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Exercise Dose Response in Muscle

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Abstract

Exercise increases peak VO_2 partially through muscle adaptations. However, understanding muscle adaptations related to exercise dose is incomplete. This study investigated exercise training dose on capillaries per fiber and capillaries per area; and citrate synthase from vastus lateralis and related both to changes in peak VO_2 . This randomized trial compared 3 exercise doses: low amount-moderate intensity ($n = 40$), low amount-high intensity ($n=47$), high amount-high intensity ($n=41$), and a control group ($n=35$). Both measures of capillary supply increased in all exercise groups ($p < 0.05$). Low amount-high intensity and high amount-high intensity improved citrate synthase ($p < 0.05$) and the low amount-moderate intensity citrate synthase approached significance ($p = 0.059$). Muscle improvements were only related to improvements in peak VO_2 in high amount-high intensity (citrate synthase, $r = 0.308$; capillaries: fiber, $r = -0.318$; $p < 0.05$ and capillaries/ mm^2 $r = -0.310$, $p < 0.05$). These data suggest muscle adaptations occur following both low and high exercise doses, but are only related to improved peak VO_2 following high amount-high intensity training.

INTRODUCTION

Physical activity and high fitness levels are associated with cardiovascular health and wellness [3,5,8,20]. Much attention has been focused recently on establishing the evidence base to support the generation of clearer, more definitive, exercise recommendations to promote cardiovascular health benefits [19]. Further, investigations of exercise dose-response effects offer an opportunity to understand how different exercise amounts and intensities affect cardiovascular risk factors and fitness. Several laboratories, including ours, have observed that different exercise programs differentially influence peak oxygen consumption (peak VO_2), lipoproteins, insulin sensitivity, visceral fat and metabolic syndrome [6,13,15,17,21,22,24].

In addition to reducing traditional cardiovascular risk factors, aerobic exercise training increases oxidative capacity of skeletal muscle through, at least in part, increases in oxidative enzyme activity, mitochondrial number and volume and transitioning fiber type percentage from Ix to more IIa [11,12]. Both capillaries per mm^2 and capillaries: fiber are greater among trained than untrained subjects and have been shown to increase after an

aerobic exercise training program [1,9,14]. Although these adaptations to aerobic exercise training following a traditional exercise prescription are well established (3 to 4 times per week, for 30 to 40 minutes per session, at 60 to 80% of peak VO_2 or heart rate reserve), little is known regarding the extent to which these responses vary as the exercise exposure varies in intensity or amount. Although both cardiac output and peripheral skeletal adaptations account for increased peak VO_2 , the primary purpose of this analysis was to investigate the exercise training dose-response effects on two well accepted oxidative markers in skeletal muscle, capillary supply (measured as endothelial cells/fiber and endothelial cells/ mm^2) and citrate synthase activity (CS), and to determine to what extent each of these measures relate to improved peak VO_2 . We hypothesized that the oxidative adaptations of skeletal muscle citrate synthase and capillary supply, measured by capillaries/ mm^2 and capillaries:fiber, would increase as the dose of exercise training increased. This investigation addresses these questions by studying middle-aged subjects in the context of a relatively large, randomized controlled clinical study.

METHODS

Subject Population

A total of 163 subjects were included in this analysis. These subjects are a cohort from the Studies of Targeted Risk Reduction Interventions Through Defined Exercise (STRRIDE) trial [16]. Subjects used for this analysis met criteria of having a muscle biopsy before and after exercise training, high adherence to the exercise training intervention and good effort on baseline and 8 month cardiopulmonary exercise tests (CPX). Subjects ($n=163$) were blindly randomized into one of the following groups: an inactive control group and 3 exercise training groups: low-amount/moderate-intensity, low-amount/high-intensity and high-amount/high-intensity exercise. Inclusion criteria were as follows: age of 40 to 65 years, sedentary, overweight or class 1 obesity (BMI 25 to 35 kg/m^2), presence of dyslipidemia (either LDL-cholesterol 130 to 190 mg/dl ; or HDL-cholesterol 40 mg/dl for men, or 45 mg/dl for women) and non-smoking status. Subjects were excluded from the study for hypertension (untreated resting blood pressure 160/90 mmHg), diabetes mellitus (fasting blood glucose 140 mg/dl), or orthopedic limitations to exercise training. Subjects had no cardiopulmonary dysfunction as indicated by history and physical examination, and none exhibited symptoms of ischemic heart disease by exercise or ECG tracing. All women were post-menopausal as defined by having had 3 or fewer menstrual periods in the last 12 months or a serum FSH concentration of 40 IU/L . This protocol has previously been described in detail [16]. All studies were performed under research protocols approved by the Institutional Review Board of the Duke University Medical Center in accordance with the Helsinki Declaration of 1975 and the guidelines of Harris and Atkinson [7]. Each subject was informed of testing protocols and the potential risks and benefits of participation. All subjects provided written consent prior to participation.

Exercise Testing

Subjects underwent a maximal cardiopulmonary exercise test (CPX) with a 12-lead electrocardiogram and expired gas analysis on a treadmill. These tests were performed twice at baseline and after completing the exercise program. Expired gases were analyzed continuously using a Sensormedics 2900 unit (Yorba Linda, CA) or a Parvo Medics unit (Sandy, UT). The protocol used consisted of 2-minute stages, increasing the workload by approximately 1 metabolic equivalent (MET) per stage. The same protocol and same metabolic cart was used pre- and post-training in each subject. The last 40 seconds were averaged to determine peak VO_2 . Subject effort and true maximal tests were ensured by peak respiratory exchange ratio (RER): no subject had an $\text{RER} < 1.01$, only six subjects had an $\text{RER} < 1.05$ and over 95% of all subjects had an $\text{RER} \geq 1.05$. In addition, reported rate of

perceived exertion (RPE) measures were 18 and both men and women percentages of predicted heart rate max were 104% and 105%.

Exercise Training

The specific exercise prescription per group differed in exercise intensity and amount (caloric expenditure). The exercise groups were as follows: high-amount/high-intensity (HAHI), the caloric-equivalent of jogging approximately 32 km (20 miles) per week at 65 to 80% peak VO_2 ; low-amount/high-intensity (LAHI), jogging approximately 19 km (12 miles) per week at 65 to 80% peak VO_2 ; low-amount/moderate-intensity (LAMI), walking approximately 19 km (12 miles) per week at 40 to 55% peak VO_2 or a non-exercising control group. For the high amount-high intensity group, the specific prescription was to expend 23 kilocalories per kilogram of body weight per week, which is the caloric-equivalent of approximately 32 km (20 miles) of walking or jogging for a 90 kilogram person [18]. For the low amount-high intensity and low amount moderate intensity groups, the prescription was 14 kilocalories per kilogram per week. All subjects walked or jogged on a treadmill under the supervision of a trained exercise physiologist. All exercise groups underwent a 2 month initial ramp period in which the amount and intensity of exercise were gradually increased to minimize the chance of injury. This was followed by 6 months of training at the assigned exercise prescription. CPX tests were repeated at the end of the ramp period to adjust the exercise prescription for improvements in peak VO_2 . Appropriate intensity for the remaining 6 month training period was maintained by an increase in work rate as needed to exercise within a specific target heart rate range. All subjects were required to wear a Polar Heart rate monitor (Polar Electro OY, Finland) during training, which was downloaded weekly to ensure compliance. To ensure a clear separation of exercise exposures between exercise groups, only data from subjects with kcal/week of adherence between 74% to 115% were used.

Muscle Biopsies

Biopsy samples were obtained from the vastus lateralis using a modified Bergstrom needle technique [2]. Biopsy sites were anesthetized with a 2% lidocaine solution, and 0.5 cm incisions were made through the skin and *fascia lata*. The needle was consistently inserted to a depth of 40 to 60 mm. Samples were then mounted in cross-section, in optimal cutting temperature (OCT) compound (Miles Pharmaceutical, West Haven, CT) beds, and snap frozen at -80°C .

Citrate Synthase

Citrate synthase activity was determined with a fluorescent based enzymatic assay using homogenized skeletal muscle [4] and expressed in units of $\mu\text{mol}/\text{min}/\mu\text{g}$ protein.

Immunohistochemical Analysis of Capillary Supply

Capillary supply, expressed as capillary density by endothelial cells/ mm^2 , and a measurement of the ratio of endothelial cells:muscle fiber was determined by examining the total number of endothelial cells relative to muscle area or the number of endothelial cells per muscle fibers via light microscopy. Endothelial cells were identified in histologic sections using immunohistological techniques with an endothelial cell-specific monoclonal antibody, CD31 (Daco, Carpinteria, CA). Sections were cut throughout the tissue block for analysis, ensuring a homogenous sample of the block. A minimum of six different 200x fields were counted and only if they were in cross section. Intra-observer variability on samples chosen for blind repeat analysis was 5%. The stained slide of human muscle was placed on the Olympus 70x microscope and transferred onto a computer screen at a magnification of 100x through an Optronics Engineering DEI-750 camera to the Adobe

Premiere 4.2.1 program. Within this program, the image of the muscle fiber was captured and saved to the Adobe Photoshop LE program, then opened into the NIH Image 1.6/ppc program. In the NIH Image program the individual muscle fiber was outlined and the total area was calculated.

Statistical Analysis

Analysis of variance (ANOVA) was used to test for baseline differences between groups (Control, LAMI, LAHI and HAHl). A general linear model was used to determine the relations between changes in peak VO_2 , citrate synthase, capillary supply as outcomes, and gender and group as mediators. By doing so, an interaction term of gender by group was created to analyze the influence each fixed factor had on the primary outcomes. Gender by group interactions were not significant, and therefore the interaction term was removed from the final model. ANOVA was used to determine if the change scores of the outcome variables differed after exercise training. Individual multivariable linear regressions were performed on each exercise dose and not the group as a whole to determine strength of variables to predict changes in peak VO_2 . Where appropriate, post hoc testing was performed with Bonferroni correction for multiple comparisons to determine differences between exercise groups. A p-value of < 0.05 was considered significant for all statistical tests. All statistics were performed using SPSS (version 17.0, Chicago, Ill). All tabular means are presented as mean $\pm$ SD and all figures as mean $\pm$ SE.

RESULTS

Differences between treatment groups

Table 1 shows the exercise prescription and adherence for each intervention group. Baseline characteristics were not different between treatment groups (Table 2). There was a graded exercise dose response improvement in peak VO_2 , reproducing our previous findings[6] (Figure 1A). Although no statistical difference was found between the LAMI and LAHI groups ($p=0.069$), the pattern of change suggest a separate and combined effect of exercise amount and intensity on peak VO_2 changes, with amount being more sensitive than intensity in this study's results. Muscle citrate synthase trended to increase more by high intensity exercise (LAHI and HAHl) than moderate intensity (LAMI), where LAHI and HAHl increased significantly more than Control, and LAMI approached significance ($p=0.059$) compared to Control (Figure 1B). For all exercise groups, both capillaries/ mm^2 and capillaries: fiber increased significantly more than in Control, but no exercise group was significantly different than any other (Figure 1C). Results for both measures of capillary supply were identical, and therefore we show only data for endothelial cells: fiber in the figures. Pre and post-training data is reported in Table 3 for both capillaries/ mm^2 and capillaries: fiber. There were no gender by group effects on the outcome variables.

Relation of Exercise Capacity with Citrate Synthase and Capillary Supply

Change in citrate synthase was positively related to change in peak VO_2 ($r=0.304$; $p < 0.05$); and capillaries: fiber was negatively related to increased peak VO_2 ($r= -0.318$, $p < 0.05$) only in the HAHl group (Figure 2). Change in capillaries/ mm^2 was also related to change in peak VO_2 ($r= -0.310$, $p < 0.05$). This finding was further supported by r^2 values when citrate synthase and capillaries: fiber were combined together in the linear model and are represented in Table 4 for all 3 exercise exposures. When citrate synthase and capillaries: fiber were combined in the model, only high amount high intensity exercise training predicted the relation between changes in these skeletal muscle factors and changes in peak VO_2 (17%, $p < 0.05$).

DISCUSSION

Based on a large body of information, both skeletal muscle and hemodynamic changes are required for the maximal change in peak VO_2 in previously sedentary individuals. This study addresses changes in the former, skeletal muscle. Specifically, we studied the effects that different exercise training amounts and intensities have on two intrinsic skeletal muscle (citrate synthase and capillary supply) parameters and their relationship to changes in peak VO_2 in middle-aged men and women at risk for cardiovascular disease. Previous studies on skeletal muscle adaptation to exercise training have been performed predominantly using a standard exercise prescription of 3–4 exercise sessions per week at 60–85% of peak heart rate for 30–40 minutes per session. Randomized controlled studies examining skeletal muscle adaptations to different exercise exposures in amount or intensity are remarkably lacking. To the best of our knowledge, this study represents the largest randomized controlled study addressing these issues. Our major finding was that although skeletal muscle oxidative capacity (as represented by citrate synthase activity and both capillaries: fiber and capillaries/ mm^2) increased in all groups compared to controls (Figure 1), these increases were only related to improvements in peak VO_2 in the highest exercise amount group (Table 4 and Figure 2). These data suggest that: 1) a tiered increases in peak VO_2 can occur following a broad range of exercise training exposures; 2) although adaptations occur in skeletal muscle following low and high exercise exposures, these responses are only related to improved peak VO_2 following high amount and high intensity training. Although a limitation to this study was that no direct measure of central hemodynamics was obtained, it is likely that while improved aerobic capacity following low amount/moderate intensity of exercise training can be explained primarily by central hemodynamic adaptations, the greater gains after a higher exercise intensity program is augmented due to a combination of central and peripheral adaptations.

Contrary to our hypothesis, our results also suggest that both measures of capillary supply are very responsive to exercise training across all doses, as all three exercise doses increased similarly (16.3%, 17.6% and 18.0%) and all were significantly different than the Control. Citrate synthase activity, which parallels mitochondrial quantity, improved significantly with LAHI and HAHl, but the response to LAMI did not reach statistical significance when compared with Control ($p=0.059$). Despite significant changes in citrate synthase between LAHI and HAHl groups compared to controls, the failure of individual exercise groups to be different makes the interpretation of exercise dose effects on citrate synthase difficult and requires additional investigation. This also suggests that any one individual skeletal muscle oxidative marker may not be adequate to explain changes in peak VO_2 following lower exercise training exposures, and that a better relation might derive with a composite score of multiple skeletal muscle oxidative markers or a systems biological multivariable approach. Further study with markers at multiple levels of gene expression and protein regulation (e.g., transcription, translation, and protein modification) and the analysis of small molecule metabolites, will likely provide more insight into exercise training-induced responses responsible for changes in exercise capacity with lower exposures [10,23]. Skeletal muscle may play a more dominant role in the ability to sustain sub-maximal exercise intensities, or may be responsible for peak VO_2 increases when exercise training is continued for periods of greater than 1 year. We were not able to address these possibilities within this analysis.

Other studies, including the present one, have reported increased capillaries: fiber and capillaries/ mm^2 density after exercise training. However, no human longitudinal randomized controlled study has demonstrated a significant relation between changes in either measure of capillary supply and increased peak VO_2 . In the present study, no relation was observed between changes in capillary supply measures and changes in peak VO_2 in either the LAMI or LAHI groups. However, changes in both capillaries: fiber and capillaries/ mm^2 had a

significant negative correlation with changed in peak VO_2 with the HAHl exercise training. That is, those with the largest increase in capillary supply with exercise training had the smallest increase in peak VO_2 . It is important to note that this does not mean values decrease from baseline, or that these variables go in opposite directions, it simply means the magnitude of the change is inversely related. These data support the lack of positive relationship in the literature between measures of capillary supply and peak VO_2 following exercise training. The negative relation in the presence of adequate power ($n = 41$) is difficult to explain. It may be speculated that changes in capillary supply, although not positively related to peak VO_2 , may be a necessary precursor to other more positively related oxidative changes. Alternatively, it is possible that as the exercise training exposure increases with vigorous intensity exercise, the greater the response in peak VO_2 , the less important are changes in capillary supply relative to improvements in central hemodynamics. This is purely speculative and the exact mechanism for this response remains unknown and deserves further investigation.

As previously mentioned, limitations to this study include a lack of direct measurement of training-induced changes in central cardiac function (e.g. stroke volume). In addition, we recognize that other factors that influence the arterial-venous difference during maximal exercise that are not accounted for. It is possible that increases in the A- VO_2 difference, either due to changes in blood flow distribution or oxygen extraction by the muscles, could account for a significant portion of peak VO_2 increases. Unfortunately, those measures were beyond the scope of this investigation which focused on 2 intrinsic oxidative markers in skeletal muscle and will require future study. The strengths of this investigation are the inclusion of both men and women, the large number of subjects, a randomized controlled design, evaluation of skeletal muscle, a direct measure of peak VO_2 , a simultaneous comparison of exercise intensity and amount and the use of heart rate monitors to ensure subject compliance. In fact, no controlled randomized trial with adequate numbers has ever directly compared skeletal muscle adaptations in both men and women with different exercise training exposures.

In conclusion, these data contribute to the current literature on how exercise dose dictates the plasticity of skeletal muscle adaptations. The results give evidence that although citrate synthase and capillary supply, measured as capillaries: fiber or capillaries/ mm^2 , can be increased across a range of exercise training exposures, these markers only relate to increased peak VO_2 following a high amount and high intensity exercise training regimen. At lower exposures, in amount or intensity, it appears that components of central hemodynamics may play a more prominent role in increasing peak VO_2 .

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Fig. 1. The effects of exercise dose response between groups. * Indicates $p < 0.05$ between controls vs. all exercise groups. § Indicates $p < 0.05$ control vs. LAHI and HAHl.

Fig. 2.

The relationship between changes in citrate synthase and capillary supply (endothelial cells: fiber) vs. peak VO_2 following high amount-high intensity exercise training.

Table 1

Exercise prescription and adherence by group (data shown as means $\pm$ SD).

	LAMI	LAHI	HAHI
exercise prescription			
intensity (% peak VO ₂)	40–55%	65–80%	65–80%
prescription amount (km/week) ^a	19.3	19.3	32.2
prescription amount (kcal/week)	1221 $\pm$ 222	1201 $\pm$ 181	2024 $\pm$ 313
prescription time (min/week)	205 $\pm$ 43	128 $\pm$ 29	200 $\pm$ 38
actual exercise dose			
adherence (%)	88 $\pm$ 14	92 $\pm$ 10	86 $\pm$ 11
actual amount (km/week) ^b	17.0	17.8	27.7
actual time (min/week) ^c	179 $\pm$ 37	114 $\pm$ 29	175 $\pm$ 36
frequency (sessions/week)	3.5 $\pm$ 0.6	3.0 $\pm$ 0.5	3.7 $\pm$ 0.7

^a Prescription amount is presented as the approximate number of km/week that are calorically equivalent to the prescribed kcal/week of 14 kcal/kg/wk for the low dose groups and 23 kcal/kg/wk for the high dose group

^b Actual amount = Prescription amount $\times$ Adherence for each group

^c Actual time = Prescription time $\times$ Adherence for each subject

Table 2

Baseline characteristics by group (data shown as means $\pm$ SD).

	CON	LAMI	LAHI	HAHI
N	35	40	47	41
men/women	19/16	20/20	26/21	22/19
age	51.2 $\pm$ 6.8	53.2 $\pm$ 4.9	51.6 $\pm$ 7.2	51.5 $\pm$ 6.0
BMI (kg/m ²)	30.5 $\pm$ 3.2	29.6 $\pm$ 3.2	29.9 $\pm$ 3.1	29.9 $\pm$ 2.7
body fat (%)	31.8 $\pm$ 7.9	33.8 $\pm$ 7.7	35.0 $\pm$ 7.1	35.9 $\pm$ 8.1
FBG	91.0 $\pm$ 10.1	93.0 $\pm$ 9.9	93.1 $\pm$ 8.6	93.1 $\pm$ 9.7

BMI = body mass index. FBG = Fasting blood glucose. Values are mean $\pm$ SDs. No characteristic was found to be different between groups

Table 3Group comparison at baseline and post-exercise training (mean $\pm$ SD).

		Peak VO ₂ (ml·kg ⁻¹ ·min ⁻¹)		Citrate Synthase (μmol/min/μg protein)		Capillary Density (endothelial cells/mm ²)		Capillary Density (endothelial cells/fiber)	
N		Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control	35	27.6 $\pm$ 6.1	27.3 $\pm$ 5.6	0.25 $\pm$ 0.1	0.24 $\pm$ 0.2	338.6 $\pm$ 76.1	336.1 $\pm$ 73.3	1.60 $\pm$ 0.4	1.60 $\pm$ 0.4
LAMI	40	27.5 $\pm$ 6.3	29.3 $\pm$ 6.7*	0.22 $\pm$ 0.1	0.27 $\pm$ 0.2	320.4 $\pm$ 46.4	371.6 $\pm$ 79.1*	1.50 $\pm$ 0.22	1.74 $\pm$ 0.36*
LAHI	47	29.4 $\pm$ 6.2	32.7 $\pm$ 6.7*	0.23 $\pm$ 0.2	0.32 $\pm$ 0.2 [†]	335.3 $\pm$ 79.7	384.3 $\pm$ 94.5 [†]	1.59 $\pm$ 0.39	1.81 $\pm$ 0.4 [†]
HAHI	41	28.1 $\pm$ 5.0	33.6 $\pm$ 6.5*	0.23 $\pm$ 0.2	0.34 $\pm$ 0.4	336.1 $\pm$ 83.9	385.6 $\pm$ 72.4 [†]	1.58 $\pm$ 0.39	1.81 $\pm$ 0.33 [†]

* p 0.001 pre vs post-training

[†] p < 0.05 pre vs post-control

Table 4

Predictive Value of Skeletal Muscle citrate synthase and capillary supply (endothelial cells:fiber) in the linear model by group.

	Citrate Synthase p value	Endothelial cells:fiber p value	Citrate Synthase + Endothelial cells:fiber r ² value
LAMI Group	0.621	0.829	0.05
LAHI Group	0.540	0.183	0.01
HAHI Group	0.027 *	0.022 *	0.17 *

* Significant at $p < 0.05$ in model