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Revision 3

Title: Assessing Maximal Exercise Capacity: Peak Work or Peak Oxygen Consumption?

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Abstract

Background: Exercise capacity assessed by cardiopulmonary exercise testing is usually measured by peak oxygen consumption (peak $\dot{V}O_2$). However, not uncommonly, patients achieve a relatively higher Work load (peak Work) compared to their peak $\dot{V}O_2$. In these situations, it is difficult to know which parameter to use in assessing exercise capacity. The purpose of this study was to determine whether there are distinguishing physiological characteristics of patients with discordance between percent predicted peak Work vs. peak $\dot{V}O_2$ in order to understand how to use these measures in interpreting exercise capacity.

Methods: We conducted a retrospective study of 172 cardiopulmonary exercise tests performed at our institution between 2003 and 2010. Subject characteristics were compared by ANOVA and multivariate logistic regression analysis.

Results: The patients in the higher peak Work group demonstrated higher ventilatory efficiency (lower V_E / $\dot{V}CO_2$ slope) and lung function (FEV_1 and FVC), a greater breathing reserve (higher BR, lower V_E /MVV), and achieved a higher maximal heart rate. Patients in the higher max $\dot{V}O_2$ group were heavier, had lower ventilatory efficiency, and had a reduced breathing reserve. Multivariate logistic regression analysis showed that the predominant independent factors associated with group assignment were BMI, breathing reserve, and peak heart rate, with patients achieving higher percent

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predicted peak Work than peak $\dot{V}O_2$ having a lower BMI, a greater breathing reserve and a higher peak heart rate.

Conclusion: The observation that there are distinguishing physiological features between those who have a higher peak Work than peak $\dot{V}O_2$ provides insight into the underlying processes determining maximal exercise capacity.

Key Words: cardiopulmonary exercise test, maximal oxygen consumption, anaerobic threshold, work capacity

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Introduction

Cardiopulmonary exercise testing is a comprehensive approach to assess exercise capacity and limitations to exercise. Exercise capacity is usually interpreted in terms of peak oxygen consumption (peak $\dot{V}O_2$) [1-7]. Indeed, peak $\dot{V}O_2$ is a robust predictor of outcomes in many cardiopulmonary diseases, such as COPD, congestive heart failure, cystic fibrosis and pulmonary hypertension [1-3,8,9]. However, we have observed that there are some patients who achieve higher percent predicted peak Work than percent predicted peak $\dot{V}O_2$, and vice versa. In these cases, it is unclear whether to use peak Work or peak$\dot{V}O_2$ as the parameter by which to judge the patient's exercise capacity. As we pointed out in an editorial [10], this fundamental question was not addressed by a 2003 statement on cardiopulmonary exercise testing published by the American Thoracic Society/American College of Chest Physicians [2]. In the majority of exercising subjects, this distinction is unimportant because the relationship between work and $\dot{V}O_2$ is linear; thus, the percentage of the predicted value achieved for either parameter is similar [7,11,12]. However, as described by Wasserman and colleagues[13], a difference in $\dot{V}O_2$ may be observed between expected and observed values when calculating the expected $\dot{V}O_2$ based on the maximum work rate achieved. The general goal of the current study was to evaluate the exercise characteristics that distinguish patients with discordant values of peak Work and peak $\dot{V}O_2$ to better understand the underlying processes that determine maximal exercise capacity. We specifically expected that patients achieving higher Work

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relative to $\dot{V}O_2$ would demonstrate better cardiopulmonary fitness and/or ability to tolerate the discomfort of high levels of exercise.

Methods

Study design

We retrospectively analyzed all cardiopulmonary exercise tests performed at the University of Vermont /Fletcher Allen Health Care, a tertiary care academic medical center, from 2003 to 2010. The study was approved by the University of Vermont Committee on Human Research in the Medical Sciences (IRB), CHRMS #10-232. A total of 172 tests were included.

All studies were performed according to standard guidelines [2]. We conducted exercise testing by using a 1 min step protocol to exhaustion on a bicycle ergometer, using work increments of 15 watts/min or 30 watts/min estimated to bring patients to maximal workloads in approximately 10 minutes, as recommended by ATS/ACCP [2] and Wasserman and colleagues [13]. We measured baseline spirometry and maximal voluntary ventilation (MVV) before exercise (or, estimated the latter as FEV_1 x 40). We continuously monitored cardiovascular parameters (heart rate (HR), blood pressure, electrocardiogram), ventilatory parameters (respiratory rate (RR), tidal volume (Vt), oxygen saturation by pulse oximetry (O_2 sat)) and metabolic parameters (CO_2 production ($\dot{V}CO_2$), $\dot{V}O_2$). Of note, we did not consistently record exercise flow-volume loops

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during the time frame of this study, so do not report data on ventilatory limitation or changes in end-expiratory lung volume. We measured dyspnea by the modified Borg scale [14]. The following factors were calculated: slope of $\dot{V}O_2$ vs. Work ($\dot{V}O_{2\ Final-Initial}$) /Work $_{Final-Initial}$), respiratory exchange ratio (RER = $\dot{V}CO_2$ / $\dot{V}O_2$), expired minute ventilation (V_E = RR x Vt), breathing reserve (max V_E/MVV and BR=MVV – max V_E), ventilatory equivalents for oxygen and carbon dioxide (V_E/ $\dot{V}O_2$, V_E/ $\dot{V}CO_2$, respectively), slope of Ve vs. $\dot{V}CO_2$ (V_E/ $\dot{V}CO_2$ slope), oxygen pulse ($\dot{V}O_2$ /HR), and anaerobic threshold (AT, by inspection of the plot of $\dot{V}CO_2$ vs. Work and of V_E/ $\dot{V}O_2$ vs. Work for their respective inflection points in slope). We used predicted values for work and $\dot{V}O_2$ based on modified Jones criteria [12]. We defined a discordance between predicted peak Work and predicted peak $\dot{V}O_2$ as any absolute difference in the percent predicted between these values of > 15 (e.g., peak Work = 110% predicted; peak $\dot{V}O_2$ = 85% predicted). This cut-off was derived empirically from exploring different levels of cut-offs of 10, 15 and 20% differences. A cut-off of 10% was too small and still within the range of experimental accuracy for peak $\dot{V}O_2$ and peak Work. A cut-off of 20% was overly sensitive and yielded a sample size in the smallest group of n=11, which we felt was too small to allow valid statistical analysis. We also assessed whether the results would appear to be substantially altered by using the normative equations of Wasserman and colleagues for Work and $\dot{V}O_2$ after adjusting for body weight [13]. We noted that the Wasserman criteria resulted in a more unbalanced distribution of patients in the predicted

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Work vs. predicted $\dot{V}O_2$ categories, which did not seem consistent with our clinical impression of the prevalence of this discrepancy. Accordingly, we used the Jones predicted equations with a discordance difference of >15.

Based on this difference, we divided all subjects into three groups: those with percent predicted peak $\dot{V}O_2$ greater than percent predicted peak Work ("peak $\dot{V}O_2$ > peak Work"), those with percent predicted peak Work greater than percent predicted peak $\dot{V}O_2$ (" peak Work > peak $\dot{V}O_2$"), and those with equivalent percent predicted peak $\dot{V}O_2$ and percent predicted peak Work ("peak $\dot{V}O_2$ = peak Work").

Data Analysis

We analyzed all data for distribution and expressed the data as mean +/- SD. We assessed differences across the three groups by ANOVA, with differences between any two groups analyzed by Tukey's HSD test. In addition, we performed a backwards, stepwise multivariate logistic regression analysis to determine which exercise parameters identified as significant between the peak Work > peak $\dot{V}O_2$ and peak $\dot{V}O_2$ > peak Work groups were independently associated with group assignment. Two-tailed p-values < 0.05 were taken as indicating statistical significance. All data were analyzed using JMP software (JMP 9.0, SAS Institute, Inc.).

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Results

A total of 172 tests were included for analysis. Patients were referred for testing for a variety of reasons, the most common of which were unexplained dyspnea (n=90, 52%) and COPD, the latter mostly for evaluation prior to pulmonary resection for lung cancer (n=28, 16%) or pulmonary rehabilitation (n=25, 14%). There were two cases of cardiac disease (cardiomyopathy and diastolic dysfunction). Other diagnoses included cough, chest pain, interstitial lung disease, sarcoidosis, scoliosis, tracheobronchomalacia and vocal cord dysfunction. All patients were instructed to exercise to exhaustion. The most common reasons for stopping exercise were leg fatigue (42%), shortness of breath (28%) and a combination of equal leg fatigue and shortness of breath (21%). None of the patients had any particular experience with bicycle ergometry, which might have given them an unseen advantage in terms of motor efficiency.

Figure 1 displays the distribution of groups based on the 15% cut-off between percent predicted peak $\dot{V}O_2$ vs. peak Work; the majority of patients (n=92) were in the equivalent group (peak Work = peak $\dot{V}O_2$). As seen in Table 1, there were distinct differences in the demographic characteristics of patients in each of the three groups. Patients who achieved higher percent predicted peak Work than percent predicted max $\dot{V}O_2$ were younger, had a lower BMI and had a more even distribution of males vs. females than those who achieved a higher percent predicted peak $\dot{V}O_2$ than percent predicted peak Work. Among the diagnostic categories, there were no overall differences in distribution

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among them between the 3 groups (p=.57). Both cardiac patients fell within the peak $\dot{V}O_2$ = peak Work group, as did the majority (62%) of the COPD patients and half (49%) of the unexplained dyspnea patients. The remaining COPD and unexplained dyspnea patients were mainly found in the peak $\dot{V}O_2$ > peak W group rather than the peak Work > peak $\dot{V}O_2$ group (32 vs. 6% and 34 vs. 17%, respectively).

As shown in Table 1, there were also differences in exercise variables between the groups. All patients had similar baseline $\dot{V}O_2$ at rest. Patients who achieved a higher percent predicted peak $\dot{V}O_2$ than percent predicted peak Work had a higher $\dot{V}O_2$ /Work slope, as at least partly expected due to their having a lower work rate increment during exercise [15]. Patients with peak $\dot{V}O_2$ > peak Work were more likely female, heavier, had lower ventilatory efficiency (higher VE/ $\dot{V}CO_2$ slope), and a reduced breathing reserve. The patients in the peak Work > peak $\dot{V}O_2$ group demonstrated higher ventilatory efficiency, lung function (FEV_1 and FVC) and a greater breathing reserve (higher BR, lower VE/MVV). The patients in this group also achieved a higher peak RER and heart rate. Multivariate logistic regression analysis showed that the independent factors associated with having a higher percent predicted peak Work than peak $\dot{V}O_2$ were lower BMI, higher breathing reserve and greater peak heart rate (Table 2).

Discussion

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In the current study, we sought to determine which physiological characteristics might distinguish those patients who have discordance between peak Work vs. peak $\dot{V}O_2$ achieved. We found that those who can perform relatively higher work relative to their maximal $\dot{V}O_2$ were less heavy, had a greater breathing reserve and a higher peak heart rate. Meanwhile, those who consume more oxygen relative to their work achieved were heavier, with less breathing reserve and a lower peak heart rate. Our data support the concept that lower weight (i.e., mean BMI 26 vs. 30 kg/m^2), better ventilatory function and ability to exercise to a higher heart rate are associated with the ability to perform higher workloads for a given $\dot{V}O_2$.

Most clinicians and researchers alike classify exercise tolerance on the basis of maximal $\dot{V}O_2$ achieved (e.g., [7,16-18]). Ideally, one would want to demonstrate maximal exercise capacity on the basis of achieving a plateau in max $\dot{V}O_2$, suggesting that the limits of aerobic energy production have been reached [19-21]. However, the visualization of such a plateau is highly variable among subjects and typically not seen in most clinical cardiopulmonary exercise tests [22] (only 22% of patients in the current study achieved such a visual plateau); for this reason, we have used the term "peak" $\dot{V}O_2$, which is more accurate and tends to confer the same information[20]. Classifying maximal exercise capacity on the basis of peak $\dot{V}O_2$ makes sense, as the majority of work performed during physical activity utilizes energy from aerobic metabolism [5,7]. In fact, the terms "work capacity" and "maximal $\dot{V}O_2$" are often used interchangeably (e.g. [7]). Indeed, max $\dot{V}O_2$ or peak $\dot{V}O_2$ is a robust measure of outcomes and influence of interventions in a wide variety of cardiopulmonary diseases [1,3,8]. Yet, the functional aerobic capacity reflected in the peak $\dot{V}O_2$ does not necessarily reflect the total work performed. This so-called "$\dot{V}O_2$ difference" as coined by Wasserman [13], may be due to many factors, such as failure to reach steady state, obesity, cardiovascular disease or improper ergometer calibration [13]. While some authors use power output or work capacity as a reflection of exercise tolerance (e.g. [5,23]), most studies continue to use peak $\dot{V}O_2$ as the primary measure of exercise capacity.

We view the cause of this discrepancy between peak $\dot{V}O_2$ and peak Work to fall into the following categories. First, some work is achieved on the basis of anaerobic energy production (i.e., that above the anaerobic threshold), and use of peak $\dot{V}O_2$ only will underestimate the total work or energy expenditure achieved [24]. Second, total work, at least in endurance athletes, is linked to other variables besides peak $\dot{V}O_2$, such as fractional utilization of peak $\dot{V}O_2$ (i.e., the percent of peak $\dot{V}O_2$ that can be sustained during exercise), and mechanical exercise efficiency [19].

Indeed, mechanical efficiency is a critical factor to consider. For example, subjects with obesity are reported to have a higher $\dot{V}O_2$ at rest, but a lower work capacity for a given $\dot{V}$

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O_2, reflecting their lower gross mechanical efficiency [25]. Indeed, the obese subjects in our study had a higher $\dot{V}O_2$ at rest (350 ± 104 vs. 298 ± 91 ml/min, $p < .01$). In addition, the obese subjects had a higher $\dot{V}O_2$-work slope, even when isolated to the subgroup of patients with peak $\dot{V}O_2$ > peak Work (obese vs. non-obese = 13.7 +/-3.7 vs. 12.2 +/-2.5 ml/min/watt, p=.08). One may consider that the patients in this study with peak Work > peak $\dot{V}O_2$ were more familiar with bicycle exercise than the patients in the peak $\dot{V}O_2$ > peak Work group, thus allowing them a potential biomechanical advantage by more efficient pedaling to generate work [26]. However, we do not think this factor was relevant because there was no overall difference in the use of or experience with bicycle ergometery in any of the three groups.

There are also other factors to consider. Muscle fiber type, specifically the relative amount of type I (slow twitch) and type II (fast twitch) fibers might be associated with greater $\dot{V}O_2$-work slope, as seen in the peak $\dot{V}O_2$ > peak Work group in our study, but data are conflicting [27,28], and we have no direct information on muscle fiber type in this study. Biochemical inefficiency may also result in peak $\dot{V}O_2$ > peak Work , such as in McArdle's disease, where there is a higher $\dot{V}O_2$ for a given amount of work due to altered substrate utilization and a greater cardiovascular response to exercise [29]. Both mechanical and biochemical factors may explain why different levels of work are achieved for the same peak $\dot{V}O_2$ depending on the exercise protocol. For example, total work achieved is higher with a greater work increment protocol, as seen here [15]. In

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addition, the work involved in an incremental exercise test is 30% greater than that achieved for a constant load test for the same level of $\dot{V}O_2$ [30]. Meanwhile, an important factor that may result in peak Work > peak $\dot{V}O_2$ is circulatory impairment. For example, in congestive heart failure, $\dot{V}O_2$ is limited for a given work load due to the inability of cardiac output to fully compensate for increased oxygen extraction by the tissues, yielding a lower $\dot{V}O_2$ vs. Work relationship [31]. We believe circulatory impairment was an unlikely contributing factor in this study because there was no clear discordance of cardiovascular disease in any of the patient groups. Finally, psychological factors, such as anxiety, fear, motivation and perception of breathlessness or fatigue, clearly play a role in limiting exercise capacity [5,32,33].

Since the amount of work for any given $\dot{V}O_2$ can vary due to all the reasons discussed above, we suggest that *overall exercise tolerance* be judged on the basis of the peak Work achieved. This is in accordance with the general concept of rating impairment vs. disability [34], wherein the former reflects physiological function, while the latter reflects the ability to perform work in the context of personal and environmental factors, a more global measure. It is important to emphasize, however, that peak $\dot{V}O_2$ remains an important measure of cardiovascular conditioning [35], preoperative risk in lung resection surgery [36], and predictor of future cardiopulmonary outcomes [1-3,8,9], and such relationships have not been found for direct measures of work.

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Our findings suggest that a lower BMI, greater breathing reserve and higher peak heart rate are important independent factors associated with the ability to achieve relatively higher peak Work than peak $\dot{V}O_2$. A lower BMI would allow a greater amount of work to be done for a given level of $\dot{V}O_2$ because of the improved mechanical efficiency of exercise [25]. A greater breathing reserve would be consistent with the ability to handle the metabolic acidosis associated with exercise above the AT [13]. The greater heart rate seen in patients achieving higher peak Work than peak $\dot{V}O_2$ likely reflects these patients' ability, effort and motivation to exercise to physiological cardiovascular limitation [37]. The higher RER in this group is consistent with this as well.

There are some limitations to our study. This was a single center, retrospective review using bicycle ergometry and a step exercise protocol. How our results would compare to a different population using different equipment or protocols is unclear; however, since our hospital is a large, tertiary care facility that cares for a wide variety of patients, we believe our results would be broadly applicable. Importantly, even though the majority of patients with COPD were within the peak $\dot{V}O_2$ = peak Work group, there were more patients with COPD in the peak $\dot{V}O_2$ > peak Work group, which might have been the cause of the lower breathing reserve associated with this group and thus confounded our findings. Our definition of equivalence of peak Work and peak $\dot{V}O_2$ was arbitrary, but seemed to best reflect our clinical impression of prevalence and importance. We were unable to assess the contribution of psychological factors involved in exercise, such as

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motivation, anxiety or thresholds for pain, although we did show that there were no significant differences in the change in Borg rated levels of perceived dyspnea. Interestingly, this lack of differences may reflect reduced sensitivity to dyspnea among the patients achieving high work loads [38]. This reduced sensation of dyspnea is supported by the lower change in Borg rating adjusted for the amount of work performed (ΔBorg/ΔWork) among patients in the peak Work > peak $\dot{V}O_2$ group. In addition, although we suggest that peak Work better reflects global exercise capacity than peak $\dot{V}O_2$, we have not validated this concept by correlating this finding with any clinically meaningful outcomes, such as response to therapy or relation to job or athletic performance. However, total workload is thought to be a critical factor involved in improving cardiopulmonary conditioning [35].

It is important to note that there was discordance between the exercise protocols used in the peak Work > peak $\dot{V}O_2$ vs. peak $\dot{V}O_2$ > peak Work groups. Namely, the group achieving higher Work than $\dot{V}O_2$ exercised in higher workload increments (30 watts/min) than the group achieving higher $\dot{V}O_2$ than work (15 watts/min). These increments were chosen by the exercise technologist on the basis of the patient's self-reported exercise capacity in order to create a protocol that would allow the patient to reach peak work capacity in approximately 10 minutes [13]. The difference in these increments may have contributed to why different relationships of peak Work vs. peak $\dot{V}O_2$ were achieved [15]. However, the altered rate of $\dot{V}O_2$ for different levels of work is usually seen for work

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rates above the AT [13,15], and there were no significant differences in slope of $\dot{V}O_2$-Work above the AT in any of the three groups (Table 1). In addition, in the study by Hansen and colleagues [15], higher work rate increments resulted in shorter total exercise time among the same healthy subjects who were tested under different work rate protocols. We found just the opposite, which was that patients who had the higher work rate increment (the majority of the peak Work > peak $\dot{V}O_2$ group) had longer total exercise times (Table 1). This suggests that other factors besides the exercise protocol are important in determining peak Work vs. peak $\dot{V}O_2$. Nevertheless, given this aspect of our study, and the finding of only modest odds ratios from the multivariate logistic regression analysis, one must interpret the findings with caution and realize that they may be of marginal clinical significance. In addition, the fact that the exercise increments were chosen on the basis of patient self-reported exercise capacity may have resulted in a selection bias that favored the more fit patients exercising on the higher work increment protocol, thus creating a self-fulfilling situation of achieving higher peak Work relative to peak $\dot{V}O_2$.

Conclusion

We have observed that patients achieving a higher peak Work than peak $\dot{V}O_2$ had a lower BMI, a higher breathing reserve, and a greater peak heart rate. While the work protocol might have primarily determined this, the fact that differences in BMI, breathing reserve

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and peak heart rate differentiate the peak Work vs. peak $\dot{V}O_2$ groups suggests that there are underlying physiological characteristics that reflect important aspects of exercise capacity that go beyond the peak $\dot{V}O_2$. The clinical corollary of this is that treating any reversible lung disease, encouraging weight loss and recommending regular, strenuous exercise are appropriate strategies to share with patients to help them improve their exercise capacity. When a cardiopulmonary exercise test is ordered to assess overall exercise tolerance, we suggest that both peak Work and peak $\dot{V}O_2$ must be taken into account in order to provide the most comprehensive interpretation of the results.

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Figure Legend

Figure 1 – Plot of Percent Predicted Peak $\dot{V}O_2$ vs. Percent Predicted Peak Work. The solid line is the line of identity, and the two dashed lines represent the 15% difference above or below the line of identity, thus defining the peak $\dot{V}O_2$ > peak Work group (above the upper dashed line) and the peak Work > peak $\dot{V}O_2$ group (below the lower dashed line).

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Table 1 – Demographics and Physiological Characteristics of the Study Subjects in Each of the Three Groups

	Peak $\dot{V}O_2$ > Peak Work	Peak $\dot{V}O_2$ = Peak Work	Peak Work > Peak $\dot{V}O_2$	p-value*
n	57	92	23	
Age (yrs)	63 ±13§	59±15	51±10†	.001
Sex (%M/F)	26/74†§	49/51	52/48	.04
BMI (kg/m2)	30±7†§	27±5	26±4	<.001
FVC (%pred)	78±17†§	86±18	95±15	<.001
FEV_1 (%pred)	66±23§	74±25	93±20†	<.001
FEV_1/FVC (abs%)	85±23§	84±21	97±14†	.03
Work Increment (15/30 watts/min, %)	91/9	66/34	9/91	<.001
Total Exercise Time (min)	4.7±1.7	5.4±1.9	6.8±2.5†‡	<.001
Peak $\dot{V}O_2$ (%pred)	97±28†	80±26	94±25	<.001
Peak Work (%pred)	70±28	78±30	119±29†‡	<.001
$\dot{V}O_2$ - Work Slope (ml/min/watt)	13±3†§	10±2	8±1†	<.001
$\dot{V}O_2$ - Work Slope Above AT (ml/min/watt)	10.6 ± 7.0	11.4±4.8	9.5±2.8	0.32
Rest $\dot{V}O_2$ (ml/min/kg)	4.3±1.2	4.1±1.1	4.1±1.3	.37
Peak $\dot{V}O_2$ (ml/min/kg)	17±7§	19±10	26±10†	<.001
VE/ $\dot{V}O_2$ @AT (L/ml)	31±8	32±8	26±3†‡	.003
VE - $\dot{V}CO_2$ slope (L/ml)	32±6	34±8	29±6†	.01
RER - peak	1.04±0.12†§	1.10±0.12	1.21±0.09†‡	<.001
VE/MVV (%)	73±20§	67±17	57±16†	.002
BR (L)	23±22§	32±25	54±27†	<.001

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Peak HR (%pred)	81±13§	79±14	89±10†	.004
Peak $\dot{V}O_2$ /HR (%pred)	102±32	93±28	105±26	.09
ΔO_2 sat (%)	0.16±0.20	0.67±0.16	-0.66±0.32†	<.001
ΔBorg/ΔWork (units/watt)	0.07±0.08	0.05±0.03	0.02±0.01	.004‡
Time to AT (% total time)	50±24	56±19	59±14	.14
Time above AT (% total time)	50±24	44±19	41±14	.14
AT (% peak $\dot{V}O_2$ pred)	63±19†	51±18	60±20	<.001

All values = mean ± SD unless otherwise noted

* p-value by ANOVA across groups

†p<0.05 in comparison to $\dot{V}O_2$ =Work group

‡p<0.05 in comparison to $\dot{V}O_2$ > Work group

§p<0.05 in comparison to Work > $\dot{V}O_2$ group

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Table 2 – Factors Associated with Being in Peak $\dot{V}O_2$ > Peak Work Group Rather Than Peak Work > Peak $\dot{V}O_2$ Group by Multivariate Logistic Regression Analysis*

Factor	Odds Ratio†	95%CI	p-value
BMI	1.18	1.03-1.38	.03
BR	0.94	0.90-0.96	<.001
Peak HR	0.94	0.88-0.99	.03

*R^2 for model = 0.42

†Odds ratio is Unit Odds Ratio

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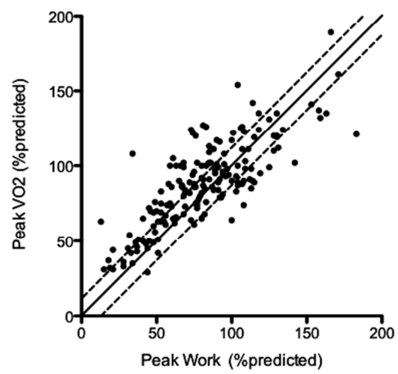

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