

V_E/VCO_2 slope in lean and overweight women and its relationship to lean leg mass[☆]

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ABSTRACT

Ventilation/carbon dioxide production (V_E/VCO_{2slope}) is used clinically to determine cardiorespiratory fitness and morbidity in heart failure (HF). Previously, we demonstrated that lower lean leg mass is associated with high V_E/VCO_{2slope} during exercise in HF. In healthy individuals, we evaluated 1) whether V_E/VCO_{2slope} differed between lean and overweight women and 2) the relationship between lean leg mass and V_E/VCO_{2slope} in overweight sedentary (OWS), overweight trained (OWTR) and lean, trained (LTR) women.

Methods: Gas exchange and ventilation were collected during a treadmill peak oxygen uptake test (VO_{2peak}) in 40 women [26 OWS (29 ± 7 yrs., mean ± SD), 7 OWTR (33 ± 5 yrs) and 7 LTR (26 ± 6 yrs)]. Body composition was measured by dual X-ray absorptiometry.

Results: VO_{2peak} was highest in LTR (46.6 ± 8 ml/kg/min) compared with OWTR (38.1 ± 4.9 ml/kg/min) and OWS women (25.3 ± 4.8 ml/kg/min, $p < 0.05$). Lean leg mass was highest in OWTR and lowest in LTR women ($p < 0.05$). V_E/VCO_{2slope} was similar between groups ($p > 0.05$). Higher lean leg mass was associated with lower V_E/VCO_{2slope} in overweight women (OWS + OWTR: $r = -0.55$, $p < 0.001$), contrasting with higher V_E/VCO_{2slope} in LTR women ($r = 0.86$, $p < 0.001$).

Conclusions: These findings suggest V_E/VCO_{2slope} may not differentiate between low and high cardiorespiratory fitness in healthy individuals and muscle mass may play a role in determining the V_E/VCO_{2slope} , independent of disease.

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1. Background

Obesity and sedentary lifestyles are a major health concern facing today's society. According to data from the National Health and Nutrition Examination Survey (NHANES), collected in 2013–2014, >2 of 3 adults are either overweight or obese and 1 of 3 adults are classified as extremely obese in the United States [1,2]. Evidence suggests that being overweight is associated with impaired lung function that extends beyond airflow limitation. For example, respiratory complications of obesity can include mechanical constraints such as decreased chest wall compliance, increased respiratory resistance and increased work of breathing, reduced lung volumes, sleep apnea and hypoventilation

syndrome [3–6]. Obesity can also affect respiratory control [7] including an increased respiratory drive [7] and a diminished hypercapnic response [8].

Peak oxygen consumption (VO_{2peak}) is widely used as a marker of exercise capacity and prognosis [9]. However, many individuals discontinue exercise far below their physiologic limitation due to fatigue or discomfort. The ventilatory equivalent to carbon dioxide production slope (V_E/VCO_{2slope}), ventilatory efficiency, is an alternative noninvasive measurement that can be quantified from submaximal or peak exercise testing. In patients with heart failure (HF), the slope generated from a plot of V_E over VCO_2 is positively correlated to HF severity. Higher V_E/VCO_2 slope indicates excessive ventilation for a given CO_2 production and is associated with increased morbidity and mortality in HF [10,11]. Indeed, V_E/VCO_{2slope} predicts mortality independently from cardiorespiratory fitness testing (VO_{2peak}) in patients with HF [11]. V_E/VCO_{2slope} measures are also independent of subject effort and BMI [12]. Recently, we have demonstrated that a higher V_E/VCO_{2slope} , or reduced ventilatory efficiency, is associated with lower lean leg mass in HF [13]. This association is important, particularly because inhibiting afferent feedback

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from the skeletal muscle by fentanyl injections abolished this relationship in patients with HF [13]. This previous work demonstrates a close link exists between leg lean mass skeletal muscle afferent feedback and ventilatory efficiency in HF. Whether the inverse relationship between lean leg mass and $V_E/VCO_{2\text{slope}}$ previously observed in HF is already present in overweight/obese sedentary adults without HF and whether these findings relate to fitness levels remains unknown. In addition, the influence of sex/gender has not been well studied. This study focused women because women experience greater reductions in whole muscle volume [14] and fiber area, particularly fast-type II fibers with muscle unloading [15,16]. Therefore, the purpose of this study was to determine 1) if $V_E/VCO_{2\text{slope}}$ is greater in overweight/obese women compared with lean women and 2) if there is a relationship between lean leg mass and $V_E/VCO_{2\text{slope}}$ in overweight sedentary, overweight trained and lean, trained women. We hypothesized that overweight sedentary women will have a higher $V_E/VCO_{2\text{slope}}$ associated with lower lean leg mass.

2. Methods

Forty adult women (18–40 years old) were included in the analysis of this study that was part of a larger clinical trial (TrainMeUpMN, NCT02150889). The participants were twenty-six overweight/obese, sedentary (OWS) (29 ± 7 yrs., mean \pm SD), seven overweight, trained (OWTR) (33 ± 5 yrs) and seven lean, trained (LTR) women (26 ± 6 yrs). Participants provided written informed consent and the study was approved by the University of Minnesota IRB and conducted in accordance with the Declaration of Helsinki.

2.1. Inclusion criteria

OWS: 1) insulin resistant based on initial screening if their Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR) was ≥ 2.5 [17], 2) BMI 25 to 40 kg/m², and 3) sedentary status defined by <30 min/week of regular exercise by self-report.

OWTR: BMI of 25 to 35 kg/m² and self-report of 3–5 aerobic exercise sessions/week, predominantly running.

LTR: BMI of 18 to <25 and self-report of 3–5 aerobic exercise sessions/week, predominantly running.

Exclusion criteria included 1) medical diagnoses such as, diabetes, cardiovascular disease, uncontrolled pulmonary disease or a history of hematologic (platelets <100), hepatic (LFTs $>2\times$ normal), renal (Cr > 1.5 mg/dL) pulmonary/cardiac abnormalities (including abnormal EKG), 2) taking medications that may affect lipid levels, specifically lipid lowering agents, or diuretics and 3) taking anticoagulation medications. All participants had a negative pregnancy test at their screening visit.

2.2. Procedures

Body composition was assessed via a dual x-ray absorptiometry (DXA) scan by iDEXA (GE Healthcare; Software encore version 16.2). Peak oxygen consumption ($VO_{2\text{peak}}$) was evaluated by using a metabolic cart (Medical Graphics Corporation, St. Paul, MN or Parvo voMedics TrueOne 2400 cart, Sandy, UT). Overweight participants were tested using the Bruce protocol [18]. Lean subjects were tested using a modified Åstrand protocol that began at subjects' self-selected race pace which was maintained throughout the duration of the test [19]. The different protocols were selected to achieve maximum effort and peak VO_2 within 10–12 min given the higher fitness levels of the LTR group. Relevant measures acquired during testing included respiratory exchange ratio (RER), respiratory rate (R_R), tidal volume (V_T), ventilation (V_E) and ventilatory equivalent for carbon dioxide (V_E/VCO_2). $V_E/VCO_{2\text{slope}}$ was calculated from rest to $VO_{2\text{peak}}$ as recommended by the American Heart Association for its additional clinical information

and relevance [20] and entered into a least squares linear regression equation ($y = a + bx$; $b = \text{slope}$) [21].

2.2.1. Statistical analysis

Nonparametric *t*-test and a Spearman Correlation analysis was used to determine differences between groups and associations between independent variables and $V_E/VCO_{2\text{slope}}$, respectively (SPSS v 22.0, IBM Analytics, Armonk, NY). Data are reported as means \pm standard deviations in text and table. Significance was considered if $p < 0.05$.

3. Results

Women in all groups were similar in age and height ($p > 0.05$). OWS women weighed more and had a higher BMI than OWTR and LTR ($p < 0.01$, Table 1). Ventilation and gas exchange data are also located in Table 1. $VO_{2\text{peak}}$ was lowest in OWS group, compared with OWTR and highest in LTR ($p < 0.05$). $V_E/VCO_{2\text{slope}}$ was similar between LTR, OWTR and OWS groups ($p > 0.05$). Absolute lean leg mass was lower in the LTR group (14.7 ± 1.3 kg) compared with the OWTR (18.8 ± 3.6 kg) and OWS group (17.9 ± 2.8 kg, $p < 0.05$). High $V_E/VCO_{2\text{slope}}$ was inversely associated with lean leg mass for all participants, but when separated by group, there was a disparate relationship between lean women and overweight women, regardless of training status (Fig. 1) ($p < 0.05$).

4. Discussion

The novel findings from this study are that 1) OWS women do not have a higher $V_E/VCO_{2\text{slope}}$ than OWTR or LTR women and 2) a disparate relationship was observed in lean leg mass and $V_E/VCO_{2\text{slope}}$ between women at extremes of clinical phenotype (LTR vs OWS). $V_E/VCO_{2\text{slope}}$ is a good clinical indicator of cardiorespiratory fitness in patients with HF [11], but it does not appear to be a relevant indicator of cardiorespiratory fitness in overweight/obese, but otherwise healthy women.

In the current study, $V_E/VCO_{2\text{slope}}$, calculated from the $VO_{2\text{peak}}$ test for the OWS, OWTR and LTR group was similar and mostly within normal levels (with seven women in the OWS group reaching levels ≥ 30). In HF patients with moderate to severe disease, $V_E/VCO_{2\text{slope}}$ is generally measured to be around 34 or higher [22]. As such, a small percentage (26%) of women in the OWS group had higher $V_E/VCO_{2\text{slope}}$, but as a group, $V_E/VCO_{2\text{slope}}$ was not greater than OWTR or LTR. Therefore, in a healthy population, $VO_{2\text{peak}}$ may be the best indicator of cardiorespiratory fitness, even though it may depend on effort and BMI [12] and $V_E/VCO_{2\text{slope}}$ may only be a relevant clinical indicator of cardiorespiratory fitness in diseased populations. As such, the current study found that $VO_{2\text{peak}}$ was significantly higher in OWTR compared with the OWS group, but as expected $VO_{2\text{peak}}$ was greatest in the LTR group.

Table 1

Participant demographics and ventilation data. Body mass index, BMI; Peak Oxygen Consumption, $VO_{2\text{peak}}$; Respiratory Exchange Ratio; RER, Ventilation, V_E ; Respiratory Rate, R_R ; Tidal Volume, V_T ; Ventilatory equivalent to carbon dioxide production, V_E/VCO_2 ; Overweight Sedentary, OWS; Overweight trained, OWTR; Trained, LTR. *indicates significance between OWS and OWTR in table and figures ($p < 0.05$); **indicates significance between OWTR and LTR in table and figures ($p < 0.05$); ***indicates significance between OWS and LTR in table and figures ($p < 0.05$).

	OWS	OWTR	LTR
n	26	7	7
Age (years)	29 ± 7	33 ± 5	26 ± 6
Height (cm)	166.1 ± 6.1	171.4 ± 6.3	166.4 ± 6.5
Weight (kg)	$103.6 \pm 24.0^*$	$91.0 \pm 15.7^{**}$	$61.0 \pm 6.2^{***}$
BMI (kg/m ²)	37.0 ± 6.8	$31.6 \pm 5.4^{**}$	$21.9 \pm 1.6^{***}$
$VO_{2\text{peak}}$ (ml/kg/min)	$25.3 \pm 4.8^*$	$38.1 \pm 4.9^{**}$	$48.6 \pm 7.9^{***}$
Peak RER	1.19 ± 0.1	1.10 ± 0.09	$1.12 \pm 0.1^{***}$
Peak V_E (l/min)	$85.1 \pm 16.2^*$	107.8 ± 20.2	95.5 ± 9.5
Peak R_R (breaths/min)	42.5 ± 7.5	$46.9 \pm 7.1^{**}$	$57.0 \pm 12.5^{***}$
Peak V_T (liters)	2.1 ± 0.5	$2.3 \pm 0.4^{**}$	$1.7 \pm 0.3^{***}$
V_E/VCO_2 slope	27.4 ± 3.6	26.1 ± 2.5	28.5 ± 1.8

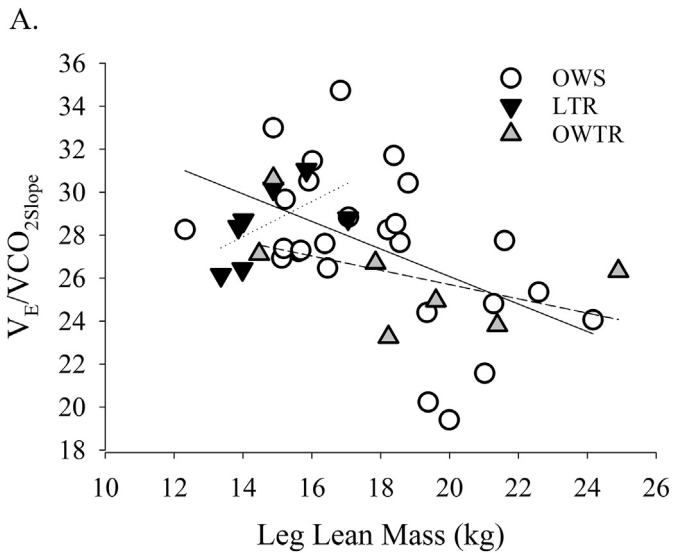


Fig. 1. Lean leg Mass and V_E/VCO_{2slope} . Lean leg mass (kg) is associated with V_E/VCO_{2slope} for all women ($r = -0.58$, $p < 0.001$). If separated into respective groups the association was opposite for the lean vs. the overweight group, but was only significant for LTR and OWS: OWS: $r = -0.49$, $p = 0.01$ (—), OWTR: $r = -0.64$, $p = 0.10$ (----) and LTR: $r = 0.86$, $p < 0.01$ (.....).

The two extreme clinical phenotypes (LTR vs OWS) appeared to have divergent relationships between lean leg mass and V_E/VCO_{2slope} . In the LTR group, higher lean leg mass was associated with a higher, but not abnormal, V_E/VCO_{2slope} . In contrast, in OWS women, higher lean leg mass was associated with lower V_E/VCO_{2slope} . The OWTR group trended similarly to the OWS group, ($r = -0.64$), although this was not statistically significant. Therefore, similar to what was previously seen in HF [13], lean leg mass is associated with V_E/VCO_{2slope} , but only in overweight/obese ($BMI > 30 \text{ kg/m}^2$) individuals, such that greater lean leg mass may be beneficial and contribute to a lower V_E/VCO_{2slope} in overweight/obese women.

The link between skeletal muscle mass and ventilatory efficiency has been demonstrated in other studies [13,23]. As such, after an 8-week aerobic training in a pediatric obesity cohort, V_E/VCO_2 was improved [23]. Although, muscle mass was not reported in Kaufman et al. 2007, there were no changes in BMI or percentage of body fat in the exercise group, which indicates that the improvement in V_E/VCO_2 is likely a result in the changes at the level of the muscle [23]. While the response to aerobic training can be variable, aerobic training reduces the proportion of type IIx muscle fibers with a corresponding increase in the proportion of type I and type IIa fibers [24]. This fiber type shift will improve the oxidative capacity of the muscle and reduce the metabolic build up during exercise. Although the exact mechanism of how skeletal muscle and ventilatory efficiency are linked cannot be determined from this study, previous work demonstrates that the link may be through augmented skeletal muscle afferent feedback contributions in patients with less lean mass [13].

4.1. Limitations

There are limitations to the study that need to be considered when interpreting the results. Data reported in this study was on women and can therefore, only be generalizable to women. An additional limitation is the small sample sizes for the OWTR and the LTR groups. A larger sample size may provide greater insight to the lean leg mass and V_E/VCO_{2slope} relationship in trained individuals. It may appear to be a limitation that our cohort of obesity participants are insulin resistant, however, insulin sensitivity is a key determinant of “metabolic health” and the majority of the population with obesity is insulin-resistant

[25]. Therefore, the interpretation derived from our data is more generalizable to the majority of obese women.

4.2. Conclusion

In conclusion, this study makes two novel observations. First, we demonstrate that although V_E/VCO_{2slope} may be an important measure of cardiorespiratory function in HF, it does not appear to differentiate between low and high cardiorespiratory fitness in otherwise healthy women. Second, higher lean mass in overweight/obese women, regardless of training, may improve ventilatory efficiency (i.e. lower V_E/VCO_{2slope}) during intense exercise. Therefore, it is feasible to suggest that muscle mass may play a role in determining the V_E/VCO_{2slope} , independent of disease state.

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