether these values represent the average during work and recovery throughout the entire session.

Reduced exertion high intensity training exhibited a significantly lower mean relative HR, VO2, and CO versus the other protocols. This may be due to the relatively brief bursts of effort attendant with REHIT (40 s) which are accompanied by 9 min and 20 s of pedaling at 20% PPO, eliciting a relatively low average cardiometabolic stimulus versus 10 X 1 and 4 X 4. Despite differences in interval duration (10 vs. 16 min) and intensity (85 vs. ~ 60% PPO), 10 X 1 and 4 X 4 reveal similar peak and mean hemodynamic and metabolic responses (Table 4). However, REHIT demonstrates similar peak values of relative VO2, absolute/relative SV, and absolute/relative CO versus 10 X 1, with significantly lower values seen in 4 X 4 (Table 4). Across protocols, 4 X 4 had the lowest overall relative power output which may mediate the lower acute hemodynamic response shown versus 10 X 1 and REHIT. Zafeiridis et al.28 required highly active men (VO2max = 49 mL/kg/min) to complete repeated 30 s efforts followed by 30 s recovery at 110% PPO and 2 min efforts at 95% PPO followed by 2 min of recovery which were matched for effort. Peak and average HR were similar across protocols, yet the longer intervals
elicited higher VO₂, mean SV, and mean/peak CO compared to the shorter efforts, supporting data from Astrand et al. It is possible that the high peak VO₂ and SV/CO characteristic of REHIT, combined with its high values of BLa, are partially responsible for significant increases in VO₂max observed long-term. However, its lower mean HR, SV, and CO compared to the higher volume HIIE protocols may induce less overload on the cardiovascular system, thereby causing lower increases in VO₂max than 4 X 4, suggesting that the training-induced increase in VO₂max may be associated more with average magnitude of stress on the cardiovascular system rather than absolute power output.

Our data (Table 4) show peak SV values exceeding that acquired from VO₂max testing as well as peak CO values approaching or equivalent to maximal values. In a prior study, Falz et al. reported peak values of SV/CO in response to the 4 X 4 protocol which were 10% higher than values derived from incremental exercise, which supports our findings. In both studies, thoracic impedance was used to estimate hemodynamic responses. Previous research in highly trained men demonstrated similar near-maximal peak CO and SV values in response to acute HIIE and SIE; however, they used arterial pressure wave analysis to estimate SV and then calculate CO. One explanation for this result is that a single assessment of VO₂max may underestimate the true value due to a learning effect, and consequently, our initial assessment of maximal oxygen uptake and SV/CO may not produce true ‘maximal' values for our participants. Our results also show that mean SV obtained from HIIE protocols differing in training volume, recovery duration, and intensity ranged from 93 – 101% of maximal values, suggesting a large aggregate strain on the cardiovascular system throughout the entire duration of each protocol. Previous research suggests that the most effective gains in cardiorespiratory fitness stem from work done at high percentages of VO₂max due to the stress on the oxygen
transport system. Our research suggests that these adaptive gains may be more dependent on high SV response, since average VO$_2$ levels were between 59 – 70% of VO$_2$max.

4.4 Limitations

The study has a few limitations. First, data were acquired in healthy, active adults, so our results cannot be applied to other populations. Second, despite these protocols being widely applied in sports science, there are infinite permutations of interval exercise which may elicit discrepant hemodynamic responses. Third, men typically have higher VO$_2$max than women due to a higher absolute SV and CO,$^5$ so different results could have occurred if our men had higher VO$_2$max than the women. In addition, treadmill exercise elicits true maximal CO and VO$_2$ compared to cycling, so our data only apply to this modality of exercise. Fourth, our men and women had a significant difference in age, although they all are considered young and healthy. However, adults ranging in age from 20 – 80 yr showed no age-related difference in the VO$_2$max response to 8 weeks of HIIT,$^{45}$ indicating that age may not impact the adaptability of the cardiovascular system to HIIT. We also did not consider effects of the menstrual cycle or oral contraceptives, and 10 of 13 women were eumenorrheic. However, data$^{46}$ show minimal effects of menstrual phase on time to exhaustion during graded exercise, suggesting minimal effects on our outcomes. Despite these limitations, this study is strengthened by precise determination of intensities for the exercise protocols, implementation of three widely used interval-based protocols, and careful standardization of methods used in estimation of CO from thoracic impedance.
5. Conclusion

Our data show no significant differences in relative SV, CO, and VO2 across protocols between men and women, suggesting a similar hemodynamic response. In addition, results show that sprint interval exercise eliciting power outputs approximately 2-fold above that associated with VO2max reveal the highest CO values yet lowest VO2, likely due to greater reliance on nonoxidative metabolism. Previously reported differences16,17 in the VO2max response to interval exercise may not be due to a unique hemodynamic or metabolic response between men and women.

6. Perspectives

HIIT has become popular for its effectiveness in increasing endurance performance and VO2max while frequently requiring less time compared to MICT. Research is equivocal, however, whether men exhibit superior VO2max response to HIIE versus women.21 Previous research recommended that HIIT protocols be individualized based on sex in order to elicit similar responses.34 Our data suggest that this may not be the case for higher-volume HIIE protocols due to similar blood lactate and hemodynamic responses. Nevertheless, when HIIE protocols require short bursts at intensities above VO2max, such as REHIT, power output and blood lactate concentration are different between sexes, which may necessitate that women undergo higher relative intensities to equalize the metabolic stress. This study will overall add to dogma regarding optimizing exercise prescription to achieve the greatest health and fitness benefits for adults.
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Conflict of Interest Statement

The authors declare no conflicts of interest.

Data Availability Statement

All data related to this study are contained in the manuscript. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Informed Consent

Participants were informed with a written consent.

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